Therapeutic interventions for patients with prostate cancer undergoing radical prostatectomy: A focus on urinary incontinence, erectile dysfunction and Peyronie's disease.

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Bachelor of Science (Physiotherapy)

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THESIS DECLARATION

I, Joanne Elizabeth Milios, certify that:

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Written patient consent has been received and archived for the research involving patient data reported in this thesis.

This thesis contains only sole-authored work, some of which has been published and/or prepared for publication under sole authorship.

[redacted]

Signature:

Date: 10/04/19

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Student Signature:
Date: 10/04/19

I, Daniel Green certify that the student's statements regarding their contribution to each of the works listed above are correct.

As all co-authors' signatures could not be obtained, I hereby authorise inclusion of the co-authored work in the thesis.

Coordinating supervisor signature:
Date: 10/04/19

ABSTRACT

Prostate cancer (PCa) is the most common cancer in men. Its incidence and mortality rate exceed that of breast cancer among women. More than 1.3 million new cases of PCa are diagnosed globally every year, at a rate of 1 in 6 or 14% of men. Health education and services for men are perhaps 20 years behind those for women, with only two countries having national men's health policies. Following a PCa diagnosis the opportunity for treatment becomes a focus and, with it, potential sequelae and side effects arise that may have significant impact on quality of life (QoL).

Radical Prostatectomy (RP), which involves surgical removal of the prostate, is the current "gold standard" surgical approach and 97% of diagnosed men can expect a 5 year survival rate. However, side effects from treatment can be devastating. These include Urinary Incontinence (UI), Erectile Dysfunction (ED) and Peyronie's Disease (PD). Strategies to help ease the burden of treatment for PCa form the basis of this thesis, which consists of 3 sections.

Part 1 Development and Validation of New Assessment Techniques

Aims

The aims of this thesis component were to:

1. Develop novel tests of pelvic floor muscle (PFM) function in men utilizing real time ultrasound (RTUS) and exercise-based physiological stimulation of fast and slow twitch muscle fibres;
2. Compare traditional, invasive methods of PFM assessment in men with the novel RTUS tests described above; and
3. Apply novel RTUS PFM function tests for the assessment of clinical presentation in men undergoing RP with a focus on UI.

Methods

This component of the thesis involved four separate studies. In the first study, the association between traditional and novel tests of PFM function in 27 post-RP patients was assessed. Study 2 compared transabdominal (TrA) and transperineal (TrP) approaches of PFM function in 47 post-RP men. Study 3 explored inter- and intra-observer reliability of two functional tests using RTUS: the Rapid Response Test (RRT)

required participants to perform 10 rapid pelvic floor muscle contractions with elapsed time recorded, and the sustained endurance test (SET) required participants to perform a single maximal sustained pelvic floor muscle contraction with task failure confirmed visually and elapsed time recorded. In the fourth study, our new tests were used to examine the impact of posture and measures of UI in 95 participants undergoing RP. The relationship between novel tests and 24-hour pad weight was determined with tests performed in both supine and standing postures.

<u>Results</u>

A modest correlation was observed between the *per rectal* assessment of squeeze pressure and objective perineometer measures (n=27, 67±7 y, r=0.51, $p<0.01$). RRT (r=0.18, $p=0.36$) and SET (r=0.18, $p=0.36$) assessments were unrelated to pelvic floor muscle squeeze pressure measured objectively by perineometry. In part 2, strong agreement was found using Bland-Altman analysis for both the RRT and SET when they were performed using TrA and TrP approaches; or when, in part 3, determining inter- and intra-observer reliability. In Part 4, participants (n=95) undergoing RP were assessed in supine and standing postures to determine the relationship between RRT and SET tests versus 24-hr pad weight as a measure of urinary continence. The TrA protocol produced moderate to good correlations between pad weight and RRT in standing (r=0.430, $p<0.001$) and supine (r=0.456, $p<0.001$), and SET in standing (r=-0.560, $p<0.001$) and supine (r=-0.560, $p<0.001$). Similar results were found using the TrP approach. All Bland-Altman analyses show no significant difference ($p>0.05$) between the two postures for RRT and SET tests using both RTUS methods.

Part 2 A Randomized Controlled Trial of a Novel High Intensity Pelvic Floor Muscle Training Strategy

<u>Aims</u>

The aims of this thesis were:

1. To investigate current practice in PFM training for the management of UI and ED in PCa patients;
2. To develop new PFM training protocols and assess their efficacy via a random controlled trial investigating ‘usual care’ exercise with a ‘high intensity’ intervention; and

3. In the absence of extant evidence-based guidelines for exercise-based management of PCa patients, to recommend a new protocol appropriate for the management of UI and ED in men following RP.

Methods

A randomized controlled trial of 97 men undergoing RP compared 'usual care' to 'high intensity' PFM training. Important outcome measures included UI, ED and QoL. A 5-week pre-operative PFM training program, followed by a 12-week intervention post-RP, was implemented. The newly developed and validated RTUS tests formed part of objective assessment of outcomes, in addition to 24-hour pad weight and patient questionnaires commonly used in urology research.

Results

At 2, 6 and 12 weeks post-surgery, the percentage of dry participants was greater across all time points in the high intensity PFM group, compared to usual care control group, with the former group demonstrating a faster return to continence. At 2 weeks post-surgery, 14% of the intervention group participants, compared to 4% of the control group, were dry. At 6 weeks, this percentage increased to 32% and 11% respectively, then 74% and 43% by 12 weeks post-surgery. QoL questionnaires, pad weights and PFM function tests showed significantly better outcomes in the intervention group across all time points.

In assessing the impact of PFM training on ED outcomes, no statistically significant difference was found between the 'usual care' and 'high intensity' training groups within the 12-week training protocol when assessing erectile function (EF). This is in line with previous studies demonstrating a minimum 3-4 month time frame for resolution of neuropraxia resulting from intra-operative tissue damage. When assessing QoL measures, the 'high intensity' training group displayed significantly better and clinically relevant outcomes when comparing overall EPIC-CP scores at 2 weeks post-RP, which included erectile function domains. This enabled intervention group participants to engage in penile rehabilitation and sexual activity earlier post-RP than the control group.

Part 3 Assessing the Benefit of a Novel Treatment Strategy for Peyronie's Disease

Aims

The aims of this thesis component were:

1. To develop and assess a new non-invasive approach to the treatment of Peyronie's disease (PD) with the administration of therapeutic ultrasound (TUS)
2. To assess the efficacy of this approach via a random controlled trial, relative to usual care; and
3. To recommend, based on this evidence, a new protocol appropriate for the treatment of PD in men following RP and the general population.

Methods

An intervention group comprising 23 men diagnosed with PD from penile duplex doppler ultrasound (PDDU) scans received 12 sessions of TUS over 4-6 weeks, in an effort to reduce plaque size and penile curvature. At the conclusion of the trial, the participants were then re-assessed. A control group comprising 20 men, also diagnosed with PD from PDDU scans, underwent delayed entry to the TUS treatment for 4 weeks, which served as a control or comparator period. Since it was considered unethical not to offer treatment, they were re-scanned with PDDU and commenced the 12-session treatment protocol after this delay. Both groups received follow up PDDU at the conclusion of the TUS sessions, as well as completing the validated questionnaires. In addition, a pilot study of 10 men diagnosed with PD following treatment for PCa was conducted.

Results

Assessment of penile plaques via PDDU score was the primary outcome measure. When assessing the effectiveness of the TUS intervention, we noted a difference between groups in PDDU measures, with only the intervention group having a reduction in PDDU scores. For the assessment of penile curvature there was a reduction in angle of 17^{o} (38%) over time for the intervention group only. Following similar scores at baseline between groups, only the intervention group improved EF (IIEF-5 scores) over time. When assessing subjective responses to PD via the Peyronie's disease Questionnaire (PDQ), when both groups were pooled, the main effect for time was borderline significant ($F = 4.102$; $p = 0.050$). Though it appeared there was a drop in

PDQ scores for the intervention group, our sample was not sufficient to provide the statistical power needed to show the impact of this intervention.

Conclusions

In Part 1, I pioneered new methods to objectively assess PFM function in men. The RTUS-based RRT and SET tests I have introduced enable non-invasive testing of PFM function that is superior to traditional *per rectal* approaches, in several respects. The tests were reliable and could be performed using TrA or TrP approaches. This bridges an important gap in men's health. These tests and approaches provide powerful and direct visual feedback and can be easily adopted in clinical practice. They have the capacity to form a viable basis for the objective assessment of differences between patients and changes in function that occur over time.

I have also developed a new, high intensity exercise protocol for PFM training in men. I compared a 5-week prehabilitation program for newly diagnosed PCa patients to usual care. The results of investigations showed a quicker return to continence, with significantly less urinary leakage from the outset and improved quality of life scores across all domains and at all time points in the intervention versus control groups. This was also significant when assessing EF at 2 weeks post-RP, an important finding, given the lesser focus on sexual health in comparison to continence, despite the negative impact of ED in this population. As seen clinically and backed up by research findings, ED is more of a concern to men in the long term than UI. The impact on male self-esteem and masculinity with the loss of erectile function can be devastating, with psychological distress and relationship difficulties common outcomes.

In a further study I investigated the relationship between RP and the development of penile deformities such as PD. Prior research confirmed a 16% likelihood of PD following RP and a 12% likelihood following radiation therapy for PCa. The RCT undertaken utilized TUS as a non-invasive approach to the treatment of PD and resulted in its confirmation as an effective strategy for decreasing penile plaques with minimal calcification. Currently, men diagnosed with PD are often encouraged to "suck it and see" for at least 12 months in order for the condition to reach a point of stabilization. After this time, corrective surgery is then encouraged. Treatments that are currently recommended in the early, acute stage of PD offer less than 40% effectiveness – similar to placebo – and may also be highly invasive, and at a significant cost. This advice does little to comfort patients when it is expected that up to 48% of curvatures will worsen over time, and a further 40% remain the same, with only 12% improving.

My aim in this series of research studies was to address a critical gap in men's health research and to lessen the burden of men following a diagnosis and treatment for PCa. These goals were achieved and this body of work reveals strategies that can be immediately translated to clinical care in the physiotherapy setting.

ACKNOWLEDGEMENTS

Casting back to October 2011, I was given the opportunity to provide feedback on my first 800 radical prostatectomy patients to a crowd of approximately 100 Urologists and radiation specialists at the ANZUS Western Australia State Conference, my first ‘professional’ presentation. As a Physiotherapist specialising in Men’s Health, I felt compelled to speak on behalf of my patients. What I was witnessing on a daily basis in my clinical rooms was a rollercoaster of emotion with many men experiencing positive outcomes from prostate cancer surgery, but some also experiencing great turmoil from what I termed the ‘Triple C’ of side effects: Cancer, Continence and Copulation. My presentation, ‘Feedback and future: Your radical prostatectomy patient from a physiotherapy perspective’ was an honest account of what I felt were poor quality of life outcomes in approximately 50% of my patients with many left unprepared for sodden continence pads, penile shrinkage, absent ejaculation and the impact on their manhood and self-esteem. At the completion of my 10 minute delivery, several older urologists gathered around me with words of praise, with one in particular stating, “That was brilliant Jo- exactly what we needed to hear”. The keynote speaker, A/Prof Declan Murphy quickly handed me his business card and invited me to attend the next APCC in Melbourne and advised me to put my findings into more formal research. It was not a thought I had ever entertained before. I was a mother of three children under 10 years, a practice partner, working and parent-sharing with my Greek husband. I had no room for research in my life.

Over the next few months, as spring rolled into summer, backyard barbeques become part of my usual weekend. At one in particular, a chance conversation with Translational Exercise Physiologist, Prof Danny Green lead to a subsequent glass of red at a Fremantle café. He proposed the idea of commencing a PhD. This was something my husband had already pleaded me not to do. So, of course, my only option was to immediately sign up! From that day forward, my ambitions were to speak, write and educate others on behalf of my patients – the everyday bloke on the street.

Looking back over the last 8 years, to the point of now scribing acknowledgements, I can only reflect that this has been an intensely personal journey. In the 20-year gap between enrolling in university courses, where the typewriter had moved to touch screen- my first library Endnote ‘workshop’ heralded an unforgettable moment. Sitting at the back of the room, immediately befuddled by the pace, I was unable to find the ‘on’ button for my computer. So, I listened and took notes in my exercise book. Prof

Green had gotten himself into deep trouble by taking me on and it's still something I'm never quite sure if he regrets. Since then however, he has been there. Side by side. Every step of the way. Grunting. Commanding. Occasionally offering a positive word. He has pushed me up a mountain, caught me when I have tumbled half way back down or hit deep crevices along the way. And there have been a fair few…. His support and guidance have been immeasurable. His standards so high I could hardly breathe sometimes, but he was always and is always, the 'true' scientist. Demanding more of me, perplexing me, correcting me, urging me forwards, striving for better, higher, stronger. In the name of science, Prof Green is nothing less than excellence. It has been my privilege and his pain- to be my primary supervisor over the PhD experience. I would never had started – and certainly not finished – had we not had that initial barbeque conversation. Grateful and humbled by his leadership, will always be key thoughts.

Conference attendances and presentations quickly became my thing. I flourished in this environment – drinking up every word of every academic I ever sat before – always eager and forever curious to learn more. As others would poise their iPad 6's overhead to capture the latest slide statistic, I would sit there scribbling every precious numeral in my note book. I would ask questions over the microphone, sometimes getting battered and bruised by the retorts, "you and your 'nuts to guts', go and do your research"…. "you've done nothing new here"…. "go back to Western Australia"… All of these criticisms were fair. I was the new kid on the block, hungry for knowledge, too eager to share, too eager to put my hand up. All of this, I soon learnt was 'academia'. A place where I had not been before. A place where my platform shoes were still too shiny. However, there were many great moments. The most poignant being the inaugural Patrick Walsh lecture in 2014, when the man himself asked, "Who teaches the professor?"...... and then, his retort, "the patient teaches the professor"…. took my breath away and made my heart do a jig. Meeting A/Prof Stacy Loeb on the dance floor at that very same conference, was another pivotal moment in my PhD career. Subsequent invitations to present on her New York Sirius XFM Men's Health radio program have been the ultimate career highlights, with a potential 32 million people listening audience. Her youth, vitality, incredible body of work, inspiring keynote presentations and commanding presence have provided me with a beacon – as a leading lady in a men's health world.

Closer to home, a great man stands in Sir Peter Dornan, a renowned Sports Medicine and Men's Health Physiotherapist based in Brisbane, Australia. Although he is not actually an ordained 'Sir' he has an AM 'Order of Australia' medal for his contributions to men's health, sports medicine, prostate cancer and military history. He is my friend, mentor and the father of men's health physiotherapy in Australia, if not the world. In 2010 when I first learnt about his book, 'Conquering Incontinence', I sent him an email of introduction. He immediately invited me to fly to Queensland and learn from him, face to face. A few weeks later, I was there. Nine years later, we talk, teach and tussle together on Twitter on a regular basis. Since this time, Sir Peter has moved into Pelvic Pain, pioneering the first map of the Pudendal nerve - 'nerve of the shamefuls'- responsible for bowel, bladder, sexual function and the pelvic floor. His published works, 'A musculoskeletal approach for patients with pudendal neuralgia: a cohort study' have been the first and foremost publications on this topic. Not only an academic, Sir Peter is also a sculptor, saxophonist, author of sports medicine and military books and a very fine gentleman - still working full time as a 70+ year old in his busy private practice. He is colossally generous in gifting his knowledge and expertise to myself and others – patients, the public and professionals- at any moment. To patients he is their hero and savior from incontinence and pain. To me he will always be the imminent 'Sir Peter'. Teacher and lover of life, his lanky lean presence a gem in any setting.

As my experiments were designed, delivered and written up, the opportunity to share my findings with colleagues became an important evolution. At the very first 'Mastering the Martians' course, with colleagues Sir Peter, Stuart Baptist and Craig Allingham, another incredible lady arrived. As the incoming President of the Australian Physiotherapy Association's Women's Health and Continence specialist interest group (APA WHC), Alexandra Lopes was a blast of energy and support. She was swift to ensure 'men's health physiotherapy' would get its place on the map, and within one year of her leadership, the special interest group had changed its name to 'Women's and Men's Pelvic Health ', only the second nation in the world to do so, after New Zealand. Subsequently, Mastering the Martians – a 4-member team of men's health physiotherapists- became a course sponsored by the APA. More than 300 Physiotherapists have been trained in this area since 2015 and Post-Graduate courses in Men's Health are currently in tender, to ensure future generations of physiotherapists will have the skills to deal with 50% of the population. Alex has contributed so very much to the men's health movement in Australia and her footprints have enabled my own to be stamped more easily. For this I will be eternally grateful.

Every kitchen needs a team. At the helm of my team sits Prof Timothy Ackland, former Head of School, Human Sciences, University of Western Australia and my co-supervisor. Every email I have sent, every word I have written or spoken, he has absorbed and responded to. He has never not been there. He has a beautiful and calming demeanor - kind, considerate and forever patient. Unlike myself. When it comes to number crunching, he is the finest thing that ever happened to me. Explaining ANOVA and Bland-Altmann plots - not 10 times, but 99, Prof Ackland has never rolled his eyes. He has only ever been gracious and understanding and the coolest cucumber I have ever encountered. His red ink across my pages have been a welcome and delightful gift, as his pursuit for succinctness spurs me forward to say more in less words (for those who know me that is difficult). I hope that we can continue to write together in the future, for his wealth of experience and sage offerings are the perfect foil to my exuberance and sometimes tangled web of words and ideas.

The youngest member of my team, Dr Ceri Atkinson deserves the biggest toast. She bundled herself into Australia as a 21-year old , fresh from the UK into her own PhD and was promptly gifted with the task of arm wrestling with me in all aspects of data analysis. As a 42-year-old IT dunce, part time PhD student and statistically-savvy- not-nervous- novice academic, Ceri also had her work cut out for her with me. But Ceri took me on, nipped me under her wings and gently lead me forwards, bridging so many gaps along the way. Ceri has now started, finished and gone well beyond her own PhD and is in back in UK, continuing her leading-edge research in the meantime. Her contributions to my initial two papers are worth their weight in gold. And English pounds.

Finally, there are the many health professionals – Dr Richard Pemberton, Dr David Sofield, Dr Sonny Lee, Dr Tanya Ha, Dr Elayne Ooi, Dr Justin Vivian, Dr Melvyn Kuan, Dr Andrew Tan, Dr David Millar, Dr Stephen Adams, Mr. Sydney Weinstein, Dr Paul Cozzi, Prof Thierry Van Caille, Talli Rosenbaum, Craig Allingham, Stuart Baptist, Dr Emma Stokes, Gerard Greene, Annette Rich, Sean Mungovan, Patrick Lumbroso (RIP), Simone Cavalli, Alexandra Lopes, Joshua Cales, Agostino Zurzolo, Holly Hermann, Melanie Bennett, Dr Alar Kaard, Barry Rochester, Chris Bevan, Donna Buchanan, Kate Taylor, Prof Grace Dorey and former PCFA Chairperson Roz Baker, who have all

supported and inspired me with their generous contributions. To each and every one of you, thank you so very much.

Last but not least, to home. At the doorstep have always been my parents, my children and my husband, Dean. The endless weekends, early mornings, holidays and late nights that I have spent tap-tapping at my laptop have often been joyless times for my family. I dreamed of studying together, spreading out our books on one communal table, listening and learning from one another as we all grew up and from within… and we have. And we do. Our spirited conversations and bountiful chatter at images of Peyronie's penises on my laptop, "Seriously mum, of all the things you could have studied…did it have to be that?" have been music to my ears. I am so proud and so thankful to have shared this educational space with you all. I am sorry for the occasional tantrum, frequent trips to the airport and monotonous lunch box fillings. Much gratitude to Dean who has held it all together throughout ,and especially in times like my typhoon-induced stranding in Osaka and in the of storms paper rejections and re-writes. Thank you so very much.

However, my greatest source of inspiration and any accolades that bestow me herewith can only be attributed to the bravery and courage of my men's health patients. They have shared with me their intensely private stories – fears around mortality, impotency, incontinence – and with this so many moments of laughter and loss. Every day, I am inspired and humbled by the everyday man on the street who sits before me, trusting me to serve him well and with respect. I have learnt that every man wants to be heard, that his unique story needs to be known and understood. That sometimes men cry and need to. That they HATE wearing continence pads, and that for as long as they are breathing, want to have penises that have the potential to work. Regrettably, along the way I have lost three great men. Tony Baker, Greg Bowden and Psychologist Patrick Lumbroso. Each of these men have stood tall in their individual battles to live. Each of them has also taught me about being human, being vulnerable and being a man. It is in their memory I dedicate my own contributions, to the everyday bloke. Thank you, one and all. PROST!

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TABLE OF CONTENTS

ABBREVIATIONS

ADT	Androgen Deprivation Therapy
BC	Bulbocavernosus muscle
BMI	Body Mass Index
CPPS	Chronic Pelvic Pain Syndrome
DRE	Digital Rectal Examination
EBRT	External Beam Radiation Therapy
ED	Erectile Dysfunction
EF	Erectile Function
EPIC-CP	Expanded Prostate Cancer Index Composite for Clinical Practice
EUS	External Urethral Sphincter
GS	Gleason Score
HRQOL	Health-related Quality of Life
IC	Ischiocavernosus muscle
ICQ	International Continence Questionnaire
IPSS	International Prostate Symptom Score
LRP	Laparoscopic Radical Prostatectomy
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
NSRP	Nerve-sparing radical prostatectomy
OF	Orgasmic function
PCa	Prostate cancer
PD	Peyronie’s disease
PDDU	Penile Duplex Doppler Scan
PDDU	Penile Duplex Doppler Ultrasound
PDE5i	Phosphodiesterase type-5 inhibitor
PDQ	Peyronie’s Disease Questionnaire
PFM	Pelvic floor muscles
PPI	Post-prostatectomy Incontinence
PSA	Prostate Specific Antigen
PTT	Penile Traction Therapy
PVD	Post void dribble
QOL	Quality of life
RALP	Robotic-assisted Radical Prostatectomy
RCT	Randomized Controlled Trial
RP	Radical prostatectomy

RRP	Retropubic Radical Prostatectomy
RRT	Rapid Response Test
RTUS	Real Time Ultrasound
SET	Sustained Endurance Test
SUI	Stress Urinary Incontinence
SUS	Striated Urethral Sphincter
TA	Tunica Albuginea
TMN	Tumour Metastasis Node
TrA	TransAbdominal
TrP	TransPerineal
TUS	Therapeutic Ultrasound
UI	Urinary Incontinence
UUI	Urge Urinary Incontinence

CHAPTER 1

Introduction

Men's health education and services are considered to be at least 20 years behind those for women, with only two countries having national men's health policies. [1,2] In almost every measurable facet, men's health is lagging and, across the globe, men can expect to have at least a 5-year reduced lifespan relative to women. [3] Recently, the Australian Government released a draft proposal to address this issue, establishing the Men's Health Strategy for 2020-2030. [4] Issues being addressed to try and understand the lifespan discrepancy in men include mental health, chronic disease and preventative health, injuries and risk taking behavior and healthy aging. [4] Male attitudes towards health may play a significant role in accounting for the sex difference in lifespan, with traditional and cultural values around strength and 'manhood' being confronted when health issues arise. [5] When assessing the top 10 leading causes of death among men globally, it is apparent that eight of these factors are preventable [6] and can be impacted through education, awareness and also bespoke exercise interventions. It is a little-known fact, however, that the most common cancer in men is prostate cancer (PCa) and that the incidence and rates of death from this disease exceeds that from breast cancer among women. [7,8] More than 1.3 million new cases of PCa are diagnosed globally every year,[3] at a rate of 1 in 6 or 14% of men. [9] Recent advances in medical technology have improved the early detection of PCa and, as a result, there is a reduced incidence of mortality, particularly in developed nations. [3,10] Following a PCa diagnosis, however, the opportunity for treatment becomes a focus and, with it, potential sequelae and side effects arise that may have significant impact on quality of life (QoL).[11,12]

Although survivorship following PCa treatment is high, especially in developed nations, QoL outcomes require consideration. Radical Prostatectomy (RP), which involves surgical removal of the prostate, is the current 'gold standard' approach to cure [13] and 97% of diagnosed men can expect a 5-year survival rate. [10] However, side effects from treatment can be devastating. These include physical, social, emotional and psychological QoL issues that can affect both the man and his partner. [11,12,14] These include urinary incontinence (UI), erectile dysfunction (ED) and Peyronie's disease (PD). [15] Significantly, depressive symptomatology occurs at a rate four times greater for men with PCa than healthy counterparts as a result of treatment, [16] so strategies to diminish the impact of side-effects and improve outcomes are necessary.

Men's health was recently launched as new frontier in Physiotherapy, the cornerstone of which was based upon a new understanding of male anatomy, pelvic floor muscle function and the role of rehabilitation following the surgical removal of PCa. [17] Strategies to help ease the burden of treatment for PCa form the original basis of this thesis. However, as my research work progressed the actual magnitude of the impact of PCa treatment became apparent, including recognition of QoL concerns and distinct clinical presentations. The aims of this PhD thesis evolved, became multi-faceted and were addressed in three parts.

Background and Aims of Each Thesis Component

Part 1: Development and validation of new assessment techniques

In recent years, much research endeavour has been directed to the development of more accurate methods of assessing PFM function which focus on the anatomical structures affecting male UI that are more anteriorly located than the traditional, posterior per rectal assessment options. [18,19] These include a move away from invasive, per rectal assessment techniques that are distressing to men and replacement with non-invasive RTUS applications. [20]

Building on this knowledge, three sub-studies were undertaken to compare traditional methods of male PFM assessment using digital rectal examination (DRE) and anal perineometry, versus real-time ultrasound (RTUS) informed functional assessment. Two novel tests of PFM function were developed and validated to assess PFM function in men following RP. Given the clinical presentation of UI is most commonly seen in upright postures and in actions that cause increased intra-abdominal pressure (such as during coughing, sneezing, sit to stand, lifting, standing and walking), the tests were applied in both supine and standing positions. Measures of UI were then correlated to the PFM function tests to provide both an assessment and training opportunity based on an individual's performance.

The aims of this thesis component were to develop new methods to assess the function of the male pelvic floor and minimize the need for traditional invasive approaches, and to investigate the relationship between objectively assessed male pelvic floor muscle (PFM) function and clinical presentation. Specifically, the studies aimed:

1. to develop novel tests of PFM function in men utilizing RTUS and exercise-based physiological stimulation of fast and slow twitch muscle fibres;
2. to compare traditional, invasive methods of PFM assessment in men with the novel RTUS tests described above; and
3. to apply novel RTUS PFM function tests for the assessment of clinical presentation in men undergoing RP with a focus on UI.

Part 2: A randomized controlled trial of a novel high intensity PFM training strategy

Physiotherapists currently offer PFM training for men following treatment for PCa, however, the supporting evidence is mixed, with the most recent Cochrane review unable to recommend it unequivocally as a first line rehabilitation approach. [21] The effectiveness of PFM training in men may be clouded by a past history of interventions stemming from female assessment and treatment programs that cannot be directly translated to the male anatomy.

Pre- and post-operative PFM training have been the focus for research on UI issues following RP for the removal of PCa. [22,23] PFM training has also been investigated for ED[24] among the general population, however, research has only recently been conducted in PCa populations. [25-27] Currently, recommendations for PFM training following RP remain elusive and this is most likely due to the wide variability in protocols used in previous investigations. [21,28] With the opportunity to observe thousands of men following RP in clinical practice, the author felt a more aggressive approach to PFM training might prove effective, along with more deliberate utilization of the time leading up to surgery for 'pre-habilitation'. Based upon the physiological structure of the PFM, and tailoring these to new protocols, the primary goals were to reduce the severity and duration of UI and ED in these patients. The impact on QoL in men undergoing RP and their partners can be devastating. A 12-week intervention comparing 'usual care' to a 'high intensity', individualized PFM training protocol was undertaken in men undergoing RP.

The aim of this thesis component was to develop new protocols for PFM training in men based on the principles of exercise physiology and, specifically:

1. to investigate current practice in PFM training for the management of UI and ED in PCa patients;
2. to develop new PFM training protocols and assess their efficacy via a random controlled trial investigating 'usual care' exercise with a 'high intensity' intervention; and
3. in the absence of extant evidence-based guidelines for exercise-based management of PCa patients, to recommend a new protocol appropriate for the management of UI and ED in men following RP.

Part 3: Assessing the benefit of a novel treatment strategy for Peyronie's disease (PD)

PD causes pain, deformity and curvature of the penis, and affects 9% of the male population. The condition can have a great impact on male self-esteem, relationships and erectile function. [29] PD is a lesser known side-effect of RP and is thought to occur due to significantly reduced cavernosal blood flow caused by injury sustained intra-operatively to the cavernosal nerves and adjacent neurovascular bundles that supply erectile blood flow. [30] Recent evidence confirms 16% of men undergoing RP will experience PD, at an average 13 months following surgery, causing penile curvature, reduced penile length and sexual dysfunction. [15,31] Similarly, new evidence reveals 12% of men will develop PD following radiation therapy for PCa and neither of these issues form part of routine clinical discussion. [32] Current options for treatment are generally invasive, with penile injections, traction devices and surgery being the most common recommendations. [29] As PD has an acute phase that may last 18 months before stability, physicians are generally reluctant to introduce treatments too early.

There is no known cure for PD and most treatments only offer approximately 30-40% improvement in symptoms. [29] Hence, non-invasive treatment options to assist in the rehabilitation of PD warrant further investigation, with the main goal being to translate findings to clinical practice. Therapeutic ultrasound (TUS) has an established role in treating soft tissue injuries since the 1930's, but its application to PD has had limited investigation. Early pilot studies in the 1950's showed promising findings, however, no random controlled trials have been conducted.

The aim of this thesis component was to develop and assess the efficacy of new treatment for PD using TUS and, specifically:

1. to develop and assess a new non-invasive approach to the treatment of PD with the administration of TUS;
2. to assess the efficacy of this approach via a random controlled trial, relative to 'usual care'; and
3. to recommend, based on this evidence, a new protocol appropriate for the treatment of PD in men following RP and the general population.

This thesis addresses the three components described above in a format which begins with a comprehensive review of literature, followed by individual papers relevant to each section. References will be added to each section separately at the end of each chapter.

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CHAPTER 2

Part 1: Review of Literature – Prostate Cancer

Prostate Cancer Today: Incidence and Expenditure

Although symptoms of prostatic diseases were reported as early as the first century AD, it has only been the advent of improved histopathology techniques in the 20th century that PCa has proven to be more prevalent than originally thought, with more men now being diagnosed than women with breast cancer.[1] Today, with one in nine men diagnosed with PCa globally,[2] and one in six men in Australia, the expenditure on diagnosis, treatment and follow up is rising.[3] A 2011 investigation evaluated PCa costs identified from published data and internet sources and concluded that per patient costs depended on cancer stage at diagnosis, survival and choice of treatment.[4] Based on data collected in 2006 and inflated to 2010 levels, in Europe this amounted to €179 million, USA $9.862 billion and in Australia $101.1 million.[4] In 2013 each individual case of PCa was reported to cost the Australian Government $25-30,000,[5] a lower level than other nations, with variation between countries attributed to differences in incidence and management practices.[4] These costs are in addition to lost wellbeing, lost productivity, lost work days and the cost of caring for individuals in the home following treatment.

Prostate Cancer Risk Factors

Senescence, coupled with genetic predisposition, remain the two biggest risk factors for PCa. The average age of Australian men at the time of diagnosis is relatively old, however this value has decreased from 72 years of age in 1993 to 70 years in 2003 and has continued to decrease by 8% per annum,[3] predicted on the basis of global trends to reach an age of 66 years currently.[2] The influence of family history and genetic predisposition is marked, with previous studies reporting an individual's risk of developing PCa to increase by 50% with a positive family history in the male line[6] and a 4-fold higher risk for PCa with a history of breast, ovarian or uterine cancer in the female line.[7] Additional risk factors include a history of smoking, diabetes, alcohol consumption, taller height, being an individual of African American race,[8] past testosterone therapy, BMI>33 and a lack of physical activity.[9]

Assessment and Classification of Prostate Cancer

The prostate, a combination of epithelial glands and a fibro muscular stroma, plays a pivotal role in the production of seminal fluid essential for the function of the male reproductive system. The pathogenesis of PCa involves the aggregation and progression of abnormal cells in the prostate that ultimately progress into either 'localised' or 'advanced' PCa disease.[10] Management is dependent upon the staging of the disease and there are two distinct pathways, based on pathology at diagnosis.

Assessment of PCa is achieved by a process of clinical examination, via digital rectal examination (DRE), blood markers detecting Prostate Specific Antigen (PSA) levels, Magnetic Resonance Imaging (MRI) to ascertain prostate tumour size and finally, biopsy to stage the cancer. The first test, *per rectal* DRE provides information pertaining to irregularities of the prostate such as nodules, increased size and changes in texture of the internal surfaces.[6,11]

A subsequent blood test for PSA levels that provides a baseline for assessment with 4.0 ng/mol or less usually indicating a normal reading.[12] As PSA levels rise with rising age and in the presence of inflammation or infection, it is the velocity of change in PSA over time that provides most information. Since 1992, a velocity change of greater than 0.75ng/ml per year has been routinely used to monitor potential cancerous change.[13] If abnormalities are detected in the combined DRE and PSA tests, multiparametric MRI is typically recommended and utilizes anatomic T2 weighted imaging and a dynamic contrast to improve specificity of PCa detection.[14] MRI results subsequently provide a more accurate sampling for the final biopsy stage of PCa assessment. Performed by transrectal (TRUS) or transperineally (TPUS) ultrasound whilst the patient is under light sedation, small prostatic tissue samples are collected for histopathological assessment and a final grading is then undertaken.[12]

Based on biopsy results, PCa will then be classified as either localized or advanced, with a Gleason Score (GS) used to accurately stage the disease[15] (Figure 2.1). A GS is a combination of both the primary and secondary grades of tumour detected in the specimen with a lower score indicating a less aggressive disease, whereby 50% of the predominant tissue type is staged in two parts. With scores in the range of 1-10, a GS of 7 or more is usually indicative of pathology at a level that requires treatment, with the lowest score of identified PCa rated as a 6 on biopsy. However, a Gleason 7, scored with 4 +3 would be more aggressive than a Gleason score of 7, where GS= 3+4. To best ascertain pathology, the GS is then combined with the Tumour, Metastasis, Nodal (TMN) staging system, which assesses the amount of cancerous growth in each separate tissue sample[16] (Figure 2.2). Localised PCa is considered to be confined to the prostate and classifies an individual as being in stage 1 or 2 of PCa.[15,17] Likewise, GS of 2-6 are typically monitored by ongoing active surveillance or a 'watch and wait' approach.

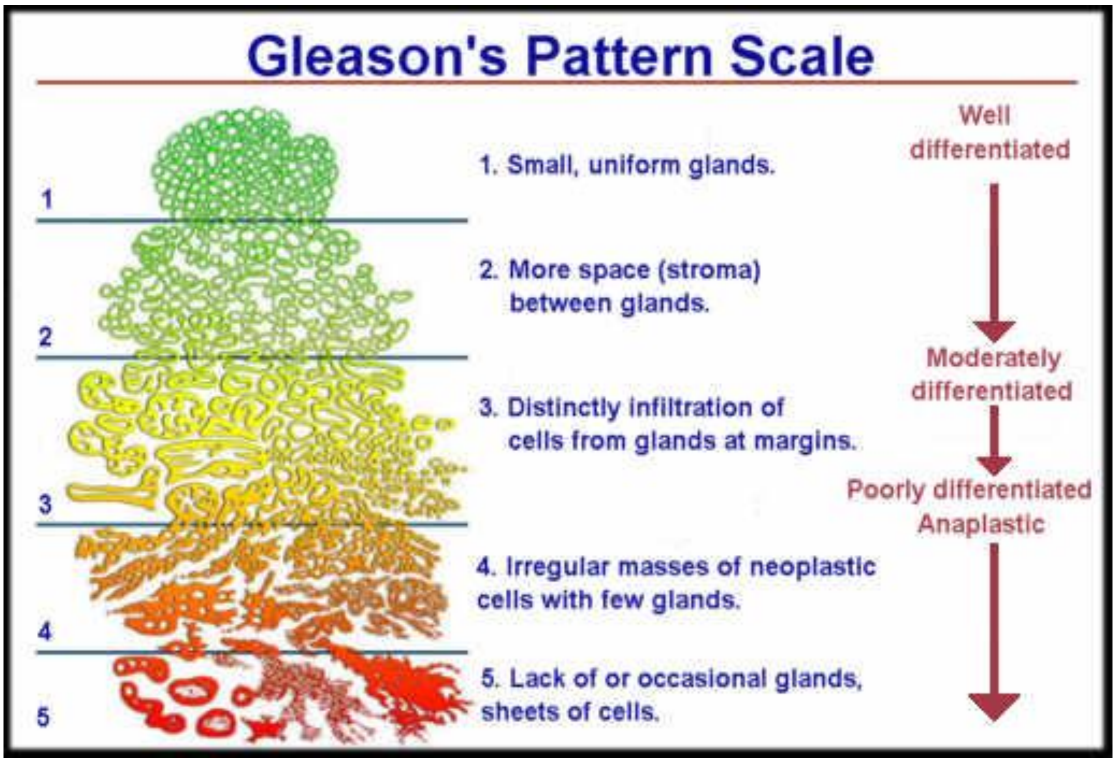

Figure 2.1 Gleason Score (reproduced from *bensprostate.com 17.03.19)*

Advanced PCa is associated with the aggregation of abnormal cells metastasizing into the seminal vesicles, lymph nodes and bone and will typically have much higher GS[18] and TMN staging.[16] These patients are typically classified as having stage 3 or 4 PCa and are expected to exhibit Gleason scores of >8-10.[15,18] It is at this point that predictions can be made for the best form of management, tailored to an individual's age, co-morbidities, social circumstances and fitness levels.

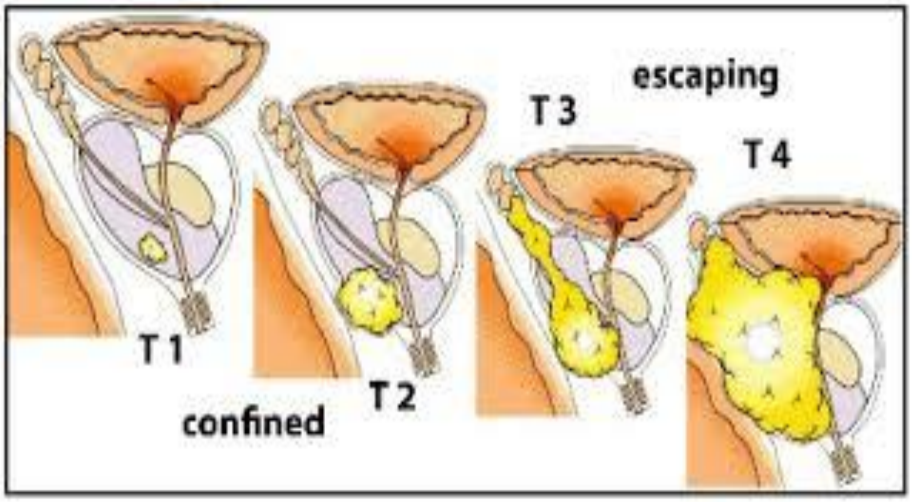

Figure 2.2. Staging of Prostate Cancer (reproduced from: *tackleprostate.org 20.11.18*)

Treatment Options for Prostate Cancer

Traditionally, stage 1 & 2 (localised) PCa is treated by either a period of active surveillance (i.e. no active treatment, but regular PSA, DRE, MRI and biopsies) or active treatment in the form of surgery, brachytherapy or external beam radiation therapy (EBRT). Surgery takes the form of radical prostatectomy (RP) to remove the entire prostate and seminal vesicles and is conducted using three common surgical interventions; retropubic (RRP), laparoscopic (LRP) and robot-assisted laparoscopic (RALP).[10] 'Advanced' PCa, Stage 3 & 4 disease, is usually treated with a combination of androgen deprivation therapy (ADT) and or/various types of radiation therapy or chemotherapy.[10] As each treatment option offers differing outcomes, it is worthwhile examining the range available to patients.

A. Active surveillance

As prostate cancer is a relatively indolent cancer and does not always result in mortality, urologists will usually recommend treatment options based on the anticipated life expectancy of each individual. If the cancer is deemed to not be aggressive, a man diagnosed with PCa over the age of 70 years will often be placed on a 'watch and wait' approach known as Active Surveillance with repeat PSA, DRE, MRI and biopsies performed 3-12 months.[19] Recently, active surveillance has been confirmed as a highly viable option with 64% of men at 5 years from commencement of monitoring not requiring active treatment.[20] Thus, it is recommended that active surveillance be the first line of treatment when PSA is <10ng/mol, Gleason 6 or less, TMN at T1c or 2A and 2-3 positive core samples that demonstrate < 50% cancer presence.[12]

B. Radiation therapy

Radiation therapy has been utilised to treat low grade, localised PCa since early in the 20th century and consists of two main types – External Beam Radiation Therapy (EBRT) and brachytherapy (internal beam radiation) to the prostate. EBRT is typically performed 5 days/week over a 7-8 week cycle and tends to be painless, however side effects such as urinary, bowel and sexual dysfunction gradually occur over time, with the full effect of treatment not reaching a point of stabilisation until approximately 3 years post EBRT commencement.[6] Brachytherapy was developed in the 1970's and offered an alternative approach to administering radiation, with radioactive gold seeds implanted into the prostate using template guidance[21] which are then applied with both low and high dose radiation rates depending on PCa staging. It is commonly reported that both forms of radiation may have less impact on continence, ED and QoL outcomes than RP, however long term cancer-specific survival rates are significantly higher when surgery is utilised.[22] If there is any rise in PSA following RP, however, EBRT is often utilized in smaller doses that specifically target any remaining PCa activity, most commonly located by radiological investigation such as bone scans, PET and PSMA scans with the prostate bed and lymph nodes being the most commonly affected tissue type.[5] Long term, any form of radiation may have continuing side effects as any pelvic tissue treated continues to degrade, scar and deteriorate, with both bladder and bowel continence potentially worsening over time.[23] Most recently, a new radiosurgical treatment called stereotactic body radiotherapy (Cyberknife®) has been introduced to Western Australia. This represents a new form of radiation therapy that offers a non-invasive robotic technology combined with real time imaging to deliver precisely targeted radiation to PCa disease. In particular, it has been found to be effective in the treatment of low and medium risk PCa patients,[24] with promising outcomes of minimal toxicity and local disease control.[25] This new treatment aims to reduce the impact on surrounding adjunctive healthy organs and tissues and may provide an optimistic future treatment option for men diagnosed with early PCa, with long term outcomes still to be determined.[24,25]

C. Androgen deprivation therapy

As PCa cannot survive without androgens, including testosterone, administration of hormones that negated the proliferation of cancer cells were first utilized in the 1930's in the form of Androgen Deprivation Therapy (ADT). Prior to this form of 'chemical castration', surgeons routinely performed a complete removal of the testicles in the form of orchidectomy, to reduce PCa metastases and or/to prolong life, with limited success. Today ADT is increasingly used in the treatment of advanced PCa, however many adverse side effects occur including hot flushes, gynaecomastia, osteoporosis, anemia, fatigue, muscular atrophy, psychiatric and cognitive problems and potentially an increase in cardio-vascular disease.[26] For metastatic disease, however ADT is the most common treatment approach as it is transported via the blood stream and able to target multiple cancerous sites.[27] In combination with exercise therapy and more sophisticated pharmacology, ADT offers difficult to treat PCa patients the opportunity for disease stabilization, symptomatic relief from cancer (temporary remission) and pain relief.[28]

D. Chemotherapy

Chemotherapy is utilized for advanced PCa, particularly when other modalities such as ADT and EBRT have failed to suppress the disease. Men with hormone refractory prostate cancer (ie are no longer responsive to hormone therapy) generally have few treatment options, however chemotherapy may have a role in controlling the disease in patients who wish to be very aggressive with continuing therapy.[6] Anti-cancer drugs are given orally or intravenously and often in combination with steroidal therapies. The most common medications used are docetaxel and cabazitaxel which have been shown to increase life expectancy, reduce the rate PCa growth and severity of symptoms, resulting in better QoL.[29] Cure is not possible, however men treated with chemotherapy can expect an average 14-17 months increased survival, based on recent studies in the USA.[29]

Radical Prostatectomy

Involving complete removal of the prostate and adjacent seminal vesicles, RP is considered the gold standard approach for the treatment of PCa and offers the best opportunity for curative intent (Figure 2.3).[30] Since its invention in 1904 when first performed by Dr Hugh

Hampton-Young, surgical techniques have undergone significant transformation, with the earlier perineal and supra-pubic approaches now surpassed by the RALP technique.

Figure 2.3. RP pre and post prostate removal (reproduced from *ArrivaGroups 20.11.18*)

Early surgical options left most men severely incontinent and with complete impotency, leading to radiation and ADT being the preferred treatments of choice for many decades. In the 1970's a team lead by Urologist Patrick Walsh developed a technique that, for the first time, was able to preserve erectile function post-operatively[30,31] and the era of 'nerve sparing' RP was pioneered (Figure 2.4). Walsh's aims to protect the erectile nerves and spare potency via careful resection of nerve tissue surrounding the prostate were further enhanced with the arrival of laparoscopic (keyhole) surgery pioneered in the 1990's and the RALP in the early 2000's, with a resultant improvement in both urinary (UI) and ED outcomes.[30] Three distinct types of nerve sparing are now available, including non-nerve sparing (NNS), unilateral nerve sparing (UNS) and bilateral nerve sparing (BNS).[10]

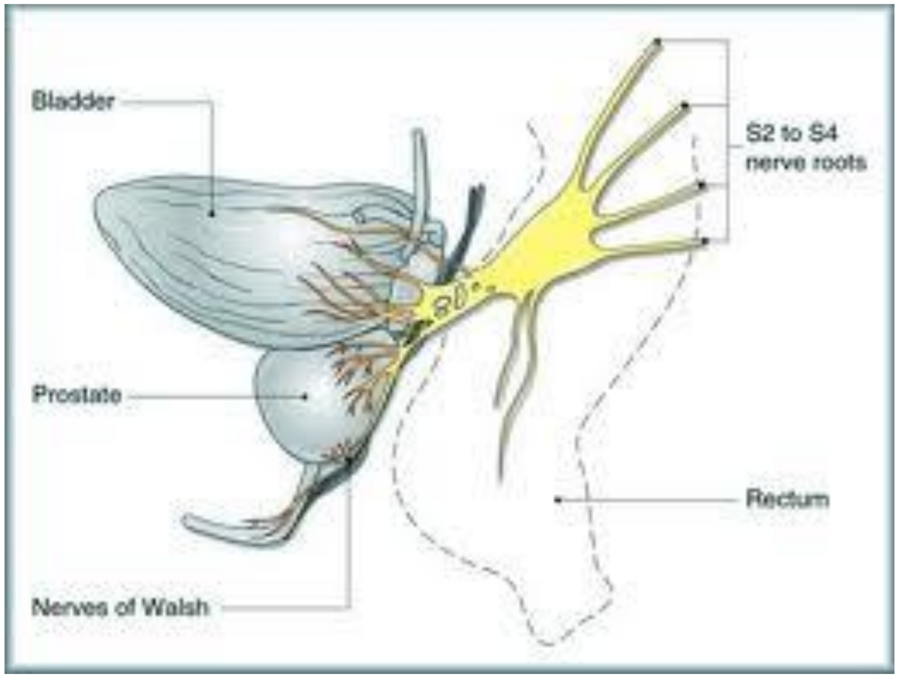

Figure 2.4. Nerves of Walsh (reproduced from *seeno.com* 20.11.18)

As RALP is a relatively new technique, research findings are only just emerging to show superior outcomes, with many urologists still providing the alternative procedures of open RP via either retropubic (RRP) or transperineal approach (TRP) and simple laparoscopic radical prostatectomy (LRP).[32] As it is a highly complex procedure, physicians performing RP require skills pertinent to not only removing the prostate gland but to also minimizing blood loss, preserving the adjacent neurovascular bundles, endo-pelvic fascia and securing a water-tight anastomosis. In addition, the recent development of a peri-urethral suspension stitch, known as the Rocco stitch, has improved bladder base reconstruction to the external urethral sphincter (EUS)/striated urethral sphincter (SUS) to provide a more stable mechanical origin with analysis of the technique showing significantly improved continence outcomes at 3 months post-operatively.[33]

In aiming to preserve erectile function, the nerve supply surrounding the prostate, known as the ‘Veil of Aphrodite’ requires careful resection as it is intimately woven with the outer fascia of the prostate gland and any traction or removal greatly impacts on sexual potency.[31] Given its improved field of view with 10-fold magnification and increased dexterity with 7 degrees of movement (similar to the human wrist), the RALP approach is emerging as the preferred option for surgeons and patients with greater than 60 % of RP, and potentially far more currently are performed in this way[34] (Figure 2.5). For most patients, RALP offers several potential benefits over open surgery, which include a shorter hospital stay, lower levels of pain, less blood loss and transfusions, lower risk of infection and complications, a faster return to normal activity levels and potentially, quicker recovery of urinary incontinence (UI) and ED.[32,35,36]

Figure 2.5 RALP in action (reproduced from *urologyassociates.com.au* 20.11.18)

Consequences of Surgical Treatment in Prostate Cancer

Surgery, despite being the most successful intervention for PCa, is known to cause UI and ED, long lasting and debilitative side effects which have become the main focus for men post-treatment. With anticipated survival rates from RP now almost 100% at 5 years, 98% at 10 years and 96% at 15 years, improved QoL is of primary concern.[6] UI is known to typically effect <1% of the population until age 75 years normally,[37] but 69-98% of all PCa patients. Likewise, ED is expected to affect up to 100%[11] of treatment candidates versus 3-64% of the normal population.[37] Thus, the search for more effective treatment options for the prevention and management of these significant side effects in PCa survivorship is essential.

Post Radical Prostatectomy Urinary Incontinence

UI is defined as the involuntary loss of urine from the bladder due to dysfunction of the urinary system[38] and following RP is commonly referred to as post-prostatectomy incontinence (PPI). There is wide variation in reported rates of PPI, with ranges of 30-89% of men reporting leakage upon removal of catheter and 5-51% at one year post RP.[39] A recent investigation comparing open versus RALP in 2625 eligible men from across 14 European centres found that, at 12 months post RALP, 366 men (21.3%) were incontinent, as were 144 (20.2%) after RRP with no significant difference between the two operative techniques.[40] A number of factors may contribute to PPI which include the experience and skill of the surgeon,[41] the surgical approach used, the size of the prostate resected, the aggressiveness of PCa, the trauma to the EUS[42] and the length of the membranous urethral length[43] (which if less than 12mm, has been confirmed to prolong recovery to continence). There is also wide variation in what constitutes the definition of continence, with incontinence pad number, pad weight and 0 continence levels lacking uniformity between all research investigations in this field.

A. The Pathophysiology of Urinary Incontinence

The mechanism of UI is complex and most authors agree that sphincteral deficiency is a prominent factor.[44-46] During the RP procedure, the apex of the prostate has to be carefully dissected from the muscular EUS and this causes localized tissue trauma and a resultant reflex inhibition of the autonomic internal bladder neck sphincter, which it is attached to during anastomosis (Figure 2.6). The male urinary system is under two separate mechanisms of control, the first being the involuntary sympathetic alpha-adrenergic bladder neck/internal urethral sphincter (IUS) smooth muscle contraction and the second being the rhabdosphincter-levator ani complex (EUS), which is under voluntary control. As a result, continence recovery is complicated. Given that the IUS, represented by the bladder neck and urethral smooth muscle is almost entirely extracted during prostatectomy, there is much reduced structural support for the maintenance of continence.[31,44] Due to the sudden increased workload, this leads to a decrease in the ability of the bladder to retain urine, particularly during increased bladder loading and intra-abdominal pressure in actions such as cough and sneeze. This condition, known as stress urinary incontinence (SUI) is possibly the most common side effect reported by RP patients and the impact on QoL can be extreme. In addition, two reflexes are innately linked to the EUS and can be trained.[47] These are the ‘guarding reflex’ which occurs to increase the magnitude of contraction during urinary storage, and the ‘cough reflex’ which increases PFM contraction during a sudden increased in intra-abdominal pressure.[44]

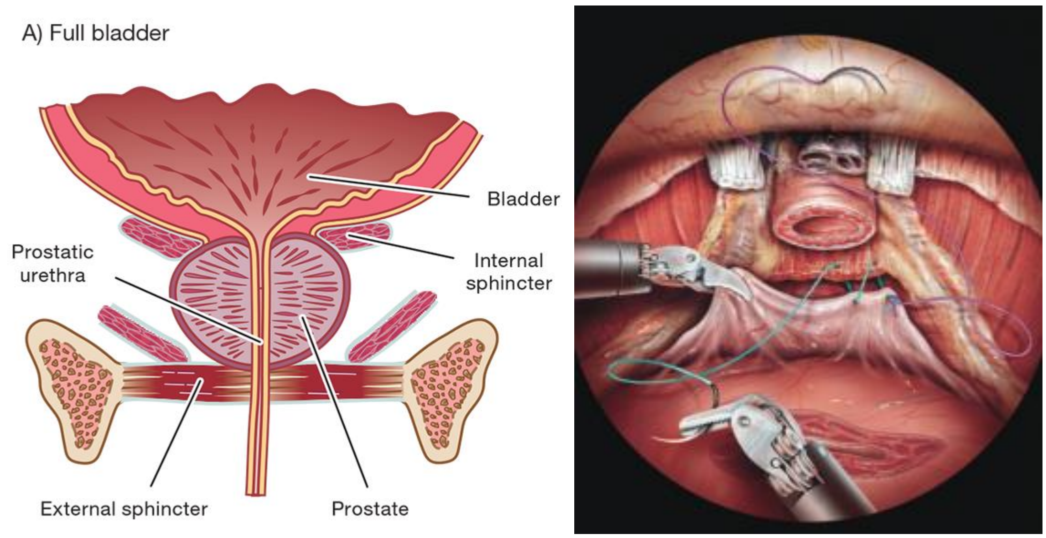

Figure 2.6 Anastomosis of IUS & EUS (reproduced from *prostate.org.au and lowurology.com 20.03.19*)

B. Urinary incontinence: impact on quality of life

Prior to surgery, the incidence of UI is low, affecting 1-2% of the male population aged up to 75 years.[37] Following RP, this immediately changes with 69-98% men affected with urinary leakage for some duration.[35] If continence is slow to recover, however, the long term negative impact on QoL can remain substantial.[48] Although highly variable due to different modes of data collection, 16-51% of men remain incontinent at 12 months post RP and this may greatly reduce the QoL of a man and his partner.[49]

Several studies have addressed the long-term impact of UI on QoL measured over 3, 5 and 7-years post RP and confirm ongoing issues in significant numbers. For example, in a post-

RP group assessed at an average 59 months from RP, 66% indicated problems with urinary function in the previous 4 weeks, with 49% reporting PPI, 22% at least one leakage episode/day ,47% impacting on sleep, and 40% feelings of frustration.[50] In a 3-year analysis of 495 men undergoing treatment for localised PCa, 2% of men reported UI at baseline, prior to treatment.[51] At 1 year post RP, 16 % reported UI and at 3 years 12% reported UI, and this matched subjective reports of urinary bother.[51] A 5 year follow up of health-related quality of life (HRQOL) by Korfage *et al.* documented higher rates of UI in men across all data points, with 12% of men complaining of intermittent leakage pre-prostatectomy of which 7% wore pads, 37% at 12 months post- RP, all of whom wore pads, and 31% at 52 months following surgery, of which 25% wore pads.[52] In the analysis of HRQOL scores repeatedly measured using UCLA-PCI and SF-36 over 5 years, steep declines in urinary function and bother were recorded. Mental health scores showed striking increases initially, but once treatment had taken place, the level of reported stress declined, quite possibly as the diagnosis and fear of outcomes was the main stressor.[52] Nonetheless, the combination of a PCa diagnosis, the need for surgery and resultant PPI are known to greatly increase the likelihood of depression,[53] cancer specific anxiety and post-traumatic stress disorder,[42] with depressive symptomatology occurring at a rate 4 times greater for men with PCa than their healthy counterparts.[54]

Men experiencing UI post-RP may use numerous strategies to minimize the impact of leakage and this may significantly affect an individual's capacity to function physically and socially. Strategies typically used by men include reducing fluid intake and type (caffeine and alcohol increase UI), limiting time and travel away from home, avoiding going out/attending social activities and planning for accidents with extra pads and changes of clothing.[50] Male toilet facilities are also lacking in the provision of sanitary bins for continence pads and this makes social outings even more difficult for men (nb. the author has started a #menshealthtoo campaign to help change this situation in response requests from patients and the Australian government's invitation for community consultation in the 2020:2030 Men's Health Policy Update).[55,56] These problems were also found to impact on the partners of these men. In a review of the existing literature by Resendes, spouses were found to be significantly more distressed than the patients in all facets of treatment for radical prostatectomy.[57] Sources of distress included lack of information, fear of the unknown and what the future will hold, and treatment related concerns.[57] In a 2018 qualitative study investigating the experience of partners of prostate cancer survivors, 5 major themes emerged; caregiver burden, knowledge deficit, isolation, changes in sexual relations and unmet needs highlighted.[58]

Hence, strategies to minimize the burden of treatment including UI and ED need to start once PCa diagnosis has been confirmed and the course of treatment decided. This includes providing patients with information to assist recovery; physically, psychologically and emotionally. Understanding the mechanisms of continence and erectile function via education for both the patient and his partner may assist in more realistic expectations and the opportunity to seek appropriate support as different situations are encountered. Fundamental to recovery, as observed clinically, is the ability of each patient to engage in his own surgical preparation and rehabilitation via a range of self-help strategies including PFM training.

Anatomy of the Pelvic Floor

The pelvic floor plays an important role in bladder and bowel function, sexual health, movement and provides integrity and support for the entire body cavity.[59,60] The PFM are bilaterally symmetrical, equal in length and form a muscular diaphragm that covers the pelvic cavity from the pubic bone to the coccyx ,and support the bladder and rectum, with deep and superficial layers (Figure 2.7).[61] In men, the prostate rests inferiorly to the bladder and at its urethral exit is immediately surrounded by the EUS to control urinary function. The rhabdosphincter at this level contains both smooth and skeletal fibres which are organized in a horseshoe-shaped loop around the urethra, arranged in deep and superficial layers and innervated by the deep branch of pudendal nerve S2-4.[62] Located posteriorly is the levator ani complex which provides structural support for the pelvic viscera and loops around the rectum from the ischium and coccyx, consisting of three distinct muscles; puborectalis, pubococcygeus and iliococcygeus. The external anal sphincter (EAS) is also located here and assists in the maintenance of bowel continence and elimination. More anteriorly located is the puboperinealis muscle which is an opposite omega shaped orientation and works in tandem with the EUS to voluntary contract to provide urethral closuring pressure.[33] Of great significance for prostatectomy patients are recent investigations that strongly favour emphasis of the EUS and the anteriorly located bulbocavernosus muscles as the superficial

PFM most likely to require activation for urinary continence control, versus the posteriorly located levator ani muscle.[63]

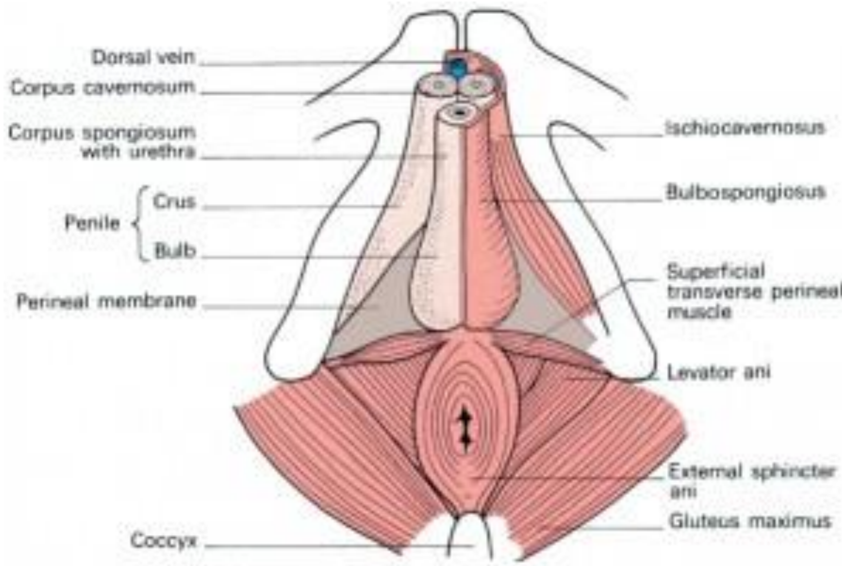

Figure 2.7 Male pelvic floor anatomy (reproduced from *Wikize.co* 20.11.18)

The PFM comprises two broad types of skeletal muscle fibres; each responsible for different functions. Slow twitch (type 1) endurance fibres make up approximately 80% of the PFM[64 65] and are capable of long-lasting but relatively weak contractions.[66] These fibres are utilised in bladder and bowel continence, assist in upright posture and help maintain PFM tone during rest or activity.[66,67] The remaining ~20% of PFM fibres are fast twitch (type 2),[65,68] which are adapted for strong, rapid contractions, required for both reflex occlusion of the urethra and for voluntary retention of urine.[66] Although they fatigue faster than type 1 fibres, type 2 fibres are primarily responsible for preventing urinary leakage during sudden actions such as coughing and sneezing.[47,69] In these scenarios, reflex reactions are required to compress the urethral wall during periods of increased abdominal pressure, critical to preventing SUI.[66,70]

Physiology of the PFM: Tonic and Phasic Activity

Physiological, spontaneous activity of the PFM is known as tonic motor unit activity and depends entirely on prolonged activation of certain tonic muscle units.[71] The amount of activity can be assessed by analysing the interference pattern by EMG, which increases with the rate of bladder filling. Any reflex or voluntary activation relates to an increase of the firing frequency of these motor units with inhibition of firing apparent on initiation of voiding. This leads to PFM relaxation and micturition, detected as a disappearance of all EMG activity, which precedes detrusor (bladder) contraction. With any stronger activation manoeuvre and for a limited period of time, as in coughing and sneezing, new phasic motor units are recruited which have a higher potential of amplitude and discharge rates.[38,60]

Reflex Activity of Pelvic Floor Muscles

It is of relevance that human urethral and anal sphincters seem to have no muscle spindles, thus PFM have the intrinsic proprioceptive 'servo-mechanism' for adjusting muscle length and tension, whereas the sphincter muscles rely on afferents from skin and mucosa with both groups integrated in reflex activity incorporated in pelvic organ function. Sudden increases in intra-abdominal pressure lead to brisk PFM reflex activity and will include feed-forward activation. As the PFM have to be involved in very complex, involuntaryreflex activity during their functional role in continence and sexual function, pattern generators within the central nervous system, principally in the brainstem, appear to be genetically inbuilt.[38,60]

Neural Control of Continence

The function of the bladder can be divided into two distinct phases, a storage phase and an elimination phase. At rest, continence control is achieved by a competent sphincter mechanism which includes the striated and smooth muscle (EUS, IUS), the PFM and adequate bladder storage function under the control of the sympathetic nervous system (Figure 2.8).[60] Normal sphincter EMG recordings show continuous activity of motor units in striated sphincter muscles at rest which is observed by continuous firing of motor unit potentials that increase with increasing bladder fullness. This differs between individuals and in experimental studies, was found to continue even after participants fall asleep.[72] Throughout this phase the detrusor muscle and bladder wall are in a state of relaxation to allow continuous filling without increasing intra-bladder pressure. Simultaneously, reflexes mediating excitatory outflow to the sphincters are organised via the guarding reflex at the spinal level and the 'storage centre' within the L region of the brainstem to exert a continuous exciting effect on the EUS during the storage phase to maintain continence.[73] Once the bladder is full, however, the parasympathetic nervous system is stimulated to cause the detrusor muscles to contract and the smooth muscle of the EUS starts to relax.[73] An ‘urge’ signal is activated and, via cortical stimulation, the individual is aroused to consciously relax the EUS, after which the bladder is emptied (Figure 2.9).

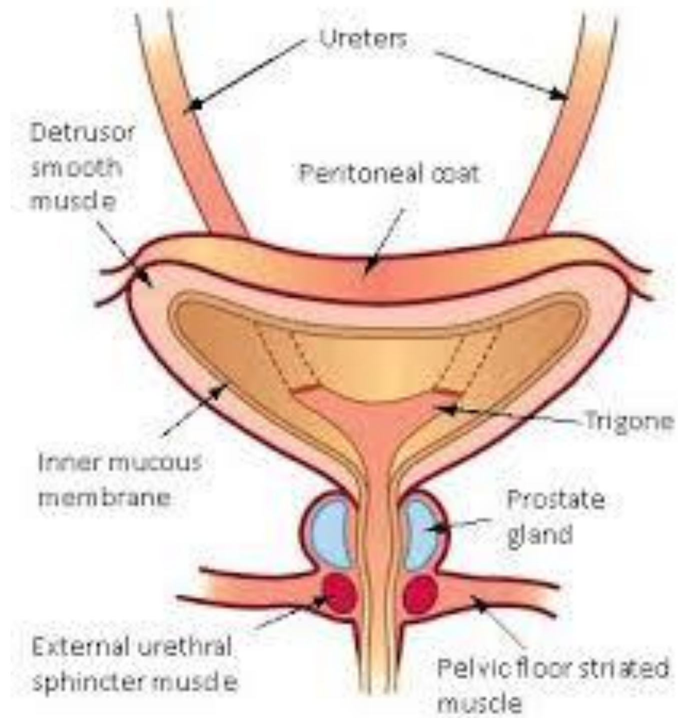

Figure 2.8. Anatomy of urinary continence (reproduced from *pinterest.com* 20.11.18)

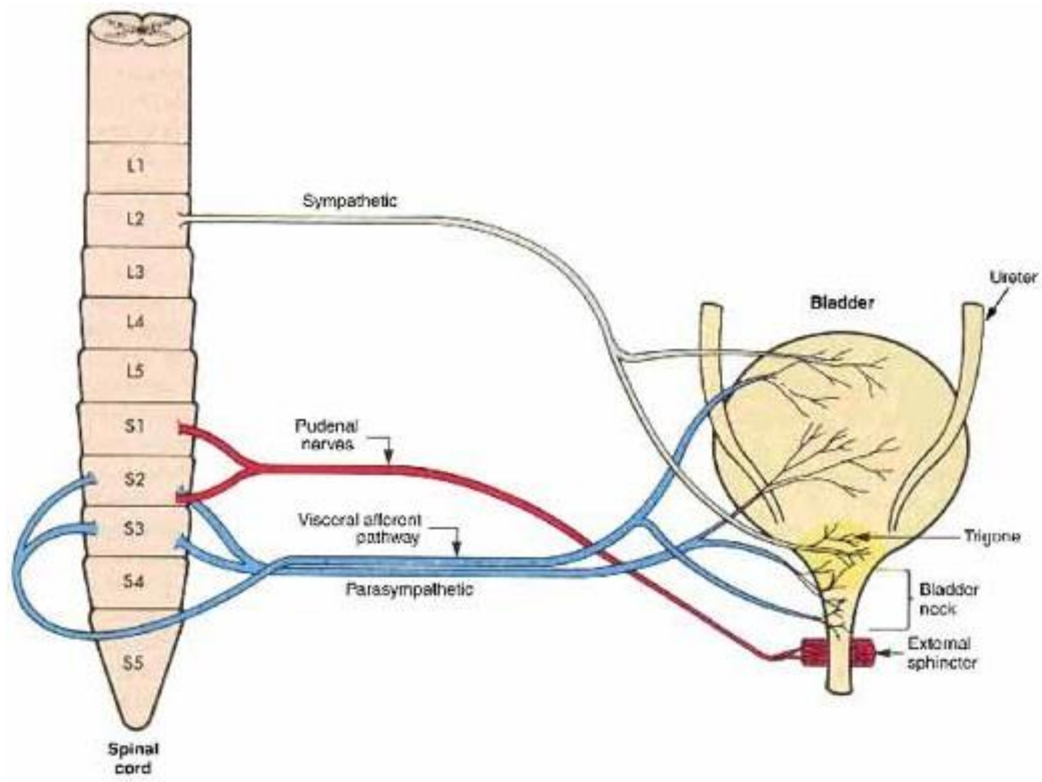

Figure 2.9 Neural control of continence (reproduced from *physiologyplus.com 17.03.19)*

During physical stress in coughing or sneezing, the urethral sphincters may not be sufficient to passively withhold pressures arising in the abdominal cavity, the bladder and lower rectum. Activation of the PFM is mandatory and in these situations is thought to be generated by individual pattern generators within the brainstem, enabling PFM recruitment as a preset coactivation.[60] Additionally, it is thought there may be an additional reflex PFM response to increased abdominal pressure due to distension of muscle spindles within PFM.[60] Already well established is the 'knack', a learned ability to voluntarily activate PFM in anticipation of increased abdominal pressure during actions such as cough, sneeze, sit to stand during which the EUS and bulbocavernosus muscle contract to prevent the leakage of urine.[47] Consequently, it is well accepted that non-invasive treatments such as PFM exercises, which repeatedly contract and relax the pelvic floor in an attempt to improve urinary control[74] and that cause no harm, are advised for both men and women as a preferred first treatment option for UI.[11,59]

Assessment and Measurement of Urinary Incontinence

Measurement of UI has typically consisted of subjective reporting by patients and assessment by physicians during consultations. Current first line treatment options for UI include PFM exercises, bladder training drills, penile clamps and anti-cholinergic medication. [11] There is however, no universally agreed measure of continence, with great variation noted in both subjective and objective methods of assessment. However, this information is critical to determining the level of treatment required. Several self-reported questionnaires for men including the International Prostate Symptom Score (IPSS) [75], International Continence Questionnaire (ICIQ) [76], and the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) [77] have been validated. These enable individuals to report their experience and 'bothersome' levels of UI. Patients can report pad number/day, but not the size of pad, type of pad used or strategies such as the use of extra tissues for additional absorbency. With some pads able to hold up to 1500 ml and others just 50 ml, recording the pad number/day does little to reflect actual urine leakage loss. From clinical experience, there is also a highly personal approach to hygiene and comfort with some individuals' content to wear one pad per day and have it overflowing, while others prefer to use 3-4 pads/ day for an equivalent leakage. In addition, comparisons between self-reported bother by patients and practitioners, can vary markedly. [78] Of the 66 RP patients in a 2010 investigation by Seung, physicians reported that 34 (52%) had obtained complete continence, however analysis of the questionnaires of these 34 patients revealed that only 5 (15%) patients reported that they never leaked during the past 4 weeks. [78] Such large discrepancies between these factors have necessitated improved measurement techniques.

A more objective method to assess UI is to provide a pad weight test, whereby 1 ml is equivalent to 1 g loss of urine with 20 minute, 1-hour and 24-hour options available.[79,80] Patients are encouraged to record fluid intake, urine volume eliminated, individual pad weight and activity levels. In the 1-hour pad weight test, [81] patients drink 500ml of water and then perform a range of set tasks to assess physical loading on the bladder and a level of UI severity is determined. However, the time of the day, level of general fatigue and time out from surgery can also impact on results. The 24-hour pad test is more commonly used clinically as it measures leakage over a much longer period of time to assess for variability in general activities of daily living and in men, have recently been determined as the most reliable non-invasive method of quantifying the severity of UI. [80,81] In recent investigations by Malik in 2016, this was extrapolated to 3 days of 24-hour/pad weight measurements, to account for variation between days and physical activity in 25 men post RP. [82] Once pad weight is ascertained, the severity of PPI can then be categorized according to pad weight scores, with grades of 'mild' <100 g,/24 hours ,'moderate' (100-400 g/24 hours) and severe (>400 g/24 hours) recorded and pad weight results utilized to determine if corrective surgery for severe incontinence is required. [83] Patients with urine loss > 450 g/ 24hours are routinely advised to have an artificial urethral sphincter fitted, with lower level loss offered a range of male urethral and obturator slings.[84] By providing objective information, clinicians caring for patients have a more targeted approach to treatment options required for each individual.

Pelvic Floor Muscle Assessment

Assessment of pelvic floor function has both subjective and objective components. Subjective assessment is based on the patient's account of existing symptoms or in preparation for surgery and includes a thorough interview analysing aspects such as bladder, bowel and sexual function, issues of leakage, frequency, urgency, flow rates or pain. Fluid intake and type, the patient's occupation, physical activity and exercise levels, body weight and BMI, past medical history are all significant components of this assessment. [85] Objective assessment includes both external and internal options with observation of the scrotum, testicles and penis performing a PFM contraction helpful in identifying correct technique. Traditionally, the standard approach to assessing PFM function in men has involved digital rectal examination (DRE) and anal manometry scoring of "squeezing" pressure on an ordinal scale (e.g. Modified Oxford Scale - a 6 point scale described as 0 = no contraction, 1= flicker, 2=weak, 3= moderate, 4= good, 5= strong) via internal examination, with the option of utilising devices such as perineometers (Figure 2.10). [68,74,86,87] DRE measures the strength of the EAS and the lift of the posterior aspect of the levator ani (puborectalis) however, this approach only provides ordinal data and has been described as physically invasive, psychologically challenging, [60,88-91]possessing poor inter-observer reliability and lacking universal standardisation (studies were predominantly undertaken in women).

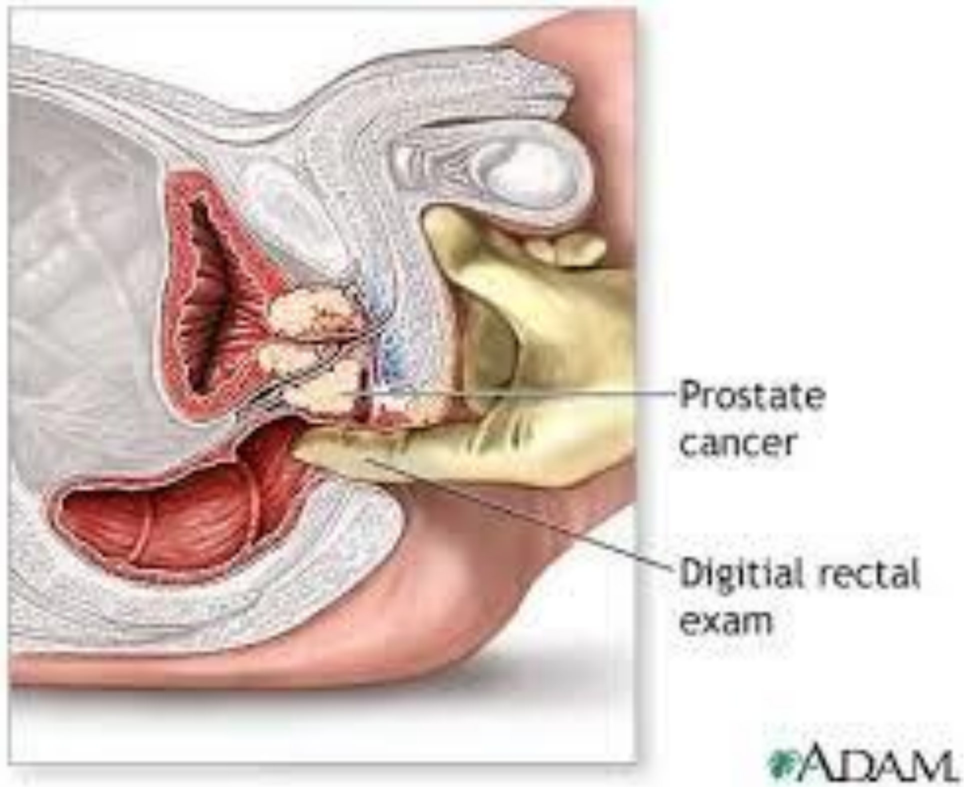

Figure 2.10. Digital Rectal Examination (reproduced from *edu.gloster.com)*

In men, these significant limitations to DRE assessment of PFM function are further supported by research indicating a sense of shame and a reluctance to receive DRE examinations due to their personal invasiveness. [92,93] In addition, *per rectal* PFM strength assessment in men has been shown to be largely unrelated to male urinary function [94] with urethral closure pressures in men more likely to be achieved by the coordinated contraction of the anteriorly located bulbocavernosal and EUS muscles. [95] Verbal instructions in these investigations assessed whether men correctly activated their PFM for UI control, when compared to more traditional commands encouraging EAS closure, with elevation of the bladder neck in a cranial direction confirmed as correct technique in 31 participants. [94,96] Studies involving manometric assessment of PFM function have also shown poor correlations with UI, hence the validity of assessing the PFM via rectal approach in men has been questioned. [90,97]

Transabdominal Real Time Ultrasound for Measuring the Male Pelvic Floor

Transabdominal real time ultrasound (TrA RTUS), is a more recent approach to objective assessment and is a valid, reliable and less invasive method for use in both men and women,[88] although specific components of the PFM that are associated with continence cannot be assessed individually due to lack of bony landmarks.[94,98,99] Applied supra-pubically, TrA RTUS assessment is performed by placing an ultrasound (US) probe on the lower abdomen at a mid-sagittal location to obtain clear, transverse images of the inferior-posterior aspect of the bladder. Any movement of the bladder base in a cephalad direction (elevation) during PFM contraction is noted as a correct action where any depression of the bladder base is noted as incorrect action (Figure 2.11).[88,90,99]

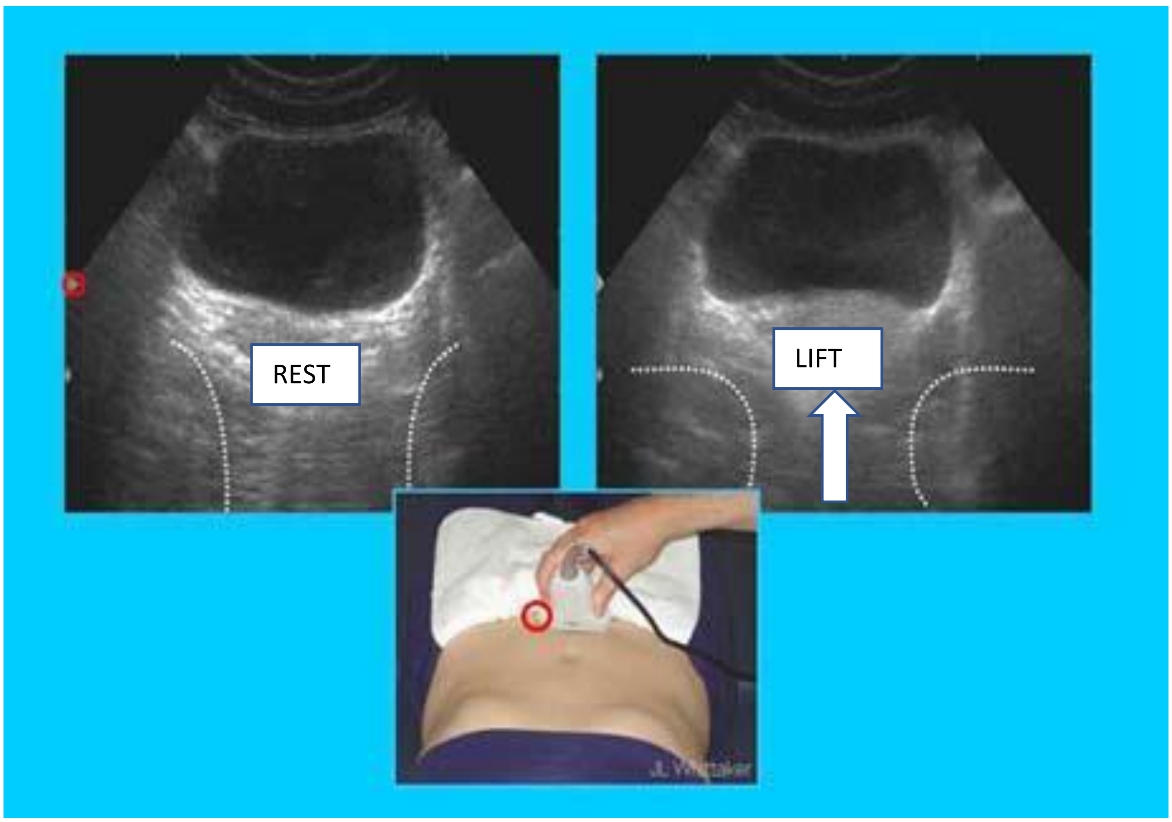

Figure 2.11. TrA RTUS image of PFM in supine (reproduced from *pelvicfloormusclesbotene.com* 20.11.18)

In addition, lift of the urethra greater than 2 mm measured with cystourethrography among post-prostatectomy patients upon catheter removal, has been correlated with an early return to continence.[100] Of significance is Nahon's investigation of 28 post-prostatectomy patients which compared the assessment of PFM function in TrA RTUS versus the DRE approach.[44] Only a moderate correlation was noted between the two forms of assessment with TrA RTUS recommended as being valid and reliable in men, particularly if DRE was contraindicated. One limitation of TrA RTUS, however, is the necessity for patients to have urine in their bladder, which for incontinent patients can be problematic.

Transperineal Real Time Ultrasound for Measuring the Male Pelvic Floor

An alternative approach to assessing PFM function in men involves transperineal real time ultrasound (TrP RTUS) which uses the pubic symphysis as a bony landmark and enables simultaneous visualisation of all three striated muscles, the SUS , the bulbocavernosous (BC) and the puborectalis (PR) that control male urinary continence (Figure 2.12).[95,101] Widely accepted and validated in females,[102] the use TrP RTUS PFM in males is a relatively new approach. To perform TrP RTUS assessment in men, an US probe is placed on the perineum in the mid-sagittal location, midway between the base of the penis and the anus, with the transducer orientated to obtain sagittal images (Figure 2.13). In addition to measuring bladder neck elevation, TrP RTUS visually demonstrates the posterior kinking of the SUS that contributes to urethral closure, and provides clear visual feedback that can assist in teaching correct PFM contractions.[103] With emphasis on the anterior structures involved in the male continence mechanism, patients can visualise correct technique immediately and be guided if anal dominance is occurring.[104]

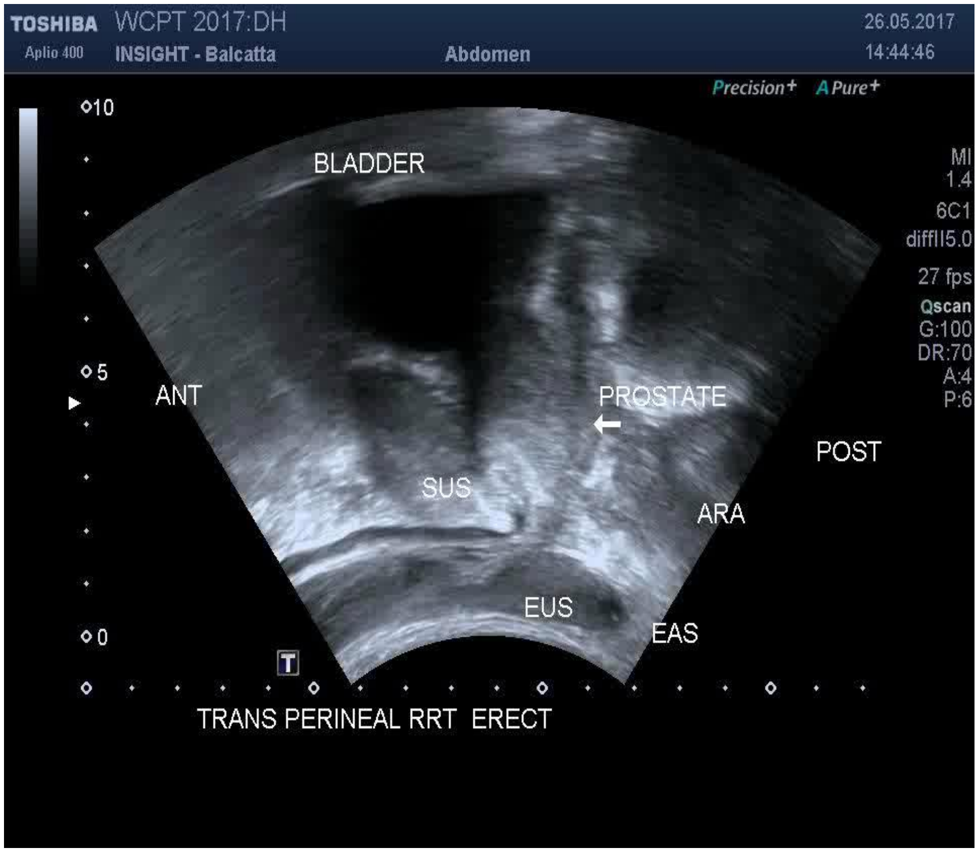

Figure 2.12 TrP RTUS of PFM in standing (Reproduced from *insightradiology.com.au* 26.05.18)

Figure 1

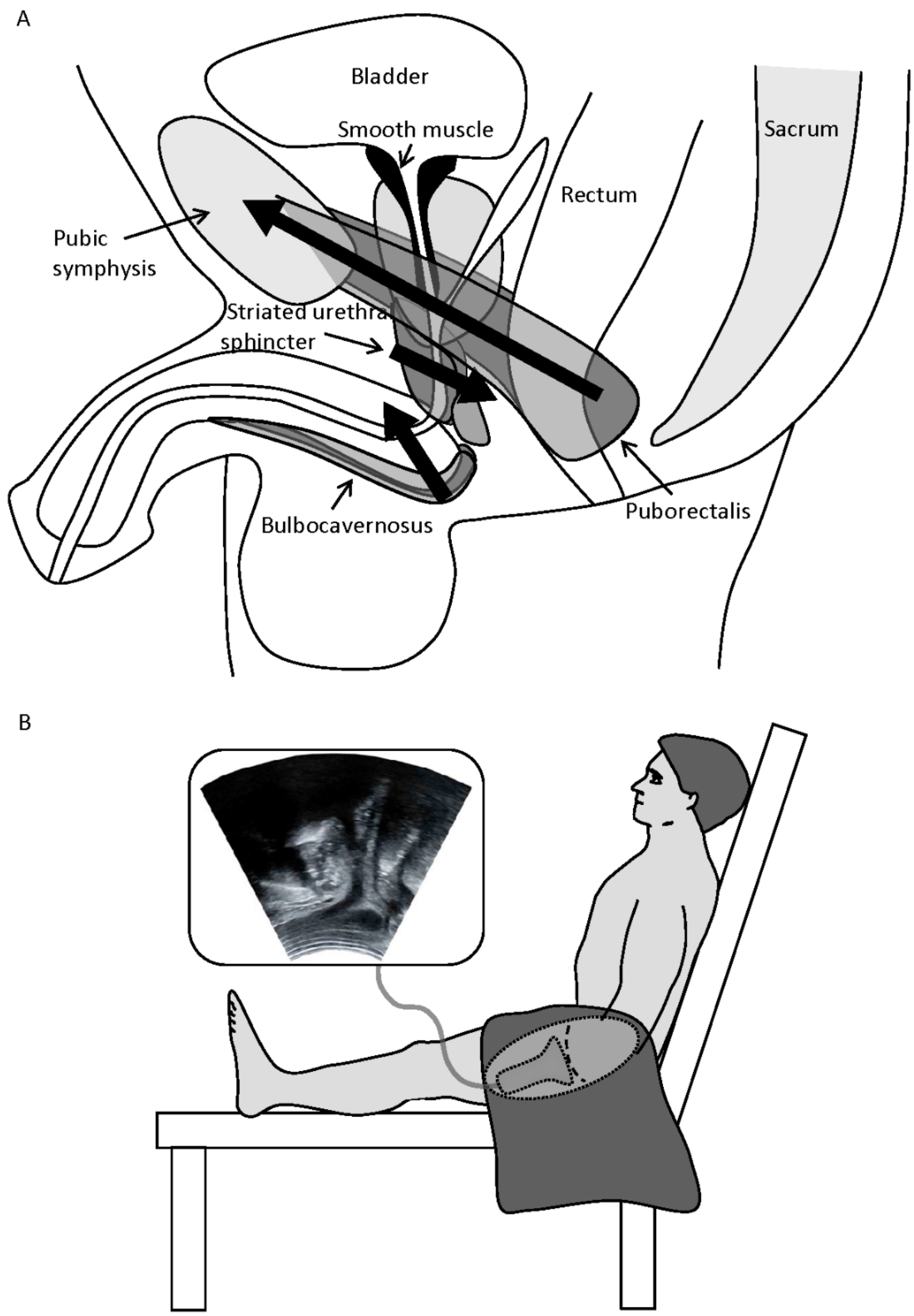

Figure 2.13 The male PFM (A) and (B) TrP RTUS application
(Provided by *Ryan Stafford 20.03.19)*

Thompson *et al*. [98,99] compared the two approaches in women[98,99,102] and were able to confirm that the reliability of TrA RTUS was excellent and comparable to TrP for measuring pelvic floor movement during PFM contraction. TrP RTUS was found to be more reliable for inter-patient comparisons as it measures from a fixed bony landmark, although the increased complexity of evaluation and increased time of assessment in a clinical setting has been noted. [99] In both approaches, however, RTUS is unable to predict the tone or stiffness of PFMs, with hypertonicity typically appearing to look 'weak' due to minimal mobility of the bladder base or neck, an indication of high resting tension.[105] In addition, increased acute angles of the anorectal angle/puborectalis have been correlated to chronic pelvic pain syndromes in men, whereby emphasis on relaxing PFM then becomes the goal of PFM training. [106] No research to date has compared TrA versus TrP RTUS measures in men and, given the QoL issues associated with traditional testing, a more contemporary approach to assessment formed a large component of the research for this thesis.

Summary

In summary, the opportunity to work with men newly diagnosed with PCa in a real time setting via clinical practice, provided a stimulus to exploring better options for the physiotherapy assessment and treatment of patients throughout their PCa experience. At the initial stages of diagnosis, there are a multitude of decisions to be made around treatment type and potential side-effects, with many men overwhelmed by the information 'overload' that is presented to them. A high percentage of men will also begin an exasperating search on the internet and within their local community for opinions on the best management pathway that minimises their personal burden. Many patients present to physiotherapy clinics in a state of shock at their diagnosis, despite feeling perfectly well.

The primary role of a physiotherapist working with this cohort is to assess and treat PFM function/dysfunction. The opportunity to provide non-invasive methods to assess PFM function, as opposed to the traditional *per rectal* approaches, which men fear, was a priority. Initially, only TrA RTUS applications were available and validated for men, however, the work of Stafford *et al* [95]introduced TrP approaches. To date, no studies had explored the relationship between the less invasive option of TrA RTUS and the more sophisticated TrP approach in determining action plans for patients, although these relationships had been addressed for female patients.. The development of two functional tests of PFM function, based on physiological properties of the human PFM, was an initial goal of this thesis. Comparing these RTUS approaches applied in different postures formed the basis of the first study.

Rather than just an observation of PFM movement, I aimed to provide an assessment of function that could be easily recorded in real time and reflected what was physically happening to the PFM. Furthermore, linking the results of these tests to PFM fatigue and exploring a possible relationship to incontinence was deemed important.

In 2012, Associate Professor Pauline Chiarelli announced at a PCa workshop in Brisbane, that men's health was "30 years behind women's health and that much needed to be done in the research space to improve outcomes for men generally". With men often reluctant to ask for help, or culturally avoiding situations that makes them feel uncomfortable, my main aim was to help bridge this sizable research void.

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CHAPTER 3

Paper 1:
Pelvic floor muscle assessment in men: comparing digital rectal examination and real time ultrasound approaches

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Abstract

This paper reports three studies. Study 1 assessed the degree of association between traditionally used digital rectal measures, and real time ultrasound assessments of pelvic floor muscle function in men who report incontinence following prostatectomy. Study 2 compared transabdominal and transperineal approaches to view the pelvic floor using real time ultrasound. Study 3 explored inter- and intra-observer reliability of two functional tests using real time ultrasound: a Rapid Response Test requiring participants to perform 10 rapid pelvic floor muscle contractions with elapsed time recorded, and a Sustained Endurance Test wherein participants performed a single sustained pelvic floor muscle contraction with task failure visually confirmed and elapsed time recorded. A modest correlation was observed between the per rectal assessment of squeeze pressure and objective perineometer measures (n=27, 67±7 y, r=0.51, $P<0.05$). Rapid response test (r=0.18, P=0.36) and sustained endurance test (r=0.18, P=0.36) assessments were unrelated to pelvic floor muscle squeeze pressure measured by perineometry. Strong agreement was found using Bland-Altman analysis for both the rapid response and sustained endurance tests when they were performed using transabdominal and transperineal approaches, or when determining inter- and intra-observer reliability. The two simple functional tests using real time ultrasound provide objective, non-invasive and reproducible assessment of pelvic floor muscle function that is more acceptable to men than per rectal approaches.

Key words: Men’s health, pelvic floor muscle, prostate cancer, prostatectomy, physiotherapy, real-time ultrasound

Introduction

Prostate cancer (PCa) is a global health problem and the second most commonly diagnosed cancer among men. [1] Radical prostatectomy (RP), involving complete removal of the prostate, is a standard surgical treatment performed via retro-pubic, perineal laparoscopy or robotic-assisted laparoscopic techniques. [2,3] After radical prostatectomy men report a high prevalence of urinary incontinence (UI) and erectile dysfunction (ED), [4-6] and compromised function of the pelvic floor musculature (PFM) is one of several contributing causes. Post-operative rehabilitative therapy includes strategies to improve PFM function, to address issues such as urinary incontinence [7] and erectile dysfunction [8] that impact on quality of life. The objective of this three-part study was to assess tests of PFM function using real time ultrasound to further enhance clinical practice.

The standard approach to assessing PFM function in men has involved digital rectal examination (DRE) and scoring of 'squeezing' pressure on an ordinal scale (e.g. Modified Oxford Scale). [8-11] However, this approach only provides ordinal data and is described as physically invasive, psychologically challenging, [12-17] possessing poor inter-observer reliability and lacking universal standardisation (studies predominantly undertaken in women). [18] Aversion to this method of assessment is supported by research indicating the procedure induces a sense of shame and men are reluctant to receive DRE examinations due to it being personally invasive. [19,20] In addition, per rectal PFM strength assessment in men has been shown to be largely unrelated to male urinary function. [21,22] The muscles assessed during a DRE can include those related to anal sphincter function (external and internal anal sphincter and puborectalis).

Using real time ultrasound (RTUS) assessment of PFM, function is observed as elevation at the base of the bladder during a PFM contraction and relaxation cycle. [14] Transabdominal real time ultrasound (TrA RTUS) is a valid and reliable method for use in both men and women, although specific components of PFM that are associated with continence cannot be assessed individually. [21,23,24] An alternative approach involves transperineal real time ultrasound (TrP RTUS) which uses the pubic symphysis as a bony landmark and enables simultaneous visualisation of all three striated muscles (the striated urethral sphincter, the bulbocavernosous and the puborectalis) that control male urinary continence via a complex 'horseshoe action'. [25,26] No research to date has compared TrA versus TrP RTUS measures in men.

The pelvic floor musculture comprises two broad types of skeletal muscle fibres; each responsible for different functions. Slow twitch (type 1) endurance fibres make up approximately 80% of the PFM [27,28] and are capable of long-lasting but relatively weak contractions. [29] These fibres are activated to maintain bladder and bowel continence, assist in upright posture and help maintain PFM tone during rest or activity. [29,30] The remaining ~20% of PFM fibres are fast twitch (type 2), [11,28] which are adapted for strong, rapid contractions, required for both reflex occlusion of the urethra and for voluntary retention of urine. [29] Although they fatigue faster that type 1 fibres, type 2 fibres are primarily responsible for preventing urinary leakage during sudden actions such as coughing and sneezing. [31,32] In these scenarios, reflex reactions are required to compress the urethral wall during periods of increased abdominal pressure. [29,33] To assess the different functional capacities of the pelvic floor in men, we used two tests; the Rapid Response Test (RRT) and Sustained Endurance Test (SET), involving real time ultrasound visualisation of PFM function.

The results of three studies are reported in this manuscript. Study 1 investigated the relationship between muscle function measured via traditional rectal examination approaches versus RTUS methods. Study 2 compared RTUS TrA and TrP approaches and study 3 assessed intra- and inter-tester reliability for the RRT and SET tests seen on RTUS.

Methods

This study was approved by the UWA HREC (Ref RA/4/1/6265) and the participants provided written informed consent.

<u>Description of studies</u>

Participants in study 1 were enlisted from a cohort of patients referred sequentially by their urologist for pre-prostatectomy PFM training to a single physiotherapy clinic. No specific inclusion or exclusion criteria were applied. Each participant underwent per rectal perineometry assessment and a per rectal squeeze pressure assessment by DRE. The Modified Oxford Scale [9] was used to assess PFM squeeze pressure in the lateral decubitus (side-lying) posture by a clinician experienced in PFM dysfunction. Prior to each examination, instructions were provided on correct PFM exercise technique, [34] to ensure a full contraction and relaxation cycle was implemented with the cue given to “*stop the flow of urine and shorten the penis while continuing to breathe*”. [34] Cues to relax abdominal muscles and avoid breath holding were also given. The DRE was performed with palpation beyond the external anal sphincter (EAS) to assess the pelvic floor musculature approximately 3-4 cm within the anal canal, to minimise contamination of EAS contraction. The use of a perineometer (Peritron A PRTN-1-1-1301135, Ontario) was to provide an objective measure of PFM squeeze pressure. The covered probe was inserted beyond the EAS, such that the hilt of the probe was adjacent to the anus, in keeping with the guidelines provided in the Peritron A instruction manual. Whilst we cannot exclude the possibility that anal sphincter pressure affected the probe reading, the pressure sensitive component of the perineometer lies on the shaft of the device, distal to the hilt, and it is therefore likely that our measurement approximated the PFM assessment described for the manual DRE approach. [35] This test was also performed in the lateral decubitus posture. On a separate day within one week of their initial clinic visit, these participants also underwent SET and RRT testing using the TrA approach. The TrP approach was not used at this stage of the experiment, with subsequent testing used to directly compare these two approaches (study 2).

Participants in study 2 were a different group, also enlisted from a cohort of patients sequentially referred by their urologist and were all assessed between two weeks and six months post-surgery. Participants were assessed (in random order) for the RRT and SET tests in the supine posture during two consecutive testing sessions, by the same tester, one week apart to determine intra-tester reliability. For each measurement, participants underwent both TrP and TrA RTUS assessments using a commercially available point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China).

In a third study, to determine inter-tester reliability, the RTUS tests were repeated by a second experienced observer within one week of the original test (at the same time of day) on a sub-sample of participants from Study 2, with instructions between testers and participants standardised. To standardise bladder volume, each participant voided their bladders and then drank 500 ml of water, and were instructed not to void again prior to testing .

Description of pelvic floor muscle function tests

Participants were assessed for PFM function in the crook lying position (the ‘supine’ posture) with a pillow underneath the head and hips and knees flexed at 60 degrees and with the lumbar spine positioned in neutral. Cues to relax abdominal muscles and avoid breath holding were also given. Instruction was provided on correct PFM exercise technique, [34] to ensure a full contraction and relaxation cycle was implemented with the cue given to *"stop the flow of urine and shorten the penis while continuing to breathe"*.[21,34] Participants were allowed one 'practice' contraction prior to the test in order to provide feedback for both tester and participant, and to avoid poor technique.

For the RRT, participants were instructed to *"perform 10 maximal PFM contractions and relaxations as fast as possible"*, with the elapsed time recorded as the outcome measure. In the SET participants were instructed to *"hold a maximal contraction for as long as possible, whilst continuing to breathe"*. The time to task failure was recorded (with a maximum time of 60 seconds), where task failure was defined as the descent of the bladder base (TrA) or bladder neck (TrP).

Transperineal RTUS assessments

Prior to the TrP RTUS each participant was asked to disrobe in private and to drape a towel around their waist, before reaching under and gently moving their genitals to one side with their hand. Standard infection control measures were observed. After applying a layer of transmission gel, TrP RTUS was performed by placing the covered probe on the perineum in the mid-sagittal location, midway between the base of the penis and the anus, with the transducer orientated to obtain sagittal images, and then the participant removed his hand. To optimise the images, the pubic symphysis (SYMP) was used as the bony reference point, with the urethra (U), bladder (BL), bladder neck (BN) and anorectal angle (ARA) visible simultaneously (Figure 1). Using screen calipers, a measure of the position of the bladder neck was taken at rest 'x' and the change from the resting position in a vertical direction was observed. In this study any cranial movement of the bladder neck was noted as a correct action, whereas no cranial movement or any caudal movement of the bladder neck was noted as incorrect action, as with previous guidelines. [21] During SET assessments, an arrow was placed at the bladder neck as a visual marker to determine whether changes in amplitude were indicative of task failure.

Any participant unable to perform the PFM contraction correctly (i.e. cranially versus caudally), was given the opportunity to rest to allow for PFM recovery. Cues to contract and relax the pelvic floor were repeated and, with the benefit of visual feedback, all participants were able to correct their technique. This approach was also adopted during the transabdominal procedure if initial contractions were incorrect.

Transabdominal RTUS assessments

Assessment via the TrA RTUS approach was performed by placing the probe supra-pubically on the lower abdomen at a mid-sagittal location with the transducer probe orientated to obtain transverse images and angled in a caudal/posterior direction such that a clear image of the inferior-posterior aspect of the bladder was obtained (Figure 1). Standard infection control measures were observed and a layer of gel was placed over the head of the probe. Screen calipers were used to place a mark 'x' on the bladder base (BB) at rest where any elevation of the bladder base was noted as a correct action and any depression of the bladder base was noted as incorrect action in accordance with previous guidelines. [14,24] As per TrP RTUS assessments, during SET measures, an arrow was placed at the bladder neck as a visual marker to determine whether changes in amplitude were indicative of task failure.

Statistical analysis

Data for the DRE, perineometer, SET and RRT tests were entered into SPSS (v22.0, SPSS, Chicago, IL) for subsequent analysis and significance was accepted for all analyses at $p<0.05$. The association between scores from DRE and perineometer measurements was analysed using a Pearson's correlation with linear regression performed to characterise association between these variables. For this paper we defined the strength of correlation as follows: [36]

- $r = 0.25-0.50$ weak to moderate
- $r = 0.5-0.75$ moderate to good
- $r > 0.75$ good to excellent

Bland-Altman analyses and plots were used to determine the limits of agreement for:

- the relationship between RRT and SET outcome scores using TrP versus TrA approaches with patients in the supine posture
- inter-observer reliability for SET and RRT tests conducted using TrA RTUS with patients in the supine posture
- intra-observer reliability for SET and RRT tests conducted using TrA RTUS with patients in the supine posture

Results

Study 1: Relationship between rectal examination approaches and RTUS tests

Test scores for 27 post-prostatectomy patients (63±7 y, 170.0±18.3 cm, 76.2±16.3 kg, all Gleason 7) averaged 3.0 ± 0.8 on the Modified Oxford Scale and 44.3±22.2 cmH_2O by perineometry. DRE results were only moderately correlated with the more objective perineometry measurements ($r = 0.5$, $p<0.05$).

RRT (r=0.18, *P*=0.36) and SET (r=0.18, *P*=0.36) assessments were unrelated to perineometry-based PFM squeezing pressure. Correlations between the digital per rectal squeeze pressure and the SET (r=0.02, *P*=0.94) and RRT (r=0.04, *P*=0.86) were also not correlated.

Study 2: Comparison of RTUS TRA and TrP approaches

Of the 100 patients recruited to Study 2, five were excluded from analysis due to post-surgery complications involving the bladder neck, which required further surgical intervention (n = 95, 63±11 y, 172.0±15.2 cm, 72.9±16.9 kg, all Gleason 7), with ± referring to the mean ± standard deviation.

The limits of agreement for each of the RRT and SET assessments, performed using TrP and TrA methods, are presented as Bland-Altman plots in Figure 2. These data show no significant difference (p>0.05) between the assessment methods. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between both methods being close to 0 and the standard deviation for difference scores low (0.9 seconds for RRT and 4.1 seconds for SET).

Study 3: Intra- and inter-tester reliability for the RRT and SET tests seen on RTUS

This sub-sample of participants were recruited from the cohort of men in study 2, who were able to attend two consecutive appointments within one week (n=47, 63±12 y, 171.0±14.9 cm, 76.1±17.2 kg). The limits of agreement for each of the RRT and SET assessments, performed on the same participants by two operators, are presented as Bland-Altman plots in Figure 3. These data show no significant difference (p>0.05) between operators. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between operators being close to 0 and the standard deviation for difference scores low (2.0 seconds for RRT and 2.7 seconds for SET).

Similarly, limits of agreement for each of the RRT and SET assessments, performed by the same operator on two occasions, one week apart, are presented as Bland-Altman plots in Figure 4. These data show no significant difference ($p>0.05$) between test sessions. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between both test sessions being close to 0 and the standard deviation for difference scores very low (0.4 seconds for RRT and 0.5 seconds for SET).

Discussion

In the present study we observed a moderate correlation between the traditional DRE approach to PFM assessment, compared to more objective perineometry. Conversely, strong agreement was found for both RRT and SET when tests were performed using TrA and TrP protocols, and when determining inter- and intra-observer reliability.

Study 1: Traditional versus RTUS assessment of pelvic floor muscle function

Our findings indicate that digital rectal squeeze pressure scores correlated only moderately with an objective pressure measurement technique. In addition, PFM strength grading was poorly correlated with our RTUS tests of function (both RRT and SET). This finding is broadly consistent with previous studies in women [12,19,37] which report poor correlations between digital strength grading and ultrasound measures. Sherburn and colleagues, [16] in particular, found no significant relationship between ultrasound measures and digital palpation. [12] In contrast, recent investigations by Arab and colleagues [38] comparing TrA RTUS versus digital palpation in females [39] reported a positive correlation if RTUS assessments were performed simultaneously with PFM contraction. These differences in study outcomes are likely due to earlier studies performing the assessments separately and the variability in per rectal methodologies. Hence, our findings concur with previous studies, mostly performed in women, and we conclude that different aspects of PFM function were assessed using the per rectal and RTUS tests. Specifically, the RTUS test measured PFM function over time with objective measures of fatigue, in contrast to the per rectal approaches. Thus, we were able to demonstrate a predictive validity favouring RTUS approaches. The latter are simple to administer, clinically relevant, [14] non-invasive, well-tolerated and provide direct visualisation of PFM contraction. [24,40]

Study 2: Transabdominal versus transperineal approaches

While TrA and TrP RTUS approaches for PFM assessment in men are validated, there is no previous direct analysis to compare these approaches. [14,25] Similar investigations in women [23,24,41] confirmed the reliability of TrA RTUS as 'excellent' and comparable to TrP for measuring pelvic floor movement during PFM contraction. The TrP approach was found to be more reliable for inter-patient comparisons as it measured from a fixed bony landmark, although the increased complexity of evaluation and increased time of assessment in a clinical setting has been noted. [24] In comparison, the TrA RTUS approach is minimally-invasive, quick to perform, does not require the person to undress and is relatively easy to learn. [24] This approach can be particularly helpful for the clinician who is working with men who wear continence pads, those unwilling to undergo perineal assessment due to culture or ethnicity, survivors of sexual abuse, those who are anxious, or children and the elderly who need PFM evaluation.

We were able to demonstrate that during PFM contraction, a strong association exists for scores derived using both the TrP and TrA approaches. This confirms that either option may be used and that clinical evaluations designed for patients can be individualised, particularly when PFM digital palpation may not be appropriate.

Of course, studies in which the assessment of individual muscle groups within the pelvic floor is an imperative should favour the TrP approach. Although not encountered in our investigations, should there be clinical presentations such as complete incontinence, whereby any holding of bladder volume is limited, the TrP RTUS option may be more appropriate, since a full bladder is not required. Obesity, scar tissue and previous abdominal surgery may also impact on the quality of imaging in TrA RTUS. Therefore, having two approaches available is helpful clinically for optimal assessment and rehabilitation.

Study 3: Inter- and intra-tester reliability of RTUS tests

The inter- and intra-tester reliability of the SET and RRT tests were high, with strong associations observed between the sets of scores. By contrast, coefficients of variation reported for repeated assessment of the Modified Oxford Scale squeeze pressure test, [9] as previously assessed in women, are >20% and the correlation for repeated assessment is substantially lower than that observed for the SET (r= 0.91) and RRT (r=0.99) in our study. [19] In the analysis of Bland-Altman plots, the relatively small range of the 95%

confidence intervals indicates that both the RRT and SET tests have good intra- and inter-tester reliability. However, the limits of agreement for the inter-tester SET test results were slightly higher than expected, which possibly relates to a difference in skill and level of experience between testers. This emphasises the importance of training for clinicians so that a narrower confidence interval may be achieved. Across all Bland-Altman plots, the difference between tests seems consistent across a large baseline of values. These data suggest that the measures we present in this paper are reliable and mostly immune to the effects of different observers.

There are several limitations of the current study. There is no universally accepted 'gold-standard' measure of PFM function in men. The DRE derived measures used in study 1 were not intended as a basis for comparing to a gold standard. Such DRE measures remain, however, widely used and considered by some to be the best currently available. The criteria used for task failure could be more objective if, for example, automatic edge detection and wall tracking software were developed for use in RTUS approaches. The posture used to perform the DRE based tests (lateral decubitus) was selected as instructed for use in the Peritron A manual, and because it was the preference of the physican who undertook these tests. It is a posture commonly used in routine clinical DRE examination in men. It differed from the posture used to undertake the SET and RRT tests (crook lying) and the lack of correlation between DRE and RTUS tests we observed in study 1 may be partly explained by this postural difference. The results of the RRT and SET tests can be affected by the technical difficulty of the selected approach. It is relevant in this regard that, whilst the TrP technique is more technically demanding, the TrA and TrP tests are highly correlated. While the SET and RRT data are specific to this study, the objective and timed nature of these tests should make the collation of normative data sets possible in larger cohorts in future. Prospective outcomes, related to performance that is scaled by normative comparison, should also be possible.

Conclusions

Both TrP and TrA approaches to RTUS of the pelvic floor had high inter- and intra-tester reliability and appear to have advantages over the DRE and/or perineometry, which are only moderately correlated and have poor inter-tester reliability. Similar scores were observed if measurements were performed by either TrA or TrP approaches, with TrA assessment potentially less problematic for those uncomfortable with the TrP approach. Future studies are needed to investigate whether the RRT and SET RTUS tests are posture dependent or relate to clinical outcomes such as post prostatectomy incontinence (pad weight).

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Figure 1. *Upper panel:* Transperineal real time ultrasound image used to assess pelvic floor muscular (PFM) function utilising screen calipers to determine correct PFM action during the rapid response test (RRT) and sustained endurance test (SET). Movement should be in a cranial direction as indicated by the arrow. BL = bladder, BN = bladder neck seen in relation to SYMP = symphysis pubis, U = urethra, ARA = anorectal angle and bladder. *Lower panel:* Transabdominal real time ultrasound images used to assess PFM action during the RRT and SET (left image = at rest ; right image = whilst contracting). BB= base of bladder and arrows indicate direction of pelvic floor muscles.

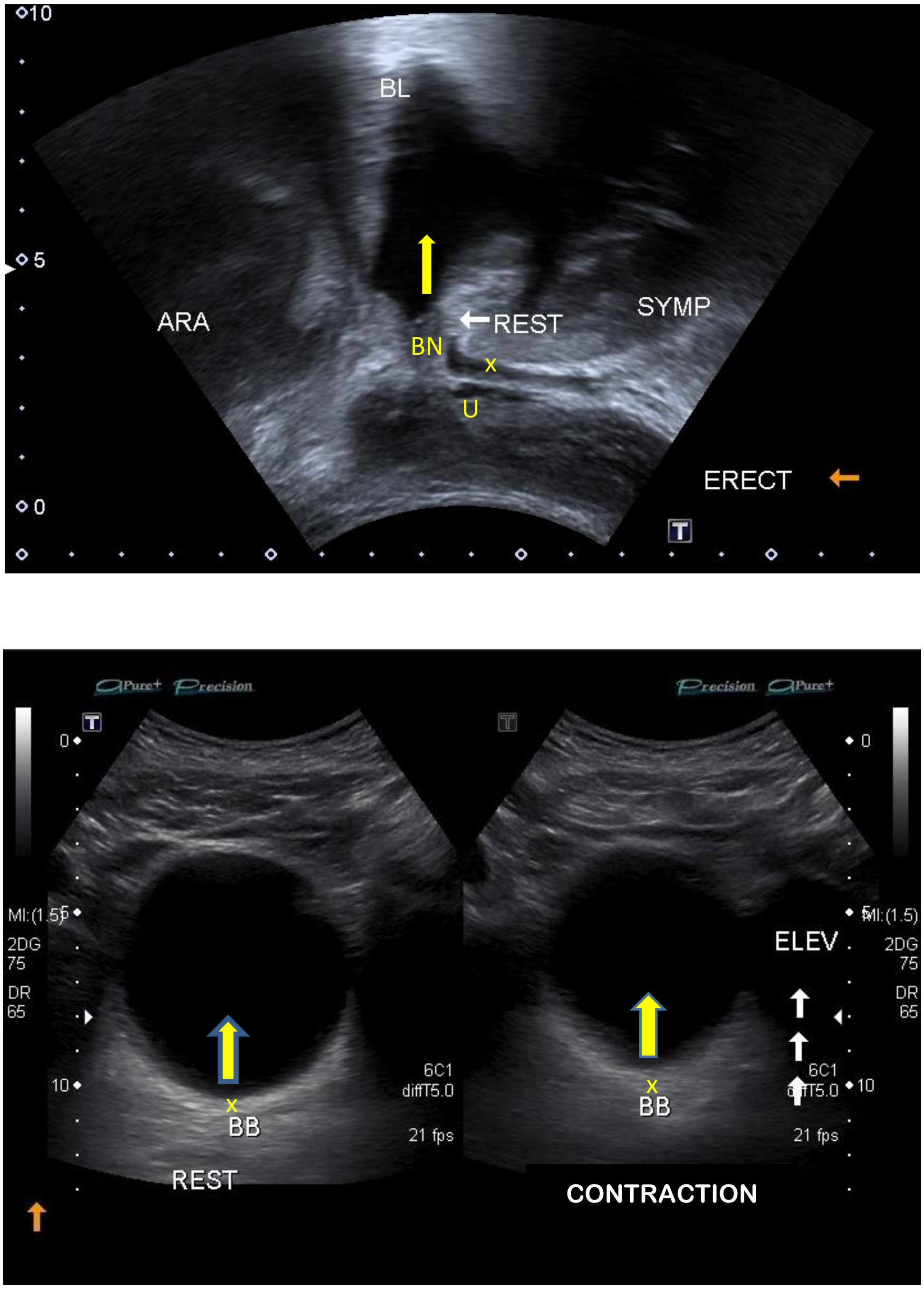
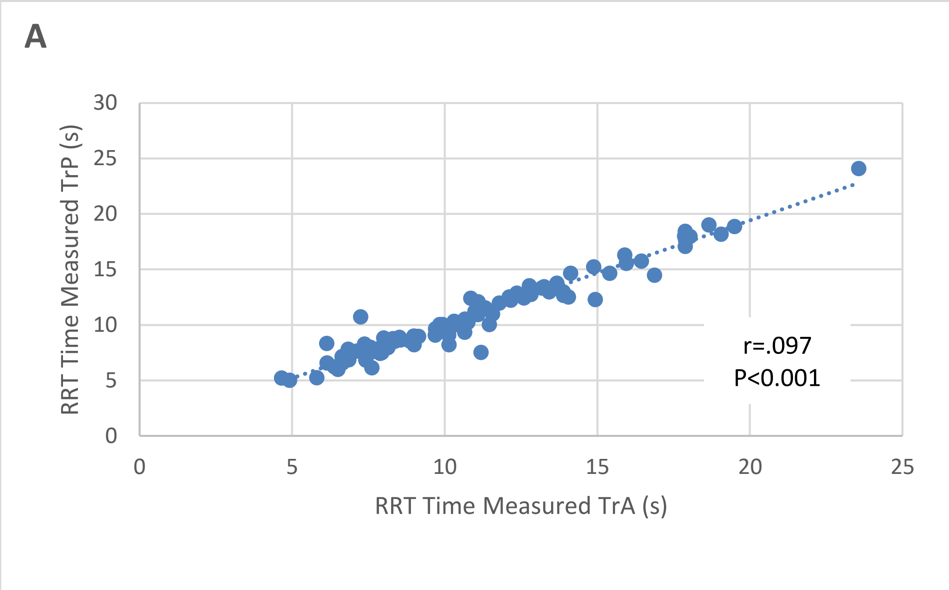


Figure 2. Bland-Altman plots presenting the limits of agreement for pelvic floor musculature function assessed by transabdominal (TrA) and transperineal (TrP) ultrasound for the Rapid Response Test (RRT) in the upper panel, and the Sustained Endurance Test (SET) in the lower panel – all tests were conducted in the supine posture.



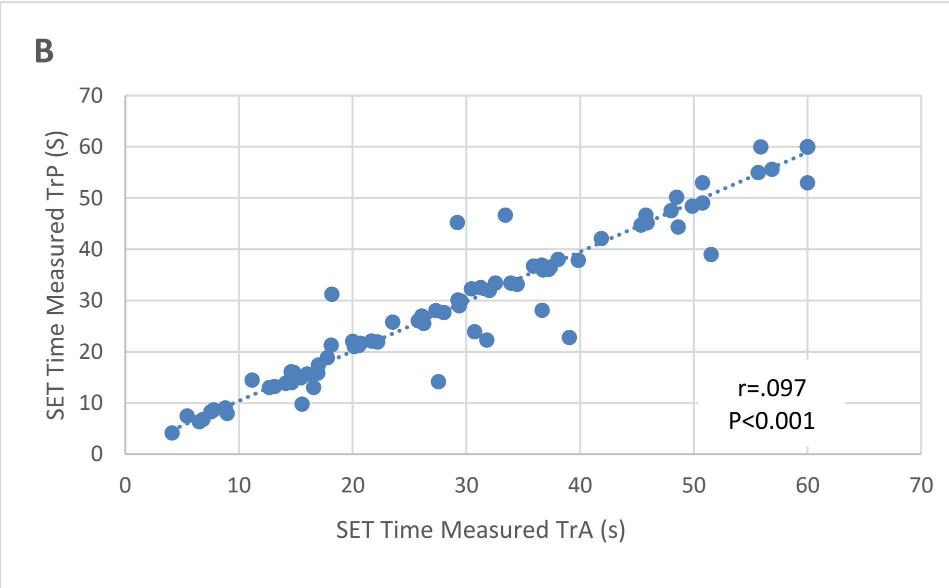
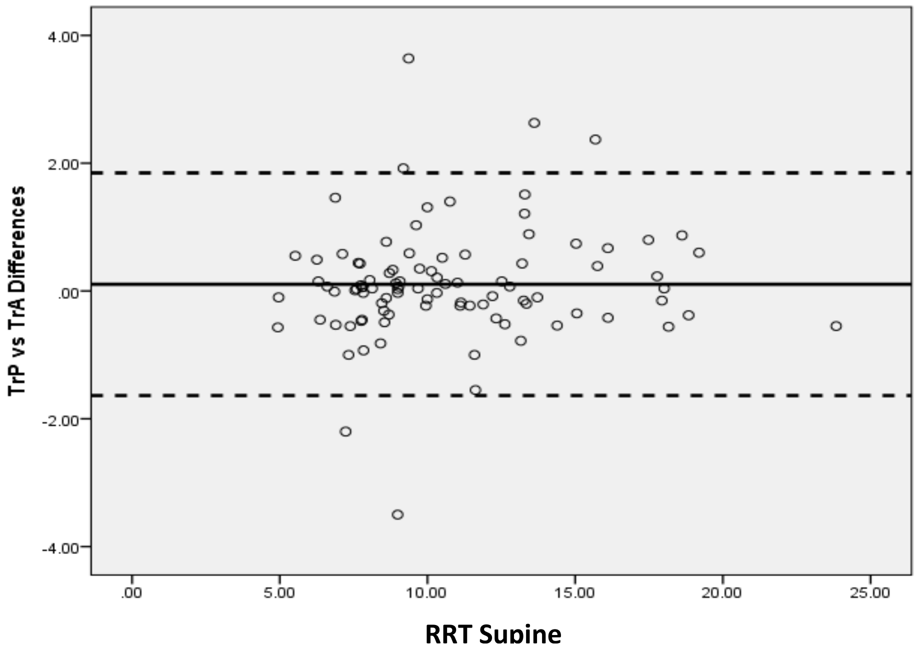


Figure 3. Bland-Altman plots presenting the limits of agreement for two assessors measuring the same patients on the Rapid Response Test (RRT) in the upper panel, and the Sustained Endurance Test (SET) in the lower panel – all tests were conducted using transabdominal real time ultrasound images with patients in the supine posture.



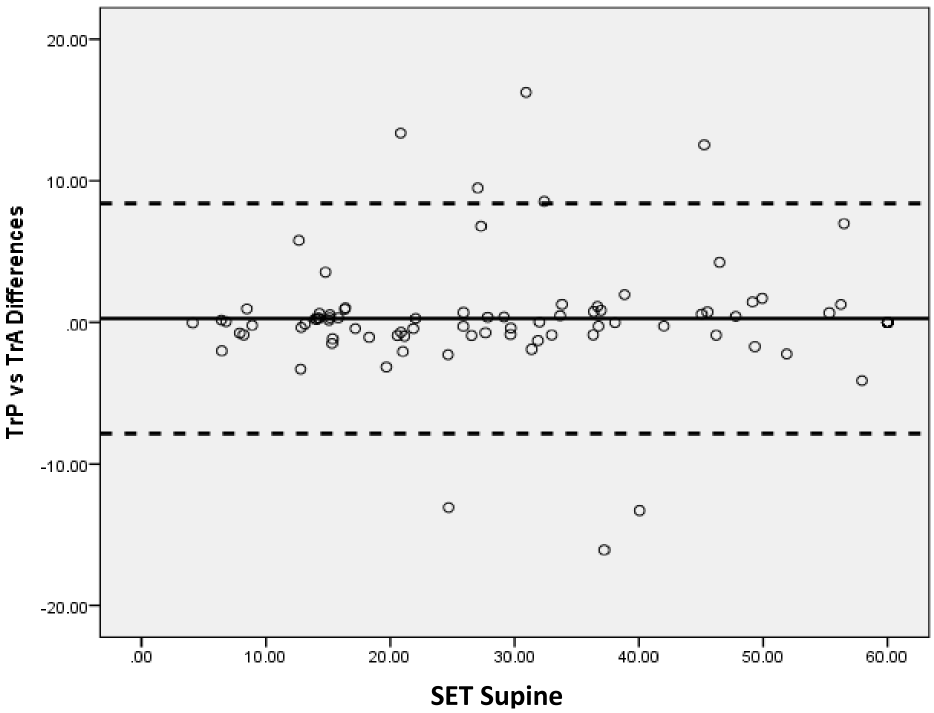
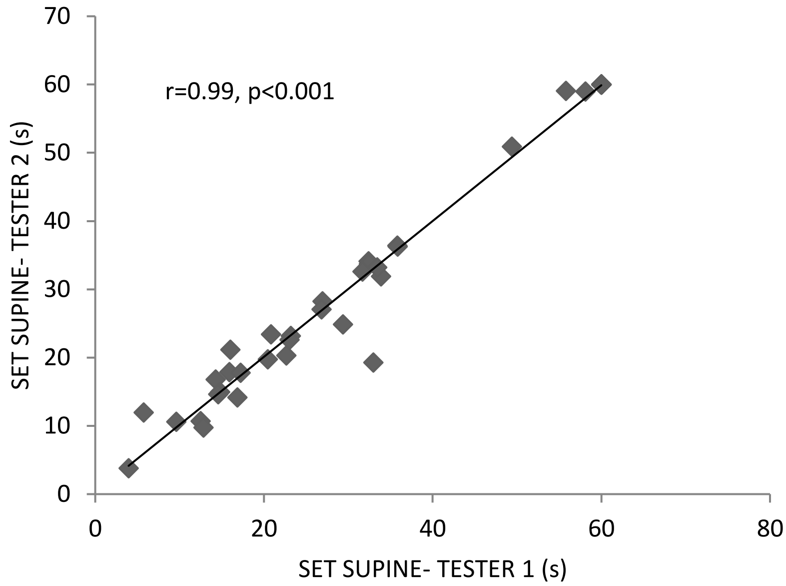
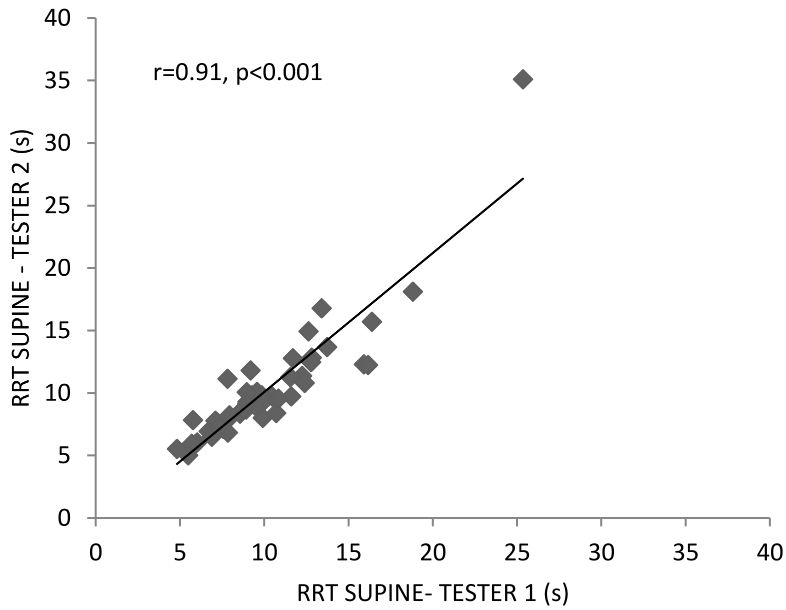


Figure 4. Bland-Altman plots presenting the limits of agreement for a single assessor measuring patients on two occasions, one week apart, on the Rapid Response Test (RRT) in the lower panel, and the Sustained Endurance Test (SET) in the upper panel – all tests were conducted using transabdominal real time ultrasound images with patients in the supine posture.





CHAPTER 4

Paper 2:
Application of two pelvic floor muscle function tests in men following radical prostatectomy: relationship to urinary incontinence

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Abstract

This study examines the impact of posture and measures of urinary incontinence relating to two non-invasive real time ultrasound based tests. Using real-time ultrasound with transperineal and transabdominal approaches, we previously assessed pelvic floor muscle function in men and found the rapid response and sustained endurance tests possessed strong reliability in both supine and standing postures, and for both ultrasound approaches. However, questions remained pertaining to the relationship of the tests to other outcome variables, including measures of urinary incontinence. Participants (n=95) undergoing radical prostatectomy were assessed to determine the relationship between incontinence and pelvic floor muscle function, as seen on ultrasound. The presence and severity of incontinence was measured via 24-hour pad weight. When related to pad weight, the transabdominal protocol produced statistically significant correlations between the rapid response test in standing ($r=0.43$, $p<0.001$) and supine ($r=0.46$, $p<0.001$), and the sustained endurance test in standing ($r=-0.56$, $p<0.001$) and supine ($r=-0.56$, $p<0.001$). Similar results were found using the transperineal approach. All Bland-Altman analyses showed no significant difference ($p>0.05$) between the two postures, for either test or scan approach. While the plots also demonstrate no heteroscedasticity or proportional bias, with the bias being close to 0, the magnitude of variation in difference scores suggests different outcomes for tests performed in standing compared to supine postures. We present two simple tests that provide objective, non-invasive, and reproducible assessment of pelvic floor muscle function in men that relate to the clinical outcome of urinary leakage.

Key words: men’s health, real-time ultrasound, physiotherapy, urinary incontinence, prostate cancer, pelvic floor muscle

Introduction

Urinary incontinence (UI) is often associated with compromised function of the pelvic floor muscles (PFM) and while most studies regarding this association have involved women, there is a high prevalence of UI in men following radical prostatectomy (RP).[1,2] It is estimated that more than one million new cases of prostate cancer (PCa) are diagnosed annually, [3] and RP is considered the gold standard surgical approach to treatment. Current opinion states that strategies to enhance PFM function may improve continence outcomes in men who undergo RP. [4,5] However, researchers have been hampered by the lack of a reliable and practical test of PFM function in men. Our search strings for acquiring this evidence included Medline, PubMed, Google Scholar and Onesearch data bases, based on the the keywords listed.

Post-prostatectomy incontinence (PPI) is one of the most distressing side effects following RP treatment with up to 91% [6] of men reporting urinary leakage initially and 30-76% [7,8] continuing to experience it one year following RP. [7] Incontinence is mostly caused by damage to the internal urethral sphincter affecting autonomic function, coupled with an increased demand on the PFM following complete removal of the prostate. [1,9] Evidence currently supporting the benefits of PFM training in men [8,10] is inconclusive and this may be due to most PFM research (both assessment and treatment) being focused on female PFM dysfunction and translating knowledge across the sexes may be difficult, particularly in the implementation of rehabilitation strategies.

Men are typically continent in supine positions following RP. In contrast, upright posture and actions such as sitting and sit-to-stand cause increased intra-abdominal pressure that leads to stress urinary incontinence, [2,11] a problem also seen in women. [12] For men with PPI the condition can worsen as the amount of time in the upright position increases over a day, particularly in association with physical activities such as walking.[11] The existing evidence does not address these incontinence issues in recovery following RP and validation of a reliable test to meet clinical presentation may help bridge this gap.

The study reported here is of two objective, real-time ultrasound (RTUS) tests, using transabdominal (TrA) and transperineal (TrP) approach, of PFM function that are specific to sustained and rapid demands placed on the pelvic floor muscles. The sustained endurance test (SET) and rapid response test (RRT) of PFM function used in the current study are non-invasive and avoid the need for rectal assessment of the pelvic floor.[13] The aim was to determine the extent to which the SET and RRT tests may be posture dependent and whether they relate to clinical outcomes such as PPI. To determine the severity of urinary incontinence, 24-hour pad weight was assessed and compared to performance on the RRT and SET tests. We chose 24-hour pad weight as our criterion measure of PPI, since pad number can be influenced by the variety of pads used and individual differences in hygiene management. In addition, 24-hour weight has been described as the most reliable non-invasive method of quantifying the severity of urine leakage over longer time frames than the previously utilised 20-minute and 1-hour tests. [14,15] In 2012, Mungovan and colleagues determined that in men most PPI episodes occur in the upright posture, [11] and so we performed the dynamic tests of pelvic floor muscle function in supine and standing for comparison.

Methods

This study was approved by the University of Western Australia HREC (Ref RA/4/1/6265). Participants received written information about the study and provided written consent. Participants, were enlisted from a cohort referred sequentially by their urologist for pre-prostatectomy PFM training. Following surgery, participants were reviewed between two-weeks and six-months post urinary indwelling catheter removal and assessed in random order for the RRT and SET tests in both supine and standing postures.

For each measurement, a commercially available point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China) was used. To standardise bladder volume for the TrA approach, each participant voided their bladder and then drank 500 ml of water, 1 hour prior to testing and were instructed not to void. A full bladder is not required routinely for TrP assessments. To assess severity of incontinence, pad weight was calculated by the collection of continence pads across a 24-hour period, on the day testing was completed. [16,17] All participants wore pads and applied their first pad of the day with an empty bladder. All pads were placed in a single plastic bag and stored in a refrigerator to avoid evaporation. The net weight was calculated by deducting dry pad weight, using a single standardised digital scale. [11] Any positive net weight, recorded in grams (g), was deemed indicative of incontinence, with ‘zero’ weight assessed as no leakage and full continence.

Participants were assessed for PFM function in the crook lying position (supine) with a pillow underneath the head and hips and knees flexed at 60 degrees and with the lumbar spine positioned in neutral. They were also assessed when standing in the anatomical position (standing). Cues to relax abdominal muscles and avoid breath holding were also given. Verbal instruction was provided on correct PFM exercise technique, as per Stafford and colleague's 2016 study, [18] to ensure a full contraction and relaxation cycle was implemented with the cue given to "*stop the flow of urine and shorten the penis while continuing to breathe*". [18,19] Participants had one 'practice' contraction prior to the test, while in view of the screen, in order to provide feedback for both tester and participant, and to promote good technique.

For the RRT, participants were instructed to "*perform 10 maximal PFM contractions and relaxations as fast as possible*", with the elapsed time recorded as the outcome measure. In the SET participants were instructed to "*hold a maximal contraction for as long as possible, and continue to breathe*". The time to task failure was recorded (with a maximum time of 60 seconds), where task failure was defined as being the onset of descent of the bladder base (TrA approach) or bladder neck (TrP approach).

Transperineal RTUS assessments

Prior to the test using the TrP approach RTUS participants were invited to disrobe in private and to drape a towel around their waist, before reaching under and gently moving their genitals to one side with their hand. Standard infection control measures were observed. After applying a layer of transmission gel, TrP RTUS was performed by placing the covered probe on the perineum in the mid-sagittal location, midway between the base of the penis and the anus, with the transducer orientated to obtain sagittal images, after which the participant removed his hand. To optimise the images, the symphysis pubis was used as the bony reference point, with the urethra, bladder, bladder neck and anorectal angle visible simultaneously. [13] Using screen callipers, a measure of the position of the bladder neck was taken at rest ('x') and the change from this resting position in a vertical direction was observed. Any cranial movement of the bladder neck was interpreted as a correct action; whereas, no cranial movement or any caudal movement of the bladder neck was noted as an incorrect action, in accord with previous guidelines. [19] During SET assessments, an arrow was placed at the bladder neck as a visual marker to determine the elapsed time (seconds) at which task failure, defined as the moment of descent toward the resting position of the bladder neck (‘x’), was observed.

Transabdominal RTUS assessments

For tests using the TrA approach, ultrasound assessment was performed by placing the covered probe supra-pubically on the lower abdomen at a mid-sagittal location with the transducer probe orientated to obtain transverse images and angled in a caudal/posterior direction to achieve a clear image of the inferior-posterior aspect of the bladder. Standard infection control measures were observed and a layer of gel was placed over the head of the probe. Screen callipers were used to place a mark (‘x’) on the bladder base at rest where any elevation of the bladder base was interpreted as a correct action and any depression of the bladder base was noted as an incorrect action in accordance with previous guidelines [20,21] As per the TrP approach, during SET assessments, an arrow was placed at the bladder base as a visual marker to determine the elapsed time (seconds) at which task failure, defined as the moment of descent toward the resting position of the bladder base (‘x’), was observed. Any participant unable to perform the PFM contraction correctly (i.e. cranially versus caudally), was given the opportunity to rest and repeat the test.

Statistical analysis

Data for the SET and RRT tests and pad weight were entered into SPSS (v22.0, SPSS, Chicago, IL) for subsequent analysis and significance was accepted for all analyses at $p<0.05$. To determine whether two scores were related, we performed correlations. For example, the association between SET and RRT (in both standing and supine postures) versus pad weight scores was determined using Pearson’s correlation. For this paper we defined the strength of all correlations as follows: [22]

- $r = 0.25$-0.50 weak to moderate
- $r = 0.50$-0.75 moderate to good
- $r > 0.75$ good to excellent

To assess agreement, Bland-Altman analysis and plots were performed. For example, the level of agreement between tests performed in supine versus standing postures was assessed with a series of Bland-Altman plots for the SET and RRT tests created using both TrA and TrP RTUS.

Results

Participants in the study were 95 men, average age 63 years (range 52 to 74 years). All participants were in a healthy weight range (height 172.0±15.2 cm, body weight 72.9±16.9 kg, all Gleason 7).

Relationship between RTUS tests and pad weight

The range of pad weights, for the pads collected from all 95 subjects, was 0 to 98 g. Pad weight averaged 46.0 g (±52.2 g). Weak to moderate, though stistically significant correlations were evident between 24-hour pad weight and both the SET and the RRT scores in all combinations of posture and probe position. The relationship between pad weight and RRT tests via TrA RTUS performed in standing ($r = 0.43$, $p<0.001$) and supine ($r = 0.46$, $p<0.001$) were moderate and moderate to good for the SET in standing TrA ($r = -0.56$, $p<0.001$) and supine ($r = -0.56$, $p<0.001$). When the relationship between pad weight and pelvic floor function was assessed via TrP RTUS, RRT in standing ($r = 0.52$, $p<0.001$) and supine ($r = 0.51$, $p<0.001$) were moderate with similar results for SET via TrP in standing ($r = -0.58$, $p<0.001$) and supine ($r = -0.54$, $p<0.001$).

Supine versus standing measurements

The limits of agreement for each of the RRT and SET assessments, performed using TrP and TrA approaches in both standing and supine postures, are presented as Bland-Altman plots in Figure 1. The results for all analyses show no significant difference ($p>0.05$) between the two postures for RRT and SET tests using each RTUS scan approach. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference (bias) in scores between postures being close to 0 (RRT: TrA = -0.15 s, TrP = -.16 s; SET: TrA = 1.59 s, TrP = 1.26 s). However, the magnitude of variation in difference scores (an average 1.8 s for RRT and an average 9.5 s for SET) suggests different outcomes for tests performed in standing compared to supine postures, especially for the SET test.

Discussion

In this study we compared pelvic floor muscle function measured by SET and RRT scores with the severity of incontinence assessed using 24-hour pad weight. Moderate correlations were observed between RTUS assessments and this widely accepted clinical measure of continence. [23] Lower RRT times related to good pelvic floor muscle function and, therefore, mild incontinence. For example, a patient performing the RRT in 15 seconds, has more PPI (ie a higher pad weight) than one who performed the test in 7 seconds, with speed of contraction being the significant functional difference. An inverse relationship was noted for the SET tests, with lower scores relating to higher levels of incontinence. For example, a patient maintaining a 15-second contraction, had more PPI (higher pad weight) than one contracting for 45 seconds, with most who achieved 60 seconds having full continence. Similar results were obtained between supine and standing postures for both the RRT and SET outcomes. In the same way, TrA and TrP approaches to assessment were very similar for both tests. These findings provide evidence that the non-invasive measures we have introduced are clinically valid and reliable for assessing PFM function, as it may relate to urinary leakage in PPI.

Traditionally, assessments of PFM function are performed in the supine or lateral decubitus positions. [12] The purpose of performing tests in the standing posture in this study was to account for the clinical presentation of PPI, which is often gravity-dependent. [11] Our results suggest that posture does have an impact on PFM function, with some variation in scores noted for SET measured in supine versus standing. These findings suggest that increased skeletal muscle activation in upright postures may be associated with incontinence. RTUS testing can be performed using whichever posture is specific to individual patient symptomology; however, we would suggest default assessment in the standing position as this corresponds with the posture and loading conditions under which PPI typically occurs. [1,8,26] In addition, an individual's RRT and SET results can be used in a clinical setting to provide guidance to both the clinician and patient, for baseline assessment and training purposes.

While outcomes regarding the prediction of pad weight, based on RTUS tests, were moderate, they were not excellent (i.e. correlations of 0.75 or greater). This is perhaps not surprising, given that many factors other than PFM function can contribute to PPI and include surgical experience and operative approach, as well as associated damage to the internal urethral sphincter and the degree of nerve sparing. [9,24,25] We did not limit our recruitment according to these factors and it is conceivable that a study stratified by surgical outcome may have produced stronger associations.In addition, it is acknowledged that by utilising a cohort with variable time points between 2 weeks and 6 months post-RP this may impacted PFM capability. It may also be possible to further improve these correlations by refining the technical approaches we used. For example, our SET and RRT measures, while reproducible, [13] may be more sensitive if edge detection algorithms had been used to better detect movement of the bladder base. In an attempt to obtain ecological validity, we did not control for factors such as measurement time of day or 24-hour fluid intake; however, such controls may have enhanced the relationships we observed. Equally, while pad weight is an accepted and simple assessment of incontinence, it may be possible in future to correlate our functional outcomes with more recently adopted and sophisticated assessments, such as MRI-derived measures of membranous urethral length. [2]

In addition, although we did not use it in this study, the three day, 24-hour pad weight method introduced by Malik in 2016 may have provided more variability in pad weight scores, given ranges that may occur with physical activity levels in individuals over subsequent days. [16]

Conclusions

In post-radical prostatectomy patients the outcomes of our RRT and SET tests were associated with the severity of urinary incontinence. These tests can be used to design personalised treatment plans. Correlations performed between PFM tests and pad weight varied according to whether the SET and RRT tests were performed in standing versus supine, but not with respect to the TrP versus TrA approach. This indicates that factors specific to the individual patient, such as the presentation of gravity dependent PPI, or sensitivity regarding perineal assessment, can be taken into account when selecting the preferred test; although based on our experience, we suggest performing tests in the standing position. One advantage of the TrP approach for the very incontinent patient is the removal of the requirement to have a full bladder, compared with the TrA approach which requires bladder volume for optimal imaging. This further enhances our findings that either TrA to TrP are appropriate options, depending on patient presentation. In conclusion, our studies indicate that the RRT and SET tests are minimally-invasive, objective, highly reproducible and may, therefore, be useful in a clinical setting. They may also prove helpful to clinicians where repeated assessment is indicated to monitor PFM changes, for example to ascertain whether spontaneous recovery is impaired following surgery, or to introduce a treat-to-target approach to rehabilitation.

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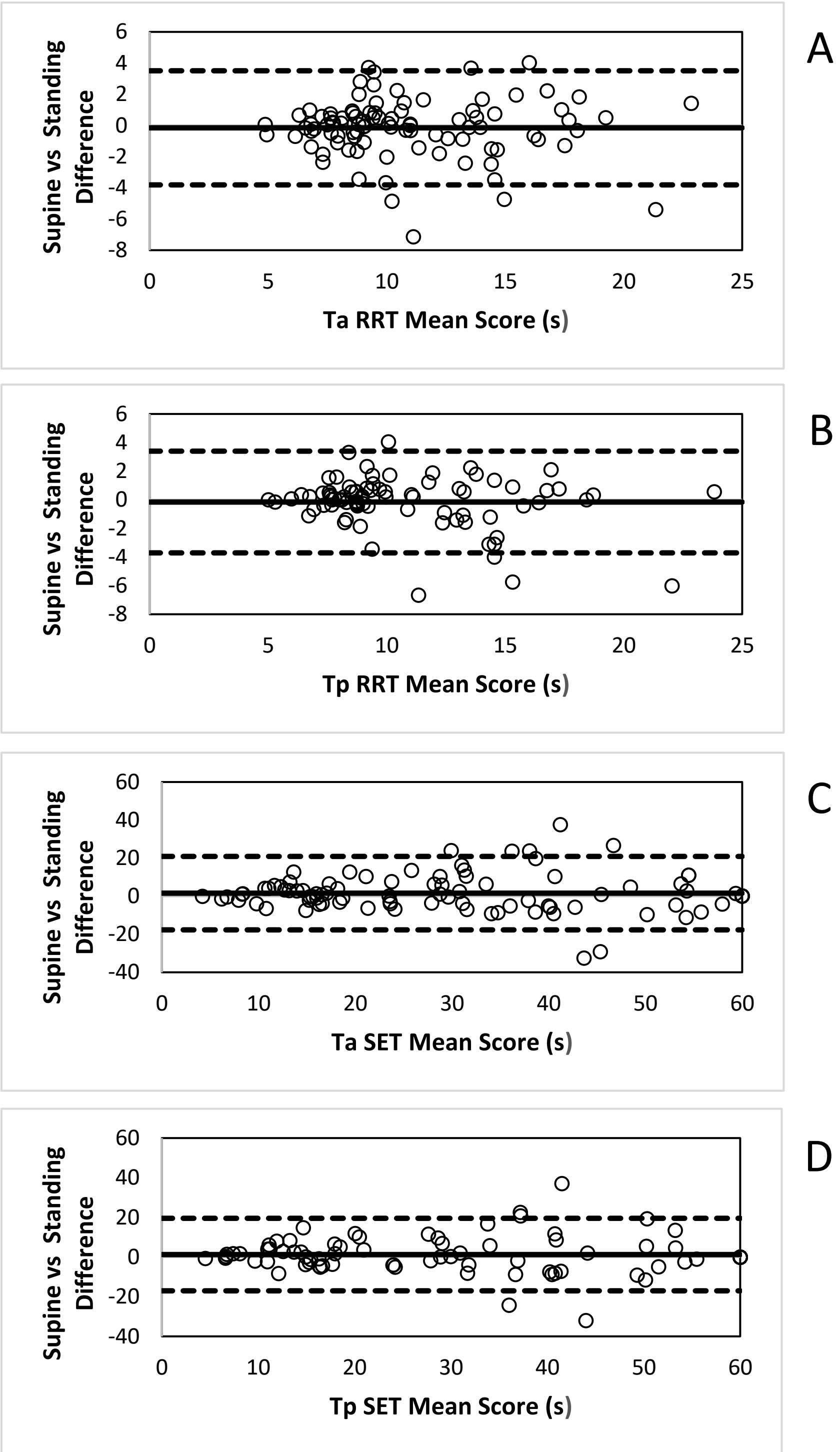
Figure 1. Bland-Altman plots presenting the limits of agreement for pelvic floor muscle function with tests conducted in the standing versus supine postures. The rapid response test (RRT) results are shown for transabdominal assessment in Panel A, and for transperoneal assessment in Panel B. The sustained endurance test (SET) results are shown for transabdominal assessment in Panel C, and for transperoneal assessment in Panel D.



CHAPTER 5

Part 2: Literature Review – Urinary Incontinence and the Pelvic Floor Muscles

Voluntary Activity of Pelvic Floor Muscles

Pelvic floor exercises have been used for decades for addressing stress urinary incontinence (SUI) in women. They were made popular by Dr Arnold Kegel in the 1950's who recommended them for enhancing PFM for urinary and sexual function following pregnancy and childbirth.[1] In 1926, Young and colleagues were the first urologists to recommend exercising the pelvic floor sphincter muscles in post-prostatectomy patients, with the instruction '*to cut off the flow of urine as long as possible*'.[2] Today, PFM exercises are defined as 'repetitive selective volitional contractions and relaxations of specific PFMs which necessitates muscle awareness in order to be sure that the correct muscles are being utilized and to avoid the unwanted contractions of adjacent muscle groups'[3] (Figure 5.1).

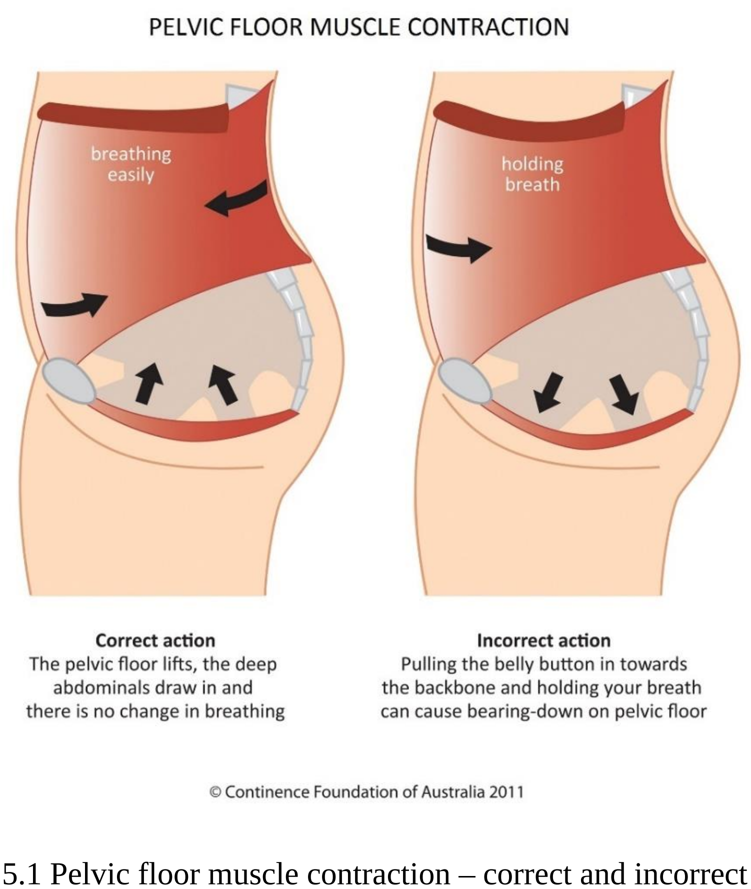


Figure 5.1 Pelvic floor muscle contraction – correct and incorrect actions (reproduced from *www.pelvicfloorfirst.org.au* 23.11.18)

To voluntarily activate a striated muscle, humans require the appropriate brain conceptualization of a particular movement pattern and this evolves through repeating executed commands.[4] Proprioception, the sense of position and movement, relies on specialized mechanoreceptors within muscle spindles and tendons which detect the contractile force. With repeated effort, these become new motor behaviours.[4] The PFM and sphincters, however, have limited sensory input mechanisms and so the brain is not well informed on their status.[4]

Recent advancements in functional MRI (fMRI) assessment of the brain are, however, increasing our knowledge of PFM activation, with confirmation that both the primary motor cortex (M1) and supplementary motor area (SMA) provide intermingled but independent neural representation to activate different PFM coordination (Figure 5.2).[5] Moreover, the results of Mohen *et al.* suggest that cortical control of the PFM overlaps with the cortical representation controlling synergistic muscles such as the gluteus maximus muscle (GMM). This supports earlier research by Asavaspon *et al.* who were the first to use electromyographic recordings to demonstrate that PFMs activate synergistically during voluntary activation of GMM, but not during voluntary activation of finger muscles.[6] Furthermore, the role of neuromotor connectivity in PFM resting states in men with chronic prostatitis/chronic pelvic pain syndrome (CPPS) was investigated by Kutch *et al.* who also observed functional connectivity between the motor cortex and pelvic-motor function of PFM in men with chronic pain versus healthy male controls.[7] Significantly, these studies were conducted in men with assessments based upon wide acceptance of PFM contribution to continence and pelvic stability ,[8] in contrast to many previous studies that investigated this issue in women.[9,10]

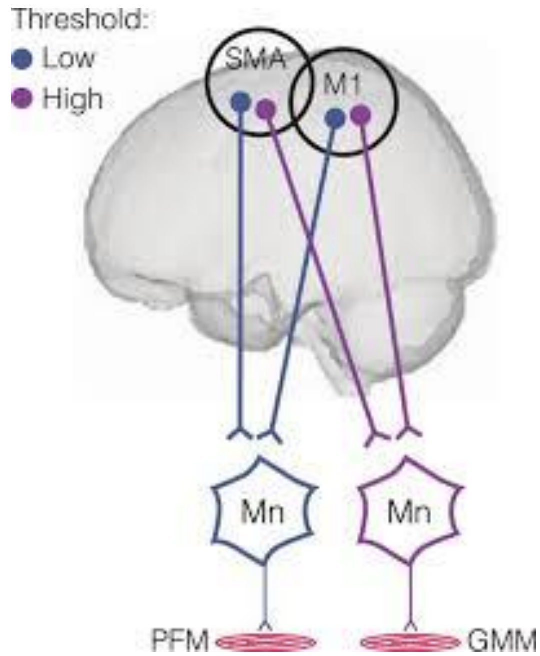


Figure 5.2 Pelvic floor muscles (PFM) and gluteus maximus muscle (GMM) represented in the primary motor cortex (M1) and supplementary motor area (SMA) (reproduced from *www.nature.com* 21.11.18).

Correct Pelvic Floor Muscle Activation

Correct PFM activation requires individuals to perform two components: 1) to squeeze around the pelvic openings and; 2) to perform an inward lift in a cranial direction.[1] Common errors in attempts to contract the PFM include contraction of the abdominal, adductor and gluteal muscles; failure to breathe during contraction; and straining or bearing down.[11,12] Explanations for this may be that the PFM are internal and difficult to visualize, that PFM contraction in both sexes is a learned function, and that most individuals are unaware of automatic contractions during actions such as in coughing or sneezing.[4] To ensure correct skill acquisition, four principal teaching tools can be used to facilitate learning; verbal instruction, visual input, direct physical input and environmental conditions.[13] In men, specific instructions to '*stop the flow of urine*' and '*shorten the penis*'[14,15] by feeling the scrotum and testicles rise have recently clarified the task. The recent development of RTUS to directly visualize the PFM via either TrP or TrA approaches (Figure 5.3 and 5.4) have improved patient awareness and enabled sophisticated teaching options for clinical education.[15-17]

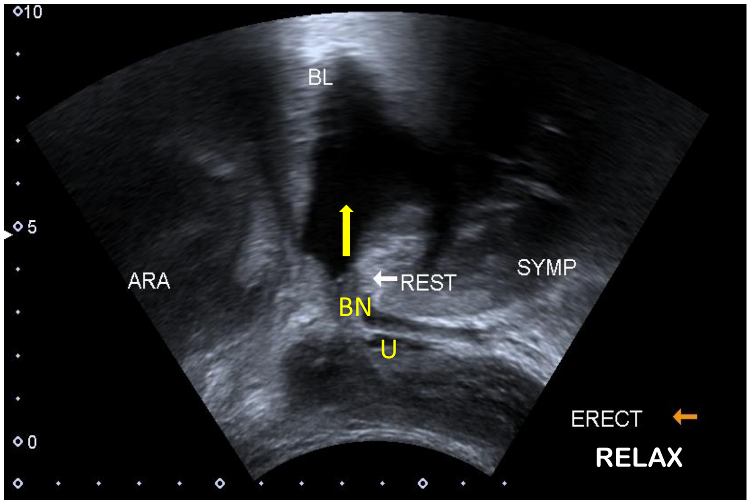


Figure 5.3 TransPerineal RTUS (author's image)

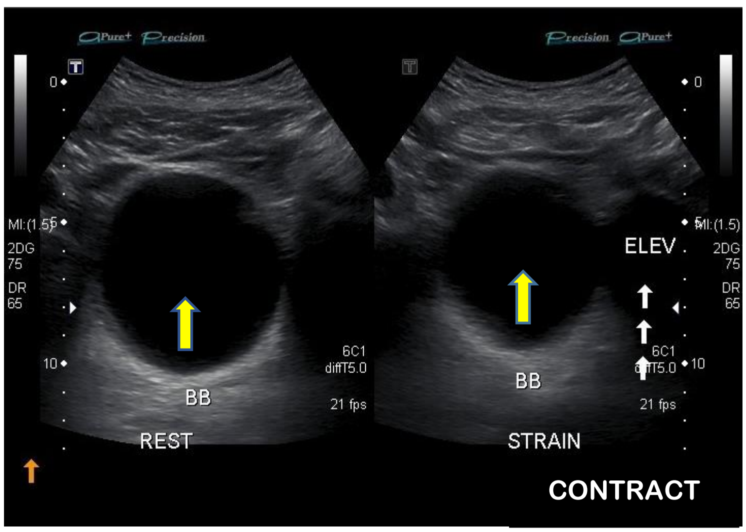


Figure 5.4 Transabdominal RTUS (author's image)

Training the Pelvic Floor: Indication in Radical Prostatectomy

The PFM are regular skeletal muscles and, therefore, adapt to strength and resistance training in the same way as any other skeletal muscle. The aims of exercise training are: 1) to change the muscle structure morphologically by increasing the cross sectional area; 2) to improve neurological factors by increasing the number of activated motor neurons and their frequency of excitation and; 3) to improve muscle tone.[18] The theoretical rationale for exercise training of the PFM is that exercise training may build up the structural support of the pelvis via hypertrophy, elevated positioning and increased tone of the levatore plate, thereby enhancing the stiffness of the pelvic floor.[4] This should, in turn, facilitate a more effective co-contraction of the PFM and prevent descent during increases in abdominal pressure, which is particularly relevant in men following prostatectomy, especially in upright postures.[19]

During RP, removal of the prostate gland causes sphincteral damage and descent of the detrusor (bladder) muscle, reducing structural support; the combination of which usually results in pelvic floor dysfunction of varying severity.[4] PPI can be classified as either stress urinary incontinence (SUI), urge urinary incontinence (UUI) or post-void dribble (PVD). Evidence has shown that these embarrassing conditions may be treated successfully with pre-operative and post-operative pelvic floor exercises, which include 'the knack' (ie pre-contracting the PFM at the moment of expected leakage),[19] urge suppression, fluid advice and a post-void contraction for PVD.[20] SUI is the major side effect of RP and so PFM training and the ‘knack’ maneuver have been recommended for women to preempt cough-related incontinence (Figure 5.5).[21,22] As seen clinically, however, male UI is different to that experienced by females, with men both unaccustomed and unaware of the need to utilize PFMs during urinary continence control, given the inherent autonomic function of the prostate and associated smooth muscle. Indeed as seen in practice, very few men attending their pre-operative physiotherapy consultation for RP have any knowledge that they even possess a pelvic floor.

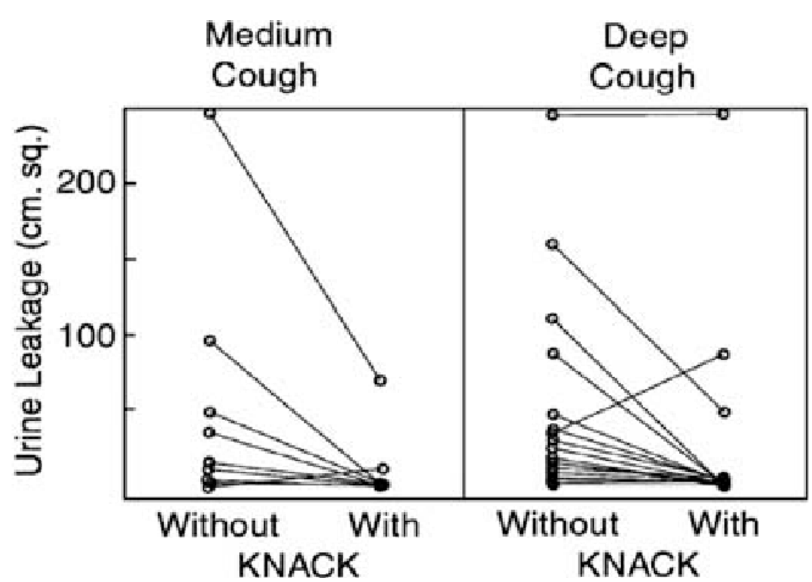


Figure 5.5 Urinary incontinence and performing ‘The Knack’ with cough.
(Reproduced from *www.gastrojournal.org* 21.11.18)

Current Pelvic Floor Muscle Training Recommendations in Radical Prostatectomy

With the increase in PCa detection and treatment options, techniques to address the QoL side effects of UI and ED have been the focus of physiotherapy studies since the late 1990's.[23,24] RCTs investigating the impact of PFM training have provided conflicting evidence, with some advocating the benefits of pre-operative exercise prescription[25,26] to reduce post-operative UI, whilst others such as the most recent Cochrane Review were unable to recommend PFM training as a first line rehabilitation approach, citing that 'men's symptoms improved over time irrespective of management'.[27] This lack of consensus most likely stems from variability in assessment of the PFM and the type and mode of delivery of PFM training. There are currently no standard protocols for PFM training post RP,[28] with most programs adapted from female interventions for SUI following pregnancy or pelvic organ prolapse. This thesis aimed to address this deficiency, by analysis of 97 men undergoing RP (see Chapter 8. Of primary focus was the opportunity to lessen the burden of PPI in both severity and duration, with early return to continence acknowledged as a major QoL outcome).

Motivation for Better Outcomes Following Radical Prostatectomy

Inspiration for a more effective protocol for men was drawn from the 3000$^+$ RP cases evaluated by the author. Early in the clinical experience, similar and persisting presentations of PPI in almost every patient became too commonplace to ignore. The typical patient presented with minimal UI in supine and sitting postures that worsened with any exertion, change in position, increase in intra-abdominal pressure or functional activity that involved strength or endurance. This included actions such as bending, lifting, coughing, rising from sit to stand, prolonged standing, walking, using stairs, jogging, hill walking, and gardening. In particular, most patients reported that UI occurred minimally in the early part of the day but continued to worsen with increasing hours spent in upright posture. Men frequently reported increased frequency, urgency and SUI over the day that was often improved by a period of daytime rest in a supine position. The most common period of leakage described was late afternoon, with the hours of 3-6pm often reported as the 'worst part of the day'. These patterns continued to guide the pathway of recovery in a clinical setting, with the author identifying PFM fatigue as perhaps the most significant, yet under-reported symptom, and seemingly common to each man undergoing RP.

Early research when evaluating this phenomenon revealed the plight of Peter Dornan, Australian Sports Physiotherapist, who himself had undergone a RP in 1993, causing him to endure PPI for 7 years. After a more aggressive approach to rehabilitation over a 6-month period, involving a combination of fast and slow twitch PFM fibre activation in functional postures, Peter was able to achieve complete resolution of his urinary leakage. Upon achieving this, Dornan decided to test his theory by climbing Mt Kilimanjaro, Africa in 2003, and was able to maintain full continence, free of pad use. Subsequently, his book 'Conquering Incontinence' was written and published as the first text for others to follow in the search for a male-focused application to PFM training. [29] Drawing from both Dornan's innovative approach and the author's subsequent clinical experience, the search for the most appropriate PFM training protocols for men undergoing RP was ignited.

Pre-Operative Pelvic Floor Muscle Training for Urinary Incontinence

In recent years, it has been hypothesized that the severity of incontinence and the time to continence are not predictable pre-operatively. [30] Hence, it makes sense to teach all men the new motor skill of correct PFM activation before surgery. [31] This enables patients to train these muscles and use them in a functional way. [26] Some authors have suggested that teaching PFM exercises pre-operatively will help the patient to understand the aims of the exercises and learn how to activate the muscles before there is any surgical damage or pain.[25] UI is most severe in the early postoperative phase and for some patients, persists for several months (and years) following RP, leading to impacts such as increased risk of depression [32] and poor QoL outcomes. [33] Physiotherapy, in the form of PFM training, commenced preoperatively, may improve the capacity to increase urethral closure during stress episodes and lessen the burden of PPI. To assess its effectiveness, Nahon's 2014 review of the literature [34] indicated that, of nine studies eligible for analysis, five had a positive effect for pre-operative PFM training, by hastening the recovery of continence post-operatively. [26,35-38] Two additional studies found that adding biofeedback to the PFM training did not change the rate of continence recovery. And two other studies compared PFM training with or without electrical stimulation, and found that the groups did not differ in their time to continence. [39,40] Within these studies, however, the amount of PFM training before surgery varied from 1-10 sessions, with variable combinations of sets per day and exercise postures. For example Bale's PFM training protocol included 10-15 contractions of 5-10 sec holds, four sets per day to a total of 40-60 contractions per day. [24] This differed markedly from Van Kampen's 90 contractions per day, with a combination of 40 contractions of 1 sec and 50 contractions of 10 sec in supine, sitting or standing. [41] Inconsistencies in PFM training protocols between studies only adds to the difficulty of recommending an optimal regime.

A subsequent meta-analysis of pre-operative PFM training by Wang et al. reviewed five RCTs [42] and concluded that additional preoperative PFM training did not improve the resolution of PPI after RP at early (<3 month), interim (6 month) or late (1 year) recovery time points. However, the results for time to continence and QoL were inconclusive because of insufficient data, with more robust RCTs recommended for evaluating the effectiveness of early PFM training. [42] In support of this, when reviewing both the PFM training protocol and outcomes measures in all the studies, once again, great variation exists between the number of pelvic floor contractions performed, positions undertaken, duration of holds, sets per day and the key measure of continence (including self-report questionnaires, number of pads, and 1- and 24-hour pad weight measures). More recent reviews in 2016 [43] and 2017 [44] also point out that many different PFM training strategies have been utilized with uncertainty around specific therapeutic management outcomes, making recommendations for rehabilitation protocols challenging. Therefore, specific protocols for men undergoing RP remain elusive. [27]

Further difficulties regarding interpretation of results also arise due to the confluence of factors that may affect continence from variable surgical technique, [44] however, it is generally concluded that pre-operative PFM training aims to shorten the duration of post-operative UI. Since it causes no harm, PFM training should be introduced in the pre-operative period. [45] Of significance is the 2014 investigation by Ocampo-Trujillo which evaluated the efficacy of 4 weeks pre-operative PFM training on histomorphometry, muscle function, UI and QoL versus a group who received general education only. [46] After the intervention, participants had an increased cross-sectional area of the muscle fibres of the EUS, higher pressure contraction of the levator ani, and continence rates of 62% at catheter removal versus 37% in the non-training group. [46] These results provided new evidence regarding the benefits of pre-operative PFM training and likelihood of an earlier return to continence.

Finally, in the most recent systematic review of pre-RP PFM training, Goonewardene et al. concluded that 'it would be prudent for all men to exercise their pelvic floor muscles to maintain normal pelvic floor function and start prior to surgery'. [47] Databases were screened from 2000 to September 2017 and included the following: CINAHL, MEDLINE (NHS Evidence), Cochrane, AMed, EMBASE, PsychINFO, SCOPUS and Web of Science. In the final analysis, the impact of pre-operative PFM training on outcomes for patients undergoing RP revealed that 'strengthening the PFM significantly improved post-prostatectomy UI, post-micturition dribble and erectile function.' [47]

Post-Operative Pelvic Floor Muscle Training

As UI impacts a significant proportion of RP patients from the immediate post-operative period and often beyond 12 months, minimizing the impact on individuals and their partners or reducing the time taken to achieve continence is an important objective. PFM training has been extensively explored in the literature as an important, non-invasive component of management of PPI. In landmark studies by Van Kampen [41] and Filocamo 2005, [30] continence was achieved earlier and was less severe in patients who had stronger and "less fatigueable" muscles with early supportive PFM training programs found to be highly beneficial. Positive outcomes achieved by Van Kampen *et al.* in men who performed PFM training, versus a control group who did not, revealed 88% continence at 3 months versus 56% in the controls. Similarly, in Filocamo *et al.* 19% of the intervention group of 300 RP patients achieved continence at 1-month post-RP and 95% at 6 months, versus a control group who only achieved 8% continence at 1 month and 65% at 6 months post-RP. Although it was found that 93% of men achieved urinary control by 12 months regardless of training, the authors suggested that PFM training should be included in the postoperative care as soon as practicable to reduce both the degree and duration of PPI. [30]

In looking at longer term outcomes, investigators [48] demonstrated that those who received ongoing physiotherapy-guided PFM training had improved continence outcomes at 1 year post-RP of 92% compared to 72% for the group who training independently. Two further trials showed that PFM training with biofeedback was significantly more effective after RP than no treatment or sham treatment in the post-operative period. [36,49] No additional positive effect was noted in five trials that added biofeedback or electrical stimulation in addition to PFM training alone. [24,50,51-53] In contrast, Ribeiro's 2010 RCT investigated 54 men over 12 months following RP, comparing PFM training plus EMG biofeedback to a control group who received only verbal instructions from their urologists. Most of the intervention group (96%) were found to be continent at 1 year compared to 75% of the control group.[31]

No significant differences were found in median time to continence between two patient groups investigated by Geraerts *et al.*, when pre- and post-operative PFM training was compared to post-operative training only. [54] The large Males after Prostate Surgery (MAPS) trial by Gleasner *et al.* provided PFM training at 6 weeks post-operatively to incontinent men utilizing either formal, individualized training by a continence therapist over 3 months, versus a control group who received standard care and lifestyle advice only.[55] The intervention group protocol consisted of three strong PFM contractions holding for as long as possible to a maximum of 10 s, twice per day in three positions – supine, sitting or standing. [56] The control group received 'standard care' with some centres providing a patient information leaflet on PFM exercises, while others gave no information on PFM training. [56] In the final analysis, 76% of the intervention group and 77% of the control group remained incontinent at 12 months post-RP, with conclusions drawn that physiotherapy was unlikely to be effective for incontinent men after RP surgery. [55]

Many have been critical of the MAPS methodology and, in particular, the lack of precise instruction for 'flow stopping' of the SUS, versus instructions to '*contract the pelvic floor as if holding onto wind*'. [57] As mentioned previously (see Figure 5.1), this approach favours anal dominance of the PFM and provides inappropriate sensory feedback, reinforcing incorrect motor control. The recent development of RTUS to visualize the PFM via either TrA or TrP approaches, has enhanced both patient and clinician awareness, enabling sophisticated teaching options for clinical education via visual feedback. [15-17] In addition to measuring bladder neck elevation, [58] TrP RTUS visually demonstrates the posterior kinking of the SUS that contributes to urethral closure, and provides simultaneous visualization of all three striated muscles (the SUS, the bulbocavernosous and the puborectalis) that control male urinary continence. [59,60,61] With emphasis on the anterior structures involved in the male continence mechanism, patients can visualize correct technique immediately and be guided if anal dominance is occurring (Figure 5.5).

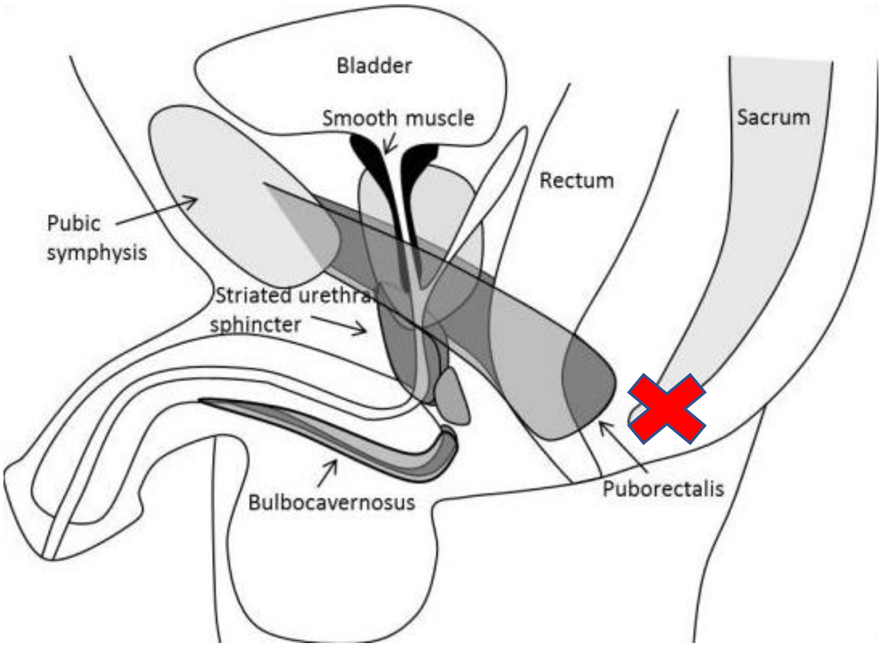


Figure 5.5 Striated pelvic floor muscles for achieving continence in men (*reproduced from Stafford (ref no) with approval*). Note: anal dominance 'x' is no longer recommended for control of urinary incontinence.

Further criticism of the MAPS study arose regarding the assessment of continence, since a pad weight was not employed. [57] Instead of using this objective measure, [62] Glazener *et al.* defined UI as any positive response to one of two questions on the International Consultation on Incontinence Questionnaire (Urinary Incontinence short form). As this questionnaire is not gender-specific and encompasses all types of UI, it is not thought to be clinically meaningful during follow up. [63] Furthermore, the study recruited only men who had UI at 'about 6 weeks' after RP, indicating that baseline parameters were likely to be highly variable. [56]

More recent trials have included the addition of synergistic training of abdominal, hip and PFM to assess the influence of co-activation of musculature to improve post-prostatectomy UI, [64] with parallels to the original protocols developed by Dornan. [29] Park *et al.*, for example, investigated outcomes for 49 patients allocated to a combined exercise intervention group (resistance, flexibility, and Kegel exercises twice a week for 12 weeks) or a control group that received only three sets per day of Kegel exercises for the same length of time. [65] Apart from grip strength, all physical functions were better in the exercise group than in the control group. Significantly, the 24-hour pad weight results at the conclusion of the trial (12.2g in the exercise group, 46.2g in the control group) and continence rate (73.1% in the exercise group, 43.5% in the control group) indicated UI recovered more promptly for the exercise group patients. Many of the exercises within Park's intervention group, such as abdominal crunches on a therapy ball, incorporated co-activation of the PFM and core muscles. [65]

The relationship of the PFM in core stability, provided the basis to landmark work by Sapsford and Hodges, whereby deep abdominal muscle co-activation was observed to be working together with PFM during functional activity, providing evidence that specific abdominal exercises activate the PFM (Figure 5.6). [8] Pedriali [64] assessed 85 men post-RP to verify the efficacy of a Pilates exercise program (in combination with three sets of daily PFM exercises) compared to a conventional PFM exercise only group and a control (no PFM exercise) group. Pedriali's results demonstrated that the Pilates exercise program was as effective as conventional PFM exercise in advancing continence recovery; they reported a higher number of fully continent patients when compared to the control group in the short-term. [64]

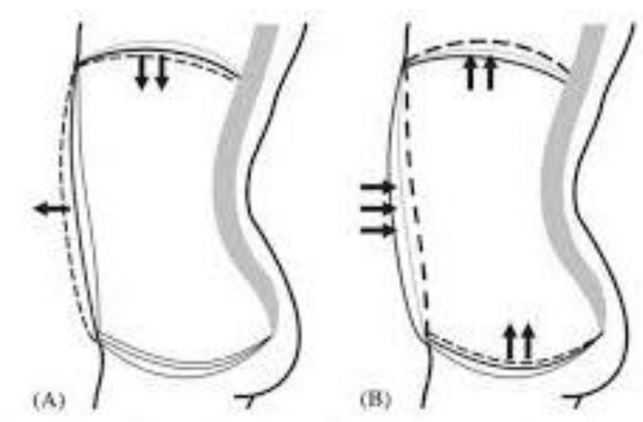


Figure 5.6 Synergistic pelvic floor (PFM), diaphragm and abdominal muscle action during coughing (reproduced from *www.slideshare.com* 24.11.18). A: Inspiratory effort before a cough requires rapid diaphragmatic descent, and the abdomen often moves further forward. B: With coughing, the abdomen pulls in hard, PFM are contracted strongly and the diaphragm is forced higher.

Further development of this concept was detailed in a pilot study of conventional versus advanced pelvic floor exercises to treat UI after RP. Santa Mina *et al.* [66] trialed two novel approaches, described by the authors as 'Pfilates' and 'Hypopressives', that aimed to co-activate the under-utilized regional muscles of the transversus abdominus, rectus abdominus and diaphragm that normally contract with the pelvic floor. [66] The authors hypothesized that, due to the efficacy of conventional exercises in the treatment of post-RP being modest, a more comprehensive strengthening of the PFM with its surrounding structures simultaneously co-contracting may prove to be an effective alternative. [66] To date, however, the study outcomes have not been published.

Considerations Pertaining to the PFM Training Prescription

<u>Strength training</u>

Increased muscle force can be generated by recruiting more motor units and increasing motor unit firing rate. [4] In practical terms, when an individual attempts to perform a maximal voluntary contraction, all available motor units are activated. [67] Kraemer *et al.* [68] suggested that untrained individuals are not able to voluntarily recruit the highest threshold motor units. This is particularly relevant when training PFMs, as very few people are aware of this muscle group. PPI is likely to occur post-RP as men may never have performed a maximal contraction in isolation, so they need time and training to develop this neuromuscular adaptation. [4]

After approximately 8 weeks of regular muscle training, muscle hypertrophy becomes the predominant factor in strength increase, [69] however, neural adaptation occurs earlier. Further strength gains require greater loading in a progressive manner. Loads greater than 80-85% of one repetition maximum (1RM) are needed to produce further neural adaptations during advanced resistance training. Strength, power and hypertrophy will only be maximized when the maximal numbers of motor units are recruited. [68] We hypothesize that the PFM are no different to other skeletal muscles in this respect and this formed our study intervention.

Research undertaken by Ocampo-Trujillo [46] evaluated the effect of pre-operative PFM training on histomorphometry and muscle function compared to a control group who did no training. The author reported an increase in cross-sectional area of the EUS muscle fibres and higher pressure contraction of the levator ani. Furthermore, in physiological studies designed for strength training, it is recognized that maximal force generation is achieved by performing three to four sets of 8-12 repetitions per day, resulting in increases in hypertrophy within type IIa muscle fibres on biopsy testing. [70] In the context of PFM training in men, however, with the removal of a whole organ following RP, exercise training for functional change may require more intensive approaches. That is, to target both fast and slow twitch fibre training, the number of sets, positioning and type of exercise may need a more bespoke approach.

Endurance training

Local muscle endurance is described as either the number of repetitions conduced or the duration of sustaining a contraction. The number of repetitions performed is inversely proportional to the percentage of 1RM (or intensity) at which the exercise is performed and varies with training, sex and amount of muscle mass needed to perform the exercise. [71] Fatigue is a necessary component of local muscle endurance training [68] and increases in maximal strength usually improve local muscle endurance, while endurance training does not improve muscle strength. [68] Training to increase muscle endurance requires the performance of a high number of repetitions and minimizing recovery time between sets. To substantiate this, greater increases in cross-sectional area and strength were noted by Kraemer *et al.* when exercise training was performed twice versus once per day. [68] In PFM training studies to date, much variability exists in the prescription for endurance gain, with recommendations to hold either sub-maximally, [56] or to sustain PFM contractions to maximal effort. [72]

Hypertrophy

One of the most prominent adaptations to strength training is skeletal muscle enlargement and this is primarily due to an increase in size of the individual muscle fibre which can be measured by cross-sectional area. [69] Although muscle fibre hypertrophy has been found in both type I (slow twitch) and type II (fast twitch) fibres, most studies have shown greater hypertrophy in type II and type IIa fibres. [73] Type II fibres also display a specialized reflex function which compresses the urethral wall during straining when a quick contraction is needed, such as during coughing. In one study, perineal contraction during coughing produced a pressure increase within the urethra of 10-20 mmHg, while voluntary contraction resulted in a similar increase of ~20 mmHg. [74]

In general terms, greater hypertrophy has been shown with high-volume, compared to low-volume, exercise programs (i.e. two versus one session per day). [68] With the initiation of a strength training regime, increased protein synthesis leads to changes in muscle fibres within 48 hours, however, a longer time frame (>8 weeks) is required to demonstrate significant hypertrophy. In most training studies, increase in muscle fibre cross-sectional area ranges from 20-40%. [69] This finding was supported in an uncontrolled PFM trial by Bernstein, who reported an increase in levator ani thickness of 7.6% at rest and 9.3% during contraction. [75] This was further supported by Ocampo-Trujillo's findings when assessing pre-operative PFM training to assist the urethral closing mechanism post-RP for the control of PPI (Figure 5.6). [46]

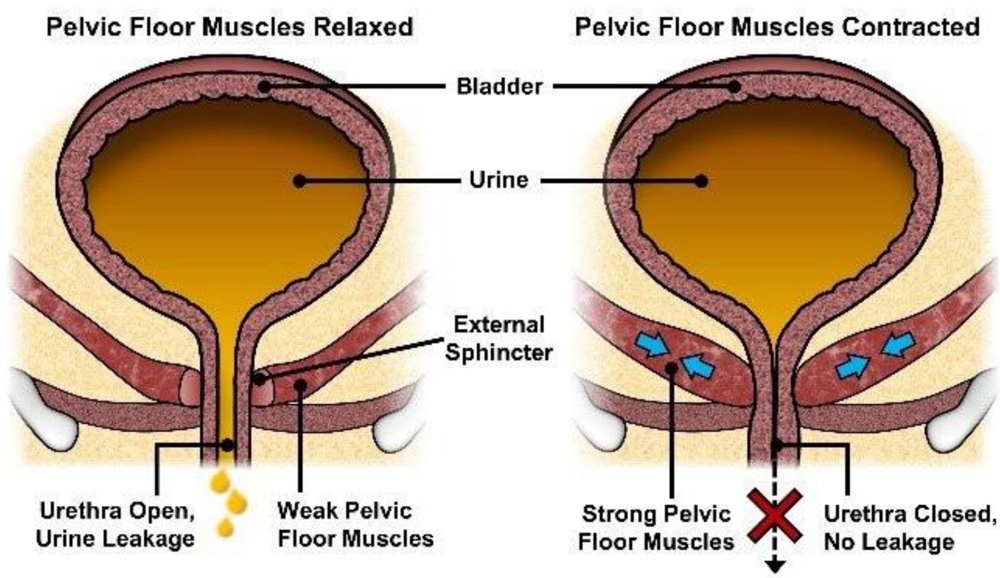


Figure 5.8 Weak versus strong pelvic floor muscles in the urethral closing mechanism, and the relationship to hypertrophy (reproduced from *www.vibrance.com.ny* 23.11.18)

<u>Dosage</u>

MRI studies have shown that although PFM action is both a concentric and isometric muscle action, movement of the coccyx during contraction is so minimal that the isometric component is considered quite large. [76,77] Holding times of 3-10 sec are currently recommended for the PFM, with 6 sec being the suggested timeframe required to reach maximal contraction. [69] In systematic reviews conducted by McDonald in 2007 and Anderson in 2015, however, there was little parity between recommended PFM doses. Frequency, volume, intensity, mode, position and duration of training regimes all widely differ among reviewed studies, and most likely account for the variability in outcomes.

Potential for improvement

In further work by Kraemer and Ratamess, the initial training status of the individual was shown to greatly affect rates of improvement, with trained individuals providing much slower rates than untrained individuals. [68] In their literature review of training effects over 4 weeks to 2 years, muscle strength was shown to improve 40% in untrained individuals, 20% in moderately trained individuals, 16% in trained individuals, 10% in advanced subjects and just 2% in the elite athlete. [68] In the only study investigating the development of PFM strength, a 100% improvement was demonstrated after 1 month of PFM exercise, possibly explained by the PFM being a totally untrained muscle with huge potential for improvement. [4] This has ramifications for the training and recruitment of PFM in men pre-RP. Given that PFMs have a role in reducing both UI and ED, the opportunity to develop specific programs that could enhance post-operative outcomes for both forms the basis of this thesis.

Summary

With clinical experience of 1000's of men undergoing RP, it is the author's appreciation that every individual presents with a unique set of characteristics with regard to urinary and PFM function prior to surgery. When given the opportunity to commence PFM training prior to RP, the author noted a more rapid improvement for those who received pre-operative exercise compared to those who did not. With the aim of developing exercise training protocols specific to the PFM dysfunction seen in men post-RP, it was hypothesized that prehabilitation would form a critical component in improving continence outcomes. Thus, although two groups of patients were analysed in subsequent studies, all received PFM training regimes that were either 'usual care' or 'high intensity' programs pre-operatively.

Furthermore, given the evidence base is still evolving and does not currently support the recommendation of PFM training for PPI, new intervention protocols – designed to address specific clinical presentations seen in most men post-RP – were needed. In particular, the realization that most leakage occurs in upright postures was pivotal in the design of Study 3. Novel approaches to PFM training, based on physiological function, with a focus on activating fast and slow twitch muscle fibres, and performed in the standing only versus 'usual care' postures, were introduced. We hypothesized that the 'high intensity' training methods commenced pre-operatively, would improve pelvic floor muscle function, reduce PPI and improve QoL, when compared to a control group who undertook 'usual care' exercises.

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CHAPTER 6

Paper 3:

Pelvic floor muscle training in radical prostatectomy: A randomized controlled trial of the impacts on pelvic floor muscle function and urinary incontinence.

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Abstract

Purpose: Pelvic floor muscle training (PFM) training for post-prostatectomy incontinence (PPI) is an important rehabilitative approach, but the evidence base is still evolving. We developed a novel PFM training program focussed on activating fast and slow twitch muscle fibres. We hypothesised that this training, which commenced pre-operatively, would improve PFM function and reduce PPI, when compared to a control group.

Methods: This randomised trial allocated 97 men (63±7 y, BMI=25.4, Gleason 7) undergoing radical prostatectomy (RP) to either a control group (n=47) performing low-volume rehabilitation, or an intervention group (n=50). Both interventions commenced 5 wks prior to surgery and continued for 12 wks post-RP. Participants were assessed pre-operatively and at 2, 6 and 12 wks post-RP using 24 hr pad weights, International Prostate Symptom Score (IPSS), Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) and real time ultrasound (RTUS) measurements of PFM function.

Results: Following RP, participants in the control group demonstrated a slower return to continence and experienced significantly more leakage ($p<0.05$), measured by 24 hr pad weight, compared to the intervention group, suggesting an impact of the prehabilitation protocol. PFM function measures were enhanced following RP in the intervention group. Secondary measures (IPSS, EPIC-CP and RTUS PFM function tests) demonstrated improvement across all time points, with the intervention group displaying consistently lower 'bothersome' scores.

Conclusions: A pelvic floor muscle exercise program commenced prior to prostate surgery enhanced post-surgical measures of pelvic floor muscle function, reduced PPI and improved QoL outcomes related to incontinence.

Trial Registration: The trial was registered in the Australia New Zealand Clinical Trials Registry and allocated as ACTRN12617001400358. The trial was registered on 4/10/2017 and this was a retrospective registration.

Keywords: Pelvic Floor Muscle, Prostatectomy, Men's Health, Urinary Incontinence, Quality of life

List of Abbreviations:

PCa- Prostate Cancer

RP – Radical Prostatectomy

SUI- Stress Urinary Incontinence

UI- Urinary Incontinence

PFM- Pelvic floor muscle

QoL- Quality of life

RALP- Robotic Assisted Laparoscopic Prostatectomy

RTUS – Real Time Ultrasound

IPSS – International Prostate Symptom Score

EPIC-CP – Expanded Prostate Cancer Index Composite for Clinical Practice

RRT- Rapid Response Test

SET- Sustained Endurance Test

BMI- Body Mass Index

Background

Prostate cancer (PCa) is the most commonly diagnosed cancer in men [1].Radical prostatectomy (RP) is highly effective, with 97% of patients surviving at least 5 years following surgery [2]. However, side effects can be severe and distressing [3,4]. Stress urinary incontinence (SUI) is the most common presentation following RP and is provoked by activities such as sneezing, coughing, bending, lifting, positional change and exercise [5]. The current gold standard approach to the assessment of UI (urinary incontinence) involves collection of 24-hour pad weight scores ('mild' <100 g, 'moderate' 100-400 g, 'severe' >400 g) [6]. Anxiety and post-traumatic stress are associated with the combination of PCa diagnosis, the need for surgery and resultant UI,[7] with depression occurring four times more often in men with PCa than their healthy counterparts [8].

Randomized controlled trials have investigated the impact of pelvic floor muscle (PFM) training on post prostatectomy UI, providing conflicting evidence. Whilst some support the benefits of exercise [9] other studies (summarized in the recent Cochrane Review [10]) do not recommend PFM training as first line rehabilitation, suggesting that UI symptoms improve over time, irrespective of management. The disparity in these findings likely stems from variability in the type of assessment performed, instructions given to subjects, and mode of delivery of PFM training [11]. Protocols that include pre-operative PFM training that continues post-surgery, and that specifically target fast- and slow-twitch muscle training performed in the clinically relevant standing posture, have not been previously been undertaken. Our primary focus was to lessen the burden of post-prostatectomy UI, since early return to continence has been widely acknowledged as a major quality of life (QoL) outcome [3]. We hypothesized that a significant difference in UI would be observed 2, 6 and 12 weeks post-surgery, when RP patients were randomized to either a PFM training intervention, or a control group.

Methods

Participants were enlisted from a cohort referred sequentially by their Urologist for pre-prostatectomy PFM training to a single physiotherapy clinic, in line with standard procedure; no patient had surgery delayed as a result of enrolment in this study. Sequential '1:1' randomization was performed as each participant attended a high volume physiotherapy clinic following diagnosis of PCa. Subjects were allocated to either a ‘usual care’ or ‘intervention’ group based on the date of initial attendance and receipt of sequentially numbered pre-set information folders (generated by one of the authors). Once consent was provided, enrolment and the randomized intervention commenced without delay. Relevant notes were recorded in participant medical files, which were collated over the trial duration, with results subsequently analysed by a blinded, independent statistician.

Patients with pre-existing UI, prior prostate surgery, or a history of receiving radiation or androgen deprivation therapy, were excluded. Both open RP (Control 8, Intervention 5) and Robotic–Assisted Laparoscopic Prostatectomy (RALP) (Control 39, Intervention 45) surgical types, performed by highly experienced surgeons operating at two high volume institutions, were included. All participants were provided with ‘usual care’ advice regarding bladder training, caffeine and alcohol consumption, and behavioural changes relevant to minimising incontinence issues.

Pre-surgery PFM training

Five weeks prior to RP surgery, participants were randomised to the intervention or control group. Both groups received initial physiotherapy-directed PFM instruction over two sessions of 30 minutes and were then prescribed a daily PFM training program. This program differed in mode and intensity, depending on randomisation. Subjects randomised to the ‘control’ group were instructed and directed to perform three sets of PFM exercises per day, with 10 contractions per set, aiming to hold for a duration of 10 s, with an equal rest time, providing a total of 30 contractions per day. Each daily exercise set was to be performed once, in supine, sitting, then standing, in accordance with previously reported interventions [12]. This intervention is in keeping with current clinical practice [13] and it was administered in preference to a “no-exercise” intervention as we considered it unethical to withhold some level of training. Nonetheless, it did not specifically target fast and slow- twitch muscle function and the intensity, number and duration of contractions were modest relative to the intervention group.

Exercise protocols in the intervention group targeted both slow and fast-twitch muscle function and subjects were required to perform six sets of PFM exercises per day, with each set comprising 10 fast (1s duration) and 10 slow (10 s duration) contractions with an equal rest time, providing a total of 120 contractions per day. All sets were performed in a standing posture for this group. The subjects were blinded to group allocation, in that they were not exercised as a group and were not aware of the existence of the alternative exercise intervention.

During the initial instruction sessions, participants were given written and verbal instructions on correct PFM exercise technique [14] to ensure a full contraction and relaxation cycle was implemented with the cue to *"stop the flow of urine and shorten the penis while continuing to breathe"* [14]. Cues to relax abdominal muscles and avoid breath holding were also communicated, and confirmation of correct technique provided with real time ultrasound (RTUS) used as a biofeedback tool. Participants completed a PFM training diary to record the number, type and position of exercises undertaken on a daily basis. Adherence to the training program in both groups was assessed via individual diary entries during fortnightly physiotherapy appointments.

<u>Post-surgery PFM training</u>

Post–operative PFM training recommenced following removal of the catheter. Members of the control group performed 3 sets per day of the same exercises performed pre-surgery, while members of the intervention group continued their exercise regime with six sets per day of fast and slow-twitch training. Both groups exercised in the postures described above and these protocols were maintained throughout the 12-week assessment period.

<u>Outcome measures</u>

Bladder diaries for recording 24-hour pad weight (the primary outcome variable) were assessed post-surgery at 2, 6 and 12 weeks as the primary outcome. None of the subjects was incontinent pre-surgery. All participants wore pads and applied their first pad of the day with an empty bladder. Used pads were placed in a single plastic bag and sealed, then stored in a refrigerator to avoid evaporation. Net weight was calculated by deducting dry pad weight, using a single calibrated digital scale. Any positive net weight, recorded to the nearest 1 g, was deemed indicative of incontinence, with 'zero' net weight assessed as no leakage and full continence.

Secondary measures of QoL using the International Prostate Symptom Score (IPSS) [15] and Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) [16] questionnaires were recorded at baseline (approximately 5 weeks prior to surgery) and again at each post-surgery time point. Participants completed the questionnaires in a quiet private room at the completion of a scheduled appointment within the physiotherapy clinic.

Additional secondary measures of RTUS guided tests of PFM function, including the Rapid Response Test (RRT) and Sustained Endurance Test (SET) [17,18] were performed by a single operator for each measurement using a commercially available point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China) at each post-surgery time point. Details of the methods used in each of these tests, along with their validity and reliability, are available in recent publications [17,18].

Statistics

Outcome data were entered into SPSS (v22.0, SPSS, Chicago, IL) for analysis. A series of two-factor, repeated measures ANOVA (Group x Time) were performed and significance was accepted for all analyses at $p<0.05$. Where necessary, post-hoc *t*-tests for independent samples were performed to determine the time points at which group scores differed.. The sample size of 101 participants was based on power calculations derived from previous studies utilizing 24 hr pad weight as an objective measure of UI. [23,24] .Of 45 RCT studies investigated in the most recent Cochrane review [10], very few recorded 24 hr pad weight as an objective measure, resulting in a recommendation for its use in future studies to enhance efficacy. Our study design, which randomized men to intensive pelvic floor muscle (PFM) training versus a usual care intervention, where each group received their intervention both pre- and post-surgery, is novel. For power estimation we selected the paper of Centemero et al [24] as the closest exemplar. This trial randomized 118 men to a pre-surgery PFM intervention, versus no intervention pre-surgery. Both groups received the same post-surgical PFM training intervention [24]. Pad weight and continence were primary outcome measures, as in the current study. Centemero *et al.* indicated that 44.1% of subjects in the prehab group were continent at 1 month post–surgery, whereas this number was 20.3% in the no intervention group (ES=23.8) [24]. This difference was statistically significant ($P=0.018$). Given *a priori* assumptions of $\alpha=0.05$, a two-tailed test and a sample size of 50 per group (100 total), our study possessed >70% power to detect a similar effect size observed by Centemero *et al.* [24].

Results

Of the 101 participants recruited to the study, 97 (63±7y, BMI=25.4, Gleason 7) completed, with three participants from the control group (n = 47) and one participant from the intervention group (n = 50) unable to finish due to medical complications, including the need for radiation therapy (n = 2) and corrective surgery (n = 2). Participants were recruited over a 12-month period from April 2016 until April 2017 with follow up over a subsequent 12 months, until April 2018 when sufficient participant numbers were achieved. There were no appreciable differences in baseline characteristics between the groups, with only a few in each group having open RP, versus robotic-assisted, surgery (see Table 1). No participant in either group was incontinent prior to surgery. Prostate size, Gleason score and days of catheterization were also similar between groups, as was rate and type of cavernosal nerve sparing.

Figure 1.A represents the number of dry participants (continence = no pads or 0g net pad weight), with all participants being continent at the baseline, pre-surgery assessment. At 2, 6 and 12 weeks post-surgery, the percentage of dry participants was greater across all time points in the intervention, compared to control group, with the former group demonstrating a faster return to continence. At 2 weeks post-surgery 14% of the intervention group subjects, compared to 4% of the control group, were dry. At 6 weeks, this percentage increased to 32% and 11% respectively, then 74% and 43% by 12 weeks post-surgery.

Figure 1B displays the measured 24-hour pad weights for the control and intervention groups pre-surgery and at 2, 6- and 12-weeks post-RP. The ANOVA results showed a significant main effect for Group ($F= 7.251$; $p=0.008$), Time ($F= 82.318$; $p<0.001$) and the Group x Time interaction ($F= 4.204$; $p=0.016$). Post-hoc t-tests demonstrated that group differences occurred at each of the post-surgery time point ($p<0.05$), however the significant interaction also indicates that rates of improvement differed between groups, favoring enhanced recovery in the intervention group.

In Figure 2A, IPSS scores that measure urinary symptoms and QoL perceptions indicated similar levels at baseline, but significant ($p<0.05$) between-group differences at 6 weeks post-surgery, with the intervention group scores being superior to those for the control group. The ANOVA results showed a significant main effect for Time ($F= 25.45$; $p<0.001$), but not for Group ($F= 3.17$; $p=0.078$) or the Group x Time interaction ($F= 1.261$, $p=0.288$).

Figure 2B describes EPIC-CP urinary incontinence scores (maximum score=12) for impact on QoL. Pre-surgery EPIC-CP scores were similar, but the intervention group scored significantly better ($p<0.05$) at 2 weeks post-surgery. There were no other group differences at 6 and 12 weeks post-surgery, although the intervention group retained some advantage. The ANOVA results show a significant main effect for Group ($F = 5.344$; $p = 0.023$) and Time ($F = 13.844$; $p<0.001$), but not the Group x Time interaction ($F = 0.486$, $p=0.487$).

Results for physiological assessments of pelvic floor muscle function are shown in Figures3A and 3B. Pre-surgery RTUS assessments were not performed so as to avoid any possible training effect for members of the control group participants. However, at all time points post-RP, (Figure 3A) the intervention group recorded faster ($p<0.05$) repeated muscle contraction (RRT scores), compared to the control group. The ANOVA results showed significant main effects for Group ($F = 16.132$; $p<0.001$) and Time ($F = 69.790$; $p<0.001$), but not the Group x Time interaction ($F = 2.12$; $p=0.123$). Figure 3B provides results for the sustained pelvic floor muscle endurance test (SET). At all post-surgery time points, the intervention group recorded longer sustained ($p<0.05$) contraction scores, compared the control group. The ANOVA results show significant main effects for Group ($F = 12.605$; $p=0.001$) and Time ($F = 137.671$; $p<0.001$), but not the Group x Time interaction ($F = 0.679$; $p=0.508$).

Discussion

The incidence of UI prior to RP surgery is very low, affecting only 1-2% of the male population to age 75 y [19]. Following RP surgery, however, this changes to 69-98% men affected with urinary leakage for some duration [20]. Fear and anxiety of the potential for UI is generally high before surgery, but levels of distress decline as symptoms improve. However, if continence is slow to recover, the long term negative impact on QoL can remain substantial [21] and with an average 16-51% of men remaining incontinent at 12 months post-surgery, the impact on the patient and his partner can be significant [22].

The pre-operative period provides an opportunity to intervene and minimize the impact of UI. With the recommendation of a 6-week period between prostate biopsy and subsequent RP surgery to avoid complications, patients can be referred for pre-operative PFM training. A recent meta-analysis was only able to find 5 heterogenous papers which had addressed the question of prehabilitation benefit for UI in RP patients and concluded that insufficient data were available to warrant conclusive interpretation [23].

Our results indicate clear outcomes of less leakage, reduced time to return to continence and improved QoL in patients who received more intensive PFM training, utilizing standing postures, compared to the comparator control group protocol. This finding is in keeping with some previous studies which indicate that PFMT of longer duration prior to surgery, , is more likely to be beneficial [24,25]. Recent developments in male pelvic floor assessment, utilizing RTUS, ensure that correct muscle activation is executed, with greater focus on anterior PFM, rather than the previously recommended anal sphincter approach. Mastery of PFM control was a novel aspect and focus of our intervention methodology [26,27], alongside the quantification of pelvic floor muscle adaptation utilizing functional testing with RTUS-informed visual confirmation. Repeated one-on-one physiotherapy training sessions pre-surgery afforded the opportunity to correct any errors in PFM training technique, to progress each patient to sustain 10 s maximal contractions and to allay any participant concerns.

Providing all participants in our study with some level of pre-operative PFM training had the potential to reduce the impact of the group differences we observed and may have been a limitation. However, given the suggestion that PFM training should be recommended as a first line option for the treatment of UI [11], we considered it inappropriate to withhold PFM training altogether in the “control” group. Our intervention group received exercise specifically designed to focus on both fast and slow-twitch fibre training, completed in the upright posture, since this is the posture most often related to the clinical presentation of UI. UI is associated with increases in intra-abdominal pressure during cough, sneeze and sit to stand actions, so it is intuitive for training to be specific to rapid responses to pressure change.

Using RTUS tests that directly visualized and quantified function of the pelvic floor muscles during standardized tests, we were able to demonstrate lower RRT scores across all time points for the intervention versus control group, reflecting faster development of urethral closing pressure. This finding provides physiological and functional data supporting the more clinically orientated outcomes presented above which relate to decreased leakage post-surgery and a quicker return to continence for men who undertook the intervention training protocol. Similarly, training the slow-twitch PFM fibres in the standing posture, as quantified by the SET, resulted in higher scores for the intervention group across post-surgery time points. This was also reflected in reduced leakage and time to continence for the intervention group. No previous PFM exercise research has combined functional imaging-based tests of pelvic floor muscle function with clinical data related to UI to cross-validate findings. Our study is also novel in that we adopted a training protocol targeting both fast- and slow-twitch muscle function for men following RP surgery.

Maintaining urethral closure pressure in the standing posture is more demanding than in supine postures, and this is seen clinically with few men leaking in the horizontal position. Upon catheter removal, however, most men will experience significant leakage in transitions from supine to sit, sit to stand, and when bending, lifting and walking. By initiating training in standing postures, the intervention group was able to experience reduced UI in all domains assessed. Matching PFM training to clinical presentations was considered an important issue for our study to address, as opposed to previous studies recommending PFM exercises be performed in sitting or lying postures. Whilst these recommendations may serve patients' needs when PFMs are weak, the opportunity to train patients pre-surgery may greatly reduce this problem. Furthermore, in physiological studies designed for strength training it is recognized that maximal force generation is achieved by performing three to four sets of 8-12 repetitions per day, which also results in greater hypertrophy of type IIa muscle fibres on biopsy testing [28]. In the context of PFM training in men who experience the complete removal of the prostate, exercise training to achieve some functional change may require more intensive approaches than that previously considered to be "usual" care.

Fatigue is one of the major issues of PFM dysfunction and patients routinely complain of worsening incontinence with increased activity, and as the day progresses. To address this issue, participants in the intervention group were prescribed 120 individual maximum PFM contractions per day, compared to only 30 for the control group. Our aim to improve PFM endurance and strength as quickly as possible for the intervention group was achieved by increasing the frequency, number of sets, position and exercise type, versus the usual standard care. Training to increase muscle endurance requires the performance of high numbers of repetitions with decreased recovery time between sets. For example, Kraemer and Ratamess [29] reported greater increases in cross sectional area and strength when participants exercised twice, compared to only once per day. In PFM training studies published to date, wide variability exists in the prescription of exercises for endurance gains, with recommendations to hold PFM contractions ranging from sub-maximal to maximal efforts. In the present study, we chose to prescribe maximal contractions in an effort to increase exercise intensity. Participants recorded their daily PFM exercise regime in a diary which indicated 92% adherence with the PFM training program.

Urinary function and its impact on QoL measures were assessed using the EPIC-CP and IPSS domains, with significant differences found at 2 weeks and 6 weeks, respectively. Men in the intervention group reported less urinary leakage, less irritation, less pad use and less impact on overall QoL. Patients often report a sense of shame, loss of control, fear of bladder accidents and a need for hypervigilance with pad application, fluid consumption and social activity, all of which can affect aspects of daily life. Given the higher levels of depression and anxiety associated with UI post-RP, any measures to reduce these potential outcomes should be encouraged.

There have been many previous studies of PFM training in post prostatectomy patients, delivered both before and after surgery [9,10,12]. Many distinct interventions have been assessed and participants have differed in terms of clinical condition and status. Whilst some studies reported positive results and concluded an important role for PFM training, others, including a prominent and large clinical trial and a Cochrane review which included it, suggested that an active intervention did not substantially accelerate the degree of spontaneous recovery. Our findings demonstrated a benefit of the prehabilitation intervention performed at a higher intensity, but we also observed evidence for improved post-op recovery in the control group. There was an increase in the speed of recovery in the more active rehabilitation intervention targeting physiological PFM function of fast and slow-twitch muscle fibres. One limitation in our study, however, was that the PFM training and assessment was performed by the same therapist and the lack of blinding may have influenced outcomes.

In conclusion, an intensive PFM training intervention, applied prior to surgery, improved post-surgical pelvic floor muscle function and decreased UI, compared to a control group. Group differences were also apparent for perceived UI and QoL post-surgery. Continence and PFM functional recovery was observed post-surgery for both groups, with some evidence for more rapid recovery by 12 weeks as a consequence of the more intense intervention. Our findings provide support for further investigation, in larger trials, of the impact of relatively intensive prehabilitative approaches to enhancing PFM function in men with prostate cancer.

Declarations:

Ethics approval and consent to participate/ Ethics, consent and permissions.

This study was approved by the University of Western Australia's Human Research Ethics Committee (Ref: RA/4/1/6327) and all participants provided written consent.

Trial Registration: The trial was registered in the Australia New Zealand Clinical Trials Registry and allocated as ACTRN12617001400358. The trial was registered on 4/10/2017 and this was a retrospective registration.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: No funding or grants were provided for this study.

Conflict of Interest: There are no potential conflicts of interest in the submitted research and all participants provided informed consent prior to inclusion in the study. This research involved human participants, however none were exposed to any potential harm, as all assessments made were either by questionnaire or non-invasive real time ultrasound approaches.

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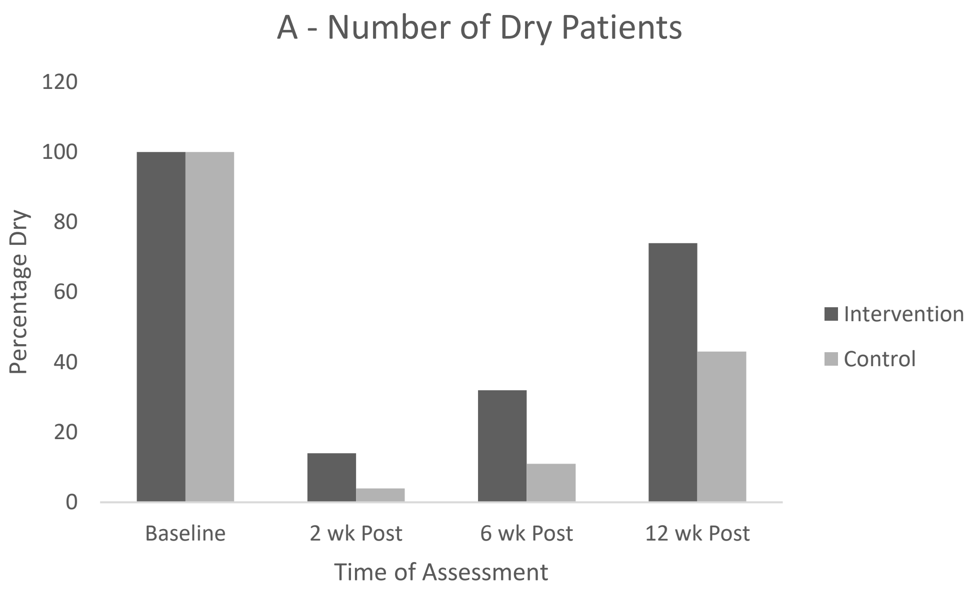
Figure 1. The number of “dry” patients (panel A) and changes in 24-hour pad weight (panel B) for patients following radical prostatectomy within the intervention and control groups at baseline, then at 2, 6 and 12 weeks post-surgery. All participants were fully continent at the pre-operative assessment (baseline). * indicates a significant difference (p<0.05) between groups at the relevant time points.



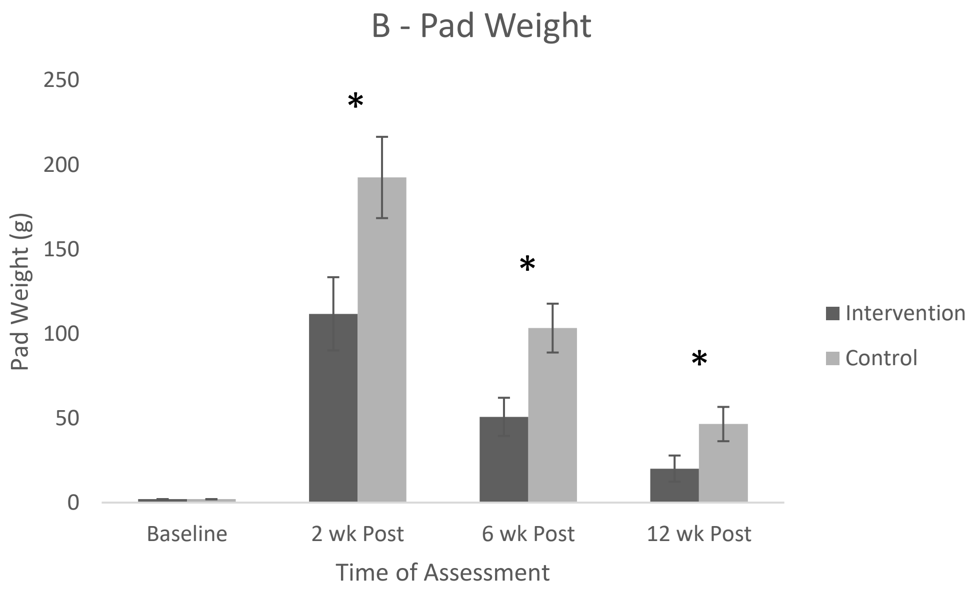
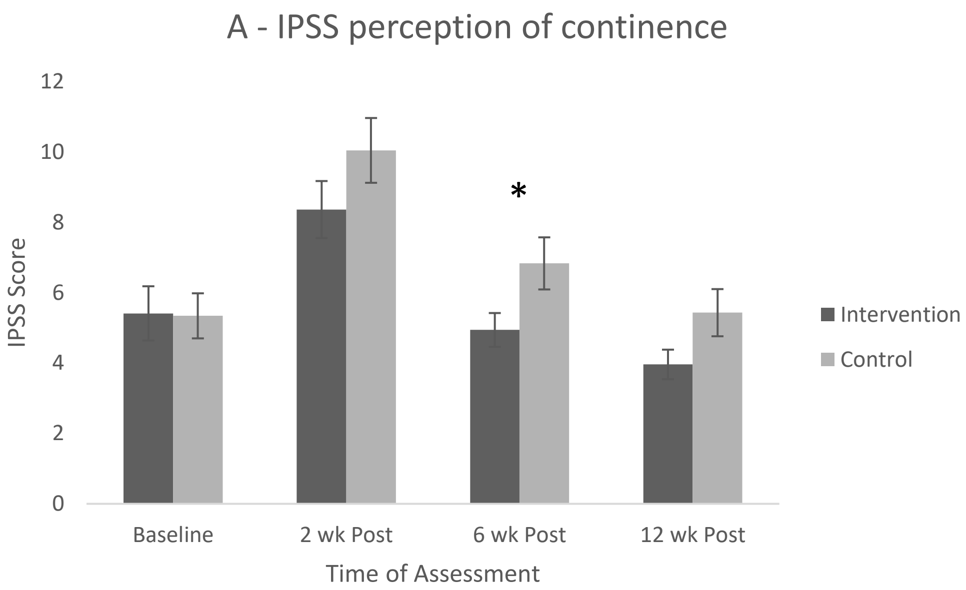


Figure 2. Changes in the International Prostate Symptom Score (panel A) and the EPIC-CP (panel B) for patients following radical prostatectomy within the intervention and control groups at baseline, then at 2, 6 and 12 weeks post-surgery. The IPSS (maximum score = 12) is as a measure of self-reported urinary symptoms and quality of life, with lower scores indicating better outcomes. The EPIC-CP is a health related quality of life measure for men following treatment for prostate cancer, wherein the urinary continence domain (maximum score = 12) assesses self-reported bother of urinary incontinence symptoms, with lower scores indicating better outcomes.
* indicates a significant difference ($p<0.05$) between groups at the relevant time points.



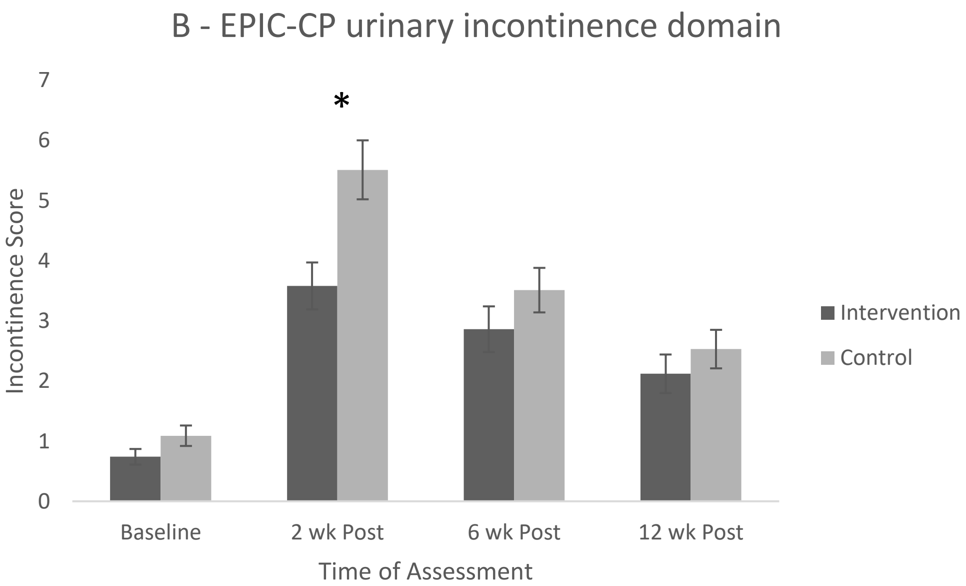
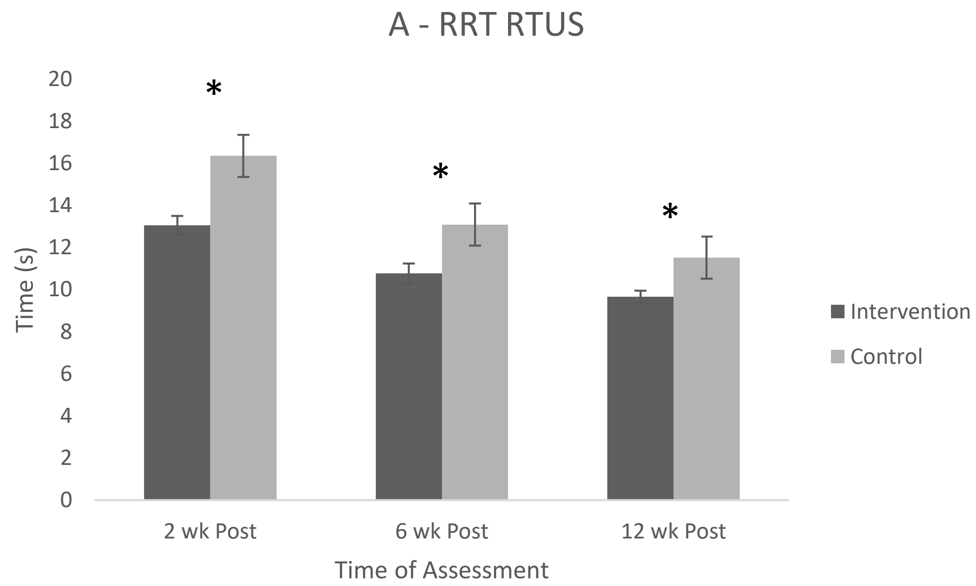
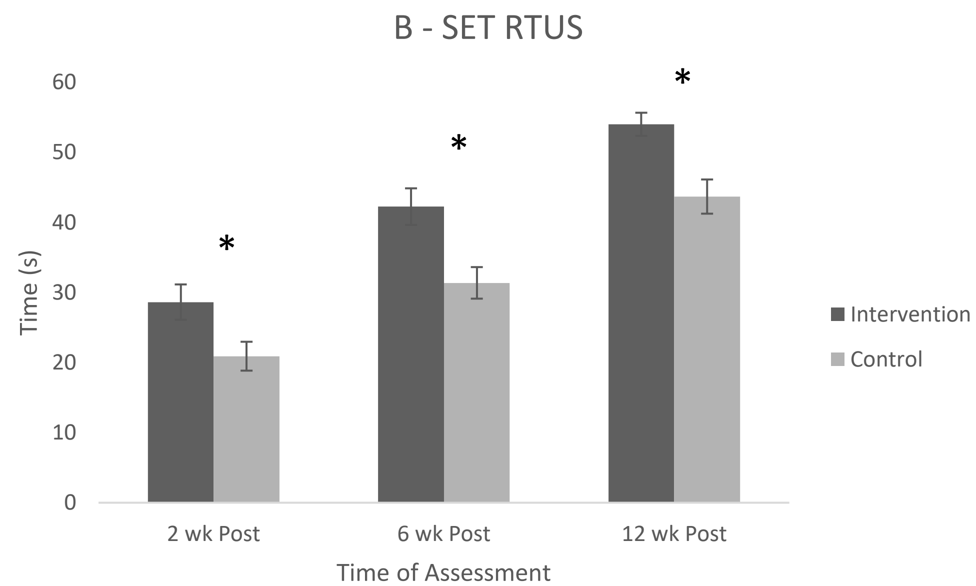


Figure 3. Changes in the Rapid Response Test (RRT – panel A) and the Sustained Endurance Test (SET – panel B) for patients following radical prostatectomy within the intervention and control groups at 2, 6 and 12 weeks post-surgery. The RRT tests uses real time ultrasound (RTUS) to measure the speed of pelvic floor muscle contractions, with lower scores representing a better outcome. The SET also uses RTUS to measure the endurance of pelvic floor musculature to sustain a contraction over time (maximum score = 60 s), with higher scores representing a better outcome.
* indicates a significant difference ($p<0.05$) between groups at the relevant time points.





CHAPTER 7

Part 2: Literature Review – Erectile Dysfunction

Background

Erectile Dysfunction (ED) is described as the persistent inability to achieve or maintain an erection firm enough or lasting long enough for sexual performance. [1] In 1995, it was estimated to affect 152 million men worldwide with the prevalence expected to double by 2025. [2] Several studies have assessed the epidemiology of ED, with the Massachusetts Aging Study demonstrating increased age as the most significant factor. At age 40 years, approximately 40% of men are affected, a rate that increases by 10% every decade to age 70.[3] Following adjustment for age, a higher probability of ED was noted in patients with cardiovascular disease, hypertension and diabetes among health practitioners assessed over an average of 8.8 years. [3] Additional recognized risk factors include alcohol use, smoking, depression, pelvic/perineal surgery or trauma, neurological disease, obesity, pelvic radiation and Peyronie's disease (PD). Hormone deficiency and hypogonadism account for a further 3-5% of ED cases, with medications and recreational drugs also affecting erectile function. However, radical prostatectomy (RP) has the most significant immediate impact on erectile function and male patients undergoing the procedure will endure an almost obligatory period of dormancy of the nerves that govern the functional aspect of erection. [4] Although ED is not usually considered a life-threatening condition, it may have significant physical and psychosocial implications that may greatly impact on the quality of life on men and their partners. [3]

Normal Erectile Function

Normal erectile function (penile tumescence) is a complex process of physiological, neural, vascular, metabolic and endocrine events [1] and has been classified into three different neurophysiological types; reflexogenic, psychogenic and nocturnal erections. [5] Reflexogenic erections originate from tactile stimulation to the genitals, causing sexual arousal. Impulses travel to the spinal erection centre via sacral sensory nerves (S2-4) and thoracic nerves (T10-L2), which stimulate sensory perception and the inducement of the erection process (Figure 7.1). Psychogenic erections originate from visual, audio or olfactory stimulation and fantasy/imagination, descending from the cerebral cortex to the spinal erection centre to activate an erection. Nocturnal erections occur during sleep, most typically during rapid eye movement and also on waking, occurring 5-8 times/night and lasting up to 30 minutes each. [5,6] Central impulses descend via the spinal cord to activate the process, with the absence of nocturnal erections commonly used to distinguish between physical and psychological causes of ED.

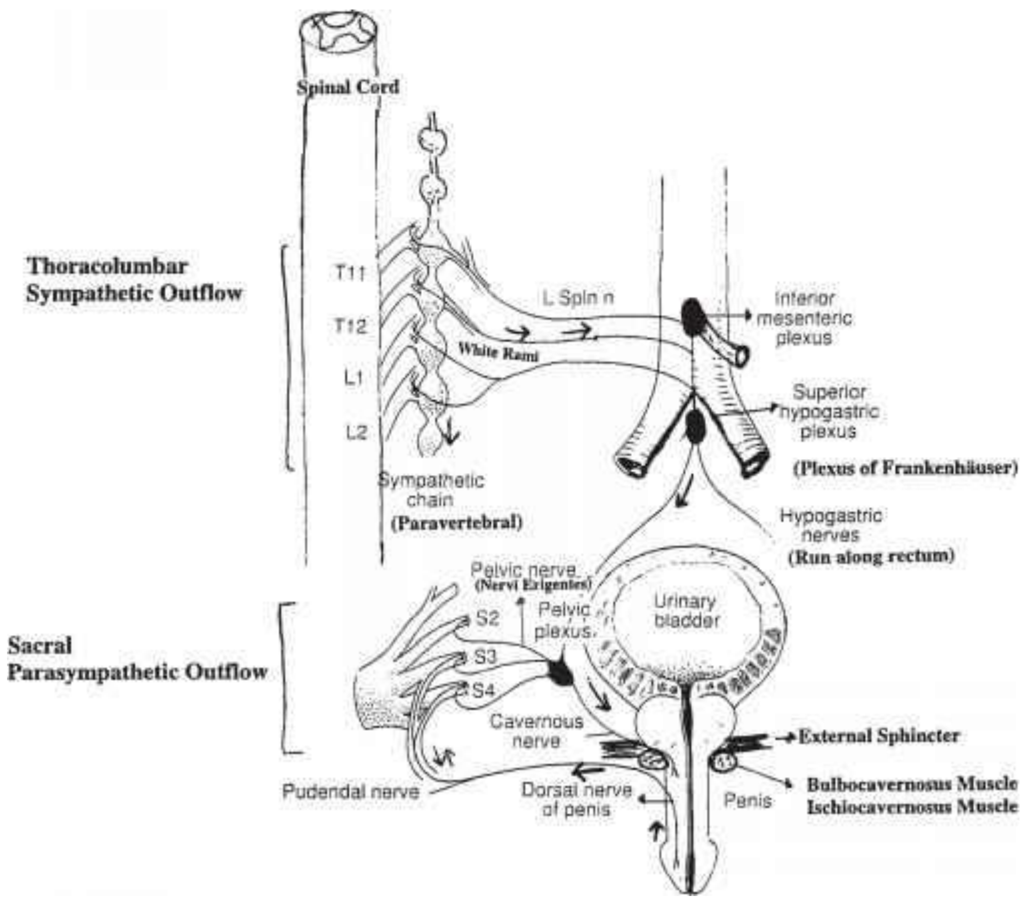


Figure 7.1 Nerve supply of erection (reproduced from *www.health.am* 25.11.18)

Innervation of Erectile Tissue

The pudendal, pelvic splanchic and pre-sacral nerves all derive from sacral S2,3,4 and are responsible for normal continence and erectile function. [7] The pelvic splanchic nerves provide sensory and motor function to the bladder and motor function to the blood vessels of the penis for erection whilst the pudendal nerve provides a motor supply to the external urethral sphincter and sensory function for the glans penis and urethra. [7] Any interference with this complex network, adjacent and posterior to the prostate, has the potential to impair function. As a consequence of removing some or all of these neurovascular regions during RP, it is of clinical significance primarily for cancer clearance and the subsequent viability of neuropraxia. [8]

Assessment of Erectile Dysfunction

It has been proposed that sexual function is best assessed in a naturalistic setting with patient self-report techniques, [9,10] so most measurements of erectile function are determined by questionnaires. The International Index Erectile Function Score (IIEF-5) [11] and the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) [12] are the favoured inventories in current scientific publications and cover quality of life, erectile function and orgasm in men following RP. The IIEF-5 is a validated measurement tool and an abridged version of the original 15-point IIEF instrument has been widely used for drug trials. The shorter version is more patient friendly, provides a simple screening measure to supplement medical examination and has been utilized in our studies to provide information on symptom severity and impact on the individual. The questionnaire comprises five questions, each ranked from 1-5, with a maximum total of 25 indicating normal erectile function. Scores of 1-7 represent severe ED, 8-15 moderate ED, 16-21 mild ED and 22-25 normal function. It does not, however, adequately address men who may not be in a relationship or do not have sexual intercourse. For men who have undergone treatment for PCa, the EPIC-CP is a more clinically applicable instrument and consists of a one page, 16-item questionnaire that measures urinary incontinence (UI), bowel, sexual and hormonal Health-Related Quality of Life (HRQOL) domains at the point of care. [12] It has been validated and provides physicians practicing in PCa care with improved emphasis and management of patient reported outcomes specifically relating to sexual function, with questions pertaining to quality of erections and orgasm. [12]

Objective measures of nocturnal penile tumescence that measure neurogenic erectile function whilst the patient sleeps are also available. [13,14] These tests record changes in penile blood flow. Penile Duplex Doppler Ultrasound (PDDU), which uses high-frequency sound waves to measure penile carvernosal arterial function, can also provide post-surgery diagnostics, given the period of potential recovery ranges from 6 to 48 months following RP. [15,16] These tests are, however, quite invasive for patients, expensive to administer and time consuming, so are not part of routine clinical care and have not, therefore, been utilized as outcome measures in this research.

Erectile Dysfunction following Radical Prostatectomy

The incidence of ED among RP patients, as for UI, varies widely with available data ranging between 16-100%. [17,18] The very high proportion of men developing ED following RP is thought to be predominately caused by nerve damage incurred during surgery. [1] During the RP procedure, the surgeon aims for clear margins and to create a buffer zone between the prostate bed, neurovascular bundle and rectal tissues, at the same time aiming for total cancer clearance. The proximity of the cavernosal nerve to the prostatic capsule, which is a diffuse and poorly visualized nerve plexus, is adherent to the lateral aspect of the prostate and represents the major surgical obstacle when aiming for minimal nerve damage.[19] The process of removing the prostate inevitably causes cavernosal nerve conductivity problems as well as diminishing the nitric oxide synthesis which is required for mediating smooth muscle relaxation and vasodilation in normal penile erection. [15] Additionally, the likelihood of intracavernosal hypoxia following surgery is considered to be one of the major determinants of post-operative ED. [8] This occurs due to the loss of daily and nocturnal erections with persistent failure of cavernous oxygenation, leading potentially to venous leakage, fibrosis and penile shortening. [4] Other ED side effects include the absence of ejaculation due to removal of the ejaculatory duct, orgasmic dysfunction with absent, reduced or painful orgasms and climacturia (the loss of urine with any sexual arousal or activity). [15,20]

Impacts of Erectile Dysfunction on Quality of Life after Radical Prostatectomy

Following RP, 60-70% of men will have long term ED and recovery of function can take up to 48 months. [16,21] ED not only relates to the lack of penile rigidity sufficient for sexual intercourse; other impairments can include:

- Changes in penile function, girth, length, appearance, shape, sensation, strength of erection and the potential development of PD, curvature of the penis and penile pain.
- Ejaculatory and orgasmic dysfunctions: loss of ejaculate fluid, absence, reduced, or altered orgasm. Orgasm induced pain and loss of urine (climacturia) occurring during arousal, at time of orgasm or afterwards.
- Psycho-sexual impairment with changes in sexual desire, intimacy and mental health. [22]

A. Erectile dysfunction

Each of the changes that occur with ED may have significant impact on a man and his partner with the majority of men reporting a moderate or severe impact on their quality of life. [23] The PCa outcomes study revealed 60% of men experienced self-reported ED at 18 months post-RP and only 28% of men reported erections with sufficient firmness for penetration at a 5-year follow up. [24] A further common complaint of men undergoing RP, but one that is rarely discussed pre-operatively, is the approximate loss of 2-3cm of penile length at 12 months post-surgery. [25] This loss of penile length is mostly attributed to parasympathetic neural trauma, associated with the cavernosal nerve injury intra-operatively and the structural changes that occur over time with cavernosal smooth muscle hypoxia, denervation induced smooth muscle apoptosis and potential fibrosis. [16] Montorsi *et al.* suggested that the combination of reduced arterial inflow, increased venous leak, and corporal fibrosis likely accounted for the post-RP penile hemodynamic changes, as well as a decrease in penile length. [26] Over time, structural changes may continue to occur, causing further distress and a potential diagnosis of PD. In the general population, PD occurs in 2-9% of men and is a symptomatic disorder characterized by a variety of penile symptoms including penile pain, curvature, shortening, narrowing, indentation, hinge deformity, palpable plaque and ED. [27] Tal and Teloken [28] investigated the incidence of PD in 1011 men undergoing RP, and reported 16% were diagnosed with the condition, with mean time to develop 13.9 ± 0.7 months. Mean curvature magnitude was 31^{o} and younger men of white race were predictive of development of PD following RP. [28]

B. Ejaculatory and orgasmic dysfunctions

Whilst substantial research has investigated ED following RP, data available on post-RP orgasmic function (OF) is very limited, with almost all available data derived from patients undergoing open surgery and no specific questionnaire for assessment. [29] Complete absence of ejaculate fluid is an immediate side-effect from surgery due to removal of the prostate and seminal vesicles that account for approximately 90% of ejaculate. This has a profound effect on sexual pleasure at orgasm. [1] In addition, orgasmic changes following RP include absence of orgasm (anorgasmia), alterations in orgasm intensity, orgasmic pain (dysorgasmia) and orgasm-associated UI (climacturia). In a small study by Koeman *et al.* only four (29%) from 17 men reported normal OF following RP, with 50% reported a weakened orgasm, 14% experienced post-ejaculatory pain and a further 29% reported complete loss of orgasm. [30] In a larger cohort of 239 men who underwent open RP, OF was investigated retrospectively by Banas *et al.* similar findings were made with 37% reporting complete absence of orgasm, 22% no change, 37% experiencing a decrease in orgasm intensity, with dysorgasmia in 14%. Of those experiencing pain with ejaculation, 63% reported penile pain, 9% abdominal pain and 24% rectal pain. A small number of men (4%), however, reported increased orgasm intensity and this has also been recorded by other authors with similar incidence levels. [23,31] In further studies by Schover *et al.*, 64% of men rated themselves distressed about OF and this decreased intensity of orgasm or anorgasmia has been considered a major psychological distress. [32,33]

<u>Climacturia</u>

Climacturia, or orgasm associated UI, is a common complication following RP, but a highly variable incidence of 20-93% has been reported by different cohorts. [20,34] Barnas, for example, reported 93% occurrence with 16% reporting climacturia during every orgasm, 44% occasionally and rarely in 33%, compared to 20% in Choi’s cohort and 79% in Lee’s study. [31,35,36] Variation in these results may depend on the time of assessment, with the development of climacturia potentially a time-dependent factor. In several studies, climacturia rates were higher in patients presenting within 12 months post-RP, with 22% reporting leakage at 6 months and just 9% at 24 months. [36] Due to limited assessment tools and minimal investigation to date, the volume of urine lost is also variable. [33] Strategies to help minimize climacturia include encouraging men to empty their bladders prior to sexual activity, to use a condom, to keep tissues/towels nearby to absorb leakage and to apply a constriction band at the base of the penis. [33,37] Medical intervention using tricyclic antidepressants and surgical applications of bulbourethral slings have also been advocated in more difficult to treat climacturia, with some positive outcomes reported. [33] Of significance, is the option for PFM training techniques introduced by Sighinolfi in 2009 [38] in a case study and backed up by the 2015 RCT conducted by Geraerts, in which men presenting with climacturia reported improvement or significant reduction after 3 months of PFM exercises at 12 months post-RP. [20] Since orgasm-associated UI may occur during any aspect of sexual activity, from arousal to post-orgasm, the impact on individuals and their partners may be extreme.

Psychosexual impairment with changes in sexual desire, intimacy and mental health

Absence of orgasm, decreased orgasm intensity, dysorgasmia and climacturia may make a man feel uncomfortable, embarrassed or ashamed. [33] The potential for psychological distress may result in avoidance of sexual activity, loss of self-confidence and self-esteem and a reduction in HRQOL. [20,31,35] Changes in sexual desire may decrease by as much as 45% in the first 6 months following RP, causing distress to 60% of participants in Schover's [32] study. Similarly, investigations by Messaoudi stated that 79% of men reported reduced frequency of intercourse post-RP, 76% loss of masculine identity, 52% loss of self-esteem and 36% anxiety about sexual performance. [39]

Given the significant impact of ED causing reduced sexual desire and intimacy, depression and anxiety have been reported in men and their partners post-RP. [40] In a qualitative analysis of 27 PCa survivors and their partners by Albaugh, issues of frustration due to changes in sexual function led to feelings of loss, grief and, in several cases, suicidal ideation. [23] Men reported the psychologically devastating effects of feeling abnormal, unnatural and "less of a man" due to their sexual dysfunction. Both patients and their partners reported that this change had a great impact on every aspect of their lives. Education and comprehensive information before and following PCa treatment was considered a significant contributor to reducing distress and, for those men who been well prepared for the sexual side effects of treatment, acceptance to the changes were far less devastating. [41] Men and their partners who were most dissatisfied with post-RP sexual dysfunction felt their care had been compromised by misinformation, too little information or inaccurate information about the expected sexual dysfunction outcomes. [41] Information pertaining to the opportunity for positive sexual experiences, such as non-penetrative sex, sensate focus management techniques and penile rehabilitation were of great benefit to couples wishing to maintain their physical and emotional relationships, with some studies reporting enhanced relationship strength. [41]

Taking all these aspects into consideration, Salonia *et al.* made a strong recommendation to implement effective psychosexual counselling from the peri-operative stage following PCa diagnosis. [33] Patient education should, they strongly suggested, become an essential part of the preparations both before and after RP. [33,42] At present, an estimated 70% of men with ED are not being treated post-surgically, however, with increasing awareness of the benefits of early penile rehabilitation, this number should improve. [15]

Nerve Sparing in Radical Prostatectomy

The opportunity to minimize poor QoL outcomes has been the primary goal of nerve sparing RP techniques, introduced by Walsh and Parlin in 1984, recognizing the importance of maintaining the integrity of the neurovascular bundles that contain the cavernous nerves of normal erectile function (Figure 7.2). [43, 1] The technique, however, is not always successful as these nerves comprise a diffuse, poorly visualized plexus that has variable anatomical localization and figuration. [15] Advancements with robotic-assisted RP since the mid 2000'shave, however, afforded the surgeon a 10-fold increase in magnification, with the opportunity to provide unilateral or bilateral nerve sparing with greater vision and dexterity, although convincing evidence of its potential superiority over open RP is still developing. [44,45,46] In addition to nerve sparing, recovery of erectile function also depends on age, other co-morbidities and pre-operative erectile function. Beyond the post-surgical time, any spared erectile tissue should begin to recover within 3-4 months with improvement potentially continuing for 3-4 years before complete resolution of neuropraxia. [15]

Penile rehabilitation (PR) is emerging as an important post-operative therapy that aims to prevent ED following RP, utilizing pharmacology, vacuum devices, compression rings, intracavernosal injections and penile implants. [17] The role of PFM training in ED rehabilitation is, however, still in its infancy and is a large focus of this study.

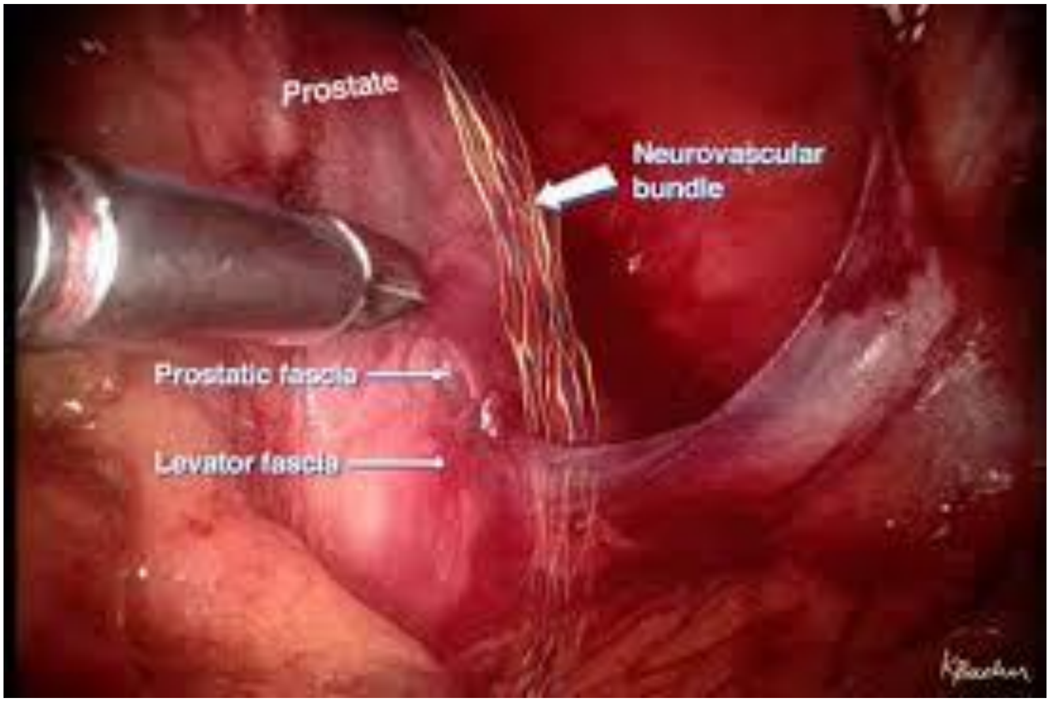


Figure 7.2 Nerve sparing during radical prostatectomy
(reproduced from *www.urology.ufl.edu* 25.11.18)

Penile Rehabilitation

PR is defined as 'the use of drug or device after RP to maximize ED recovery' and involves the use of any intervention or combination (medications, devices, or actions) to recover erectile function. [47] The concept of PR was introduced in the 1990's following the introduction of cavernosal nerve sparing surgeries and the advent of phosphodiesterase type-5 inhibitors (PDE5i) medications, both of which revolutionized approaches to treatment. [22] Subsequently, rehabilitation strategies aim to focus on three interrelated concepts: (1) improving cavernosal oxygenation; (2) preserving endothelial structure and function and; (3) preventing smooth muscle structural changes. [19,47] Both ED and treating potential penile deformities need addressing, with recommendations to initiate treatment as soon as possible after RP now considered essential for potential recovery. [22] However, evidence to recommend an irrefutable PR regime has not yet been established, although it is known that over 90% of physicians start PR within the first 4 months post-operatively. [48,49] The most commonly utilized options for treatment will be outlined below.

A. First Line Treatment Options: Phosphodiesterase 5 Inhibitors (PDE5i)

Medications are considered the first line treatment in PR and include four main PDE5i drugs which are taken orally: Viagra (Sildenafil), Levitra (Vardenafil), Cialis (Tadalafil) and Avanafil (Stendra). Since entering the market in 1998, these medications have been popular amongst physicians and patients, given their safe profile and easy to administer approach, with minimal and relatively short lasting side-effects. [49] PDE5i treatments work by decreasing the breakdown of cyclic guanosine monophosphate (cGMP) to result in elevation of intracellular calcium, causing smooth muscle relaxation and erection, and have shown favorable outcomes in patients with ED after nerve sparing RP. [19,50] A number of authors have reported higher IIEF scores and spontaneous erection rates, with investigations by Padma-Nathan [51] and Montorsi [52] providing the first multi-center, double-blind randomized controlled trials to show positive benefits. Subsequent research by Zelefsky, [53] and Mulhall and Montorsi [54] have further enhanced knowledge of erectile function recovery following RP. Unfortunately, these small series have had common limitations of selection bias and lacked biological evidence of erectile function recovery, such as via penile doppler scans. [19] In addition, it is acknowledged that the pre-operative status of each individual, including age and erectile function, are well known predictors of post-operative ED and may also alter the impact of functional recovery and, therefore, the impact of PDE5i treatments. [55]

B. Second Line Treatment Options

For men who do not respond to first line treatment PDE5i medications, second line treatment options include vacuum erection devices (VED), intracavernosal injection therapy (ICI), vibratory stimulation and extracorporeal shockwave therapy (ECSW). A third-line treatment option is also available in the form of penile prosthesis implants and each of these treatments will be discussed below.

<u>Vacuum erection device (VED)</u>

The vacuum erection device (VED) is useful for men with or without NSPR and has gained popularity due to its low complication rates, few side-effects and cost-effectiveness when compared to other PR options. [49] The basic pump design consists of a cylinder which is applied to the flaccid penile shaft and pushed against the patient’s pubic region to create an airtight seal (Figure 7.3). [56] VED activation causes erection by creating a negative pressure around the penis and draws both venous and arterial blood into the corpus cavernosum, resulting in tumescence. [57] In animal studies VED therapy has been demonstrated to preserve erectile function by alleviating tissue hypoxia to help inhibit apoptosis and prevent cavernosal fibrosis, [58] although there have been few clinical trials in men following RP.

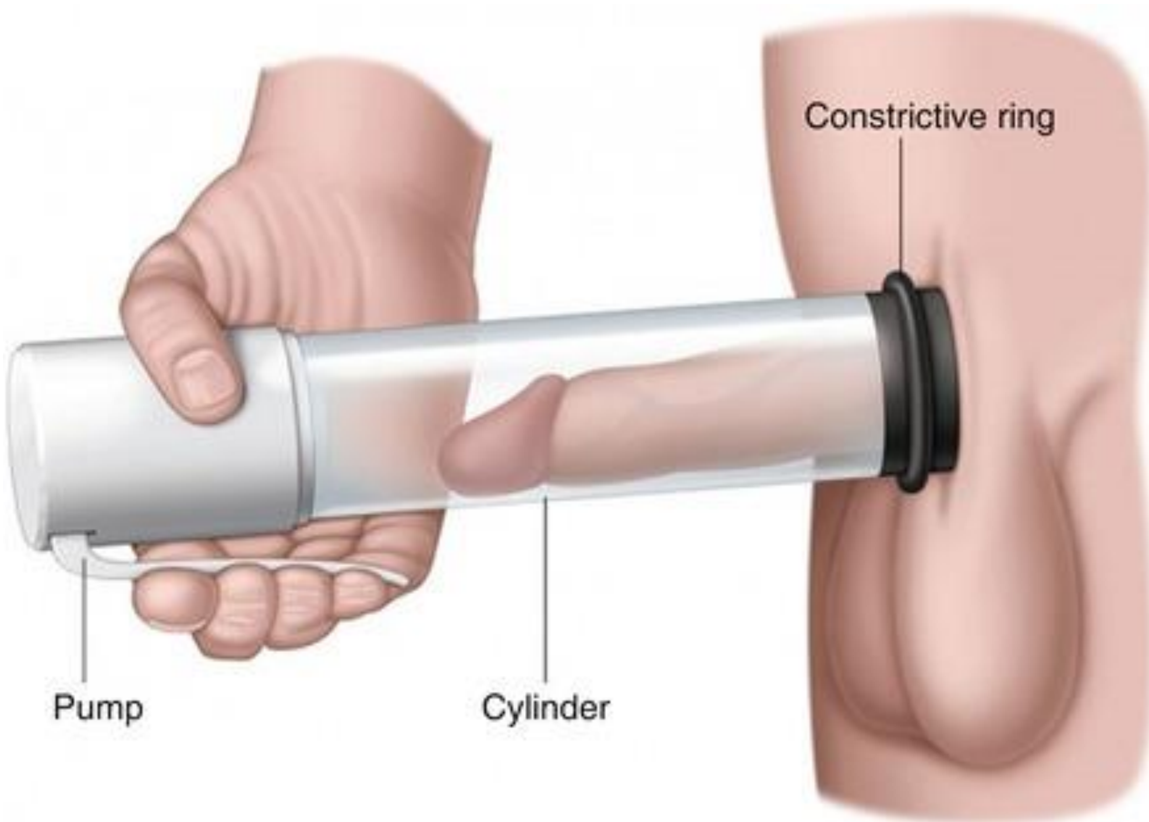


Figure 7.3 Application of vacuum erection device
(reproduced from *www.link.springer.com* 25.11.18)

Intracavernosal injections

Intracavernosal injections (ICI) using alprostadil (prostaglandin E1 derivative) either alone or in combination with papaverine or phentolamine, are a useful second line treatment for men who had NSRP or are unresponsive or cannot tolerate PDE5i medications. [19] When injected directly into the cavernosal tissues, ICIs work primarily on specific receptors found on cavernosal smooth muscle to stimulate the activity of cyclic adenylate cyclase (cAMP) to cause a fall in intracellular calcium and resultant smooth muscle relaxation and erection

(Figure 7.4). [56] Individual doses require gradual adjustment until satisfactory combinations are reached, aiming to have an erection satisfactory for sexual intercourse, but not too long-lasting (>4 hours) to avoid possible priapism.

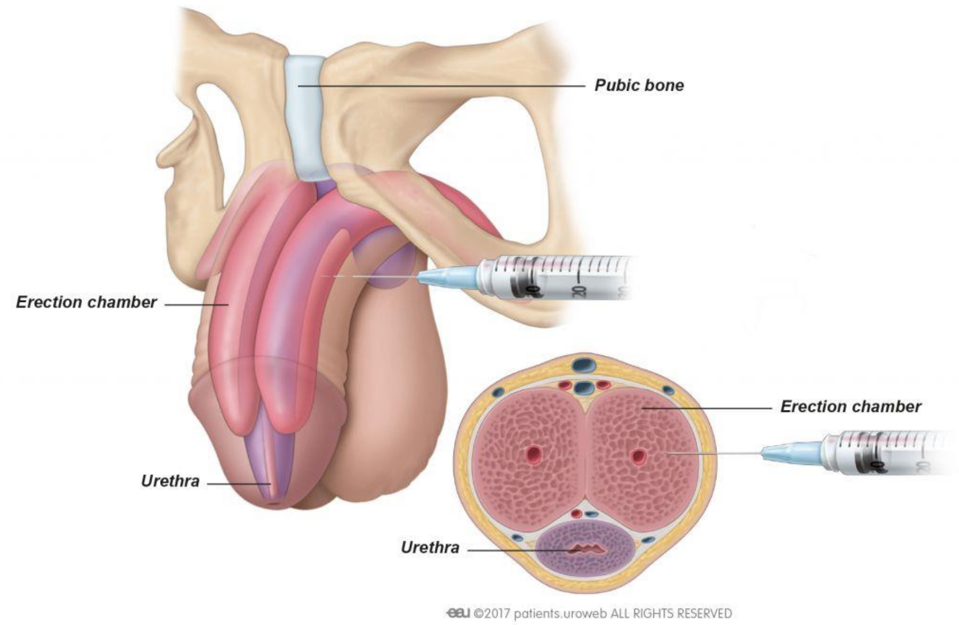


Figure 7.4 Intracavernosal injections for erectile dysfunction
(reproduced by *www.patients.uroweb.org* 25.11.18)

The first researchers to assess the effectiveness of ICIs in a clinical population were Montorsi *et al.*, who randomized 30 post-BNS-RP to two groups, to receive either 3 x ICI weekly or none (control) over a 12-week period. [59] At 6-month follow up, 67% of men in the treatment group and 20% of the men in the control group achieved spontaneous erections sufficient for penetration, indicating the likelihood of reduced hypoxia-induced tissue damage with ICI therapy. [59] Comparisons between early and delayed use of ICI in a further study by Mulhall in 2009, demonstrated better erectile function with 48% of men in the early intervention versus 30% in the delayed group having unassisted erections at 2 years post-NSRP, to further enhance recommendations for the timing and/or benefits of PR.[47]

C. Third-Line Treatment Options

Penile prosthetic implants

Penile prosthesis is the most invasive and expensive treatment for ED, however it provides the greatest patient satisfaction (89%) of all available penile rehabilitation options (Figure 7.5). [19,60] Men who underwent implantation reported higher quality of life, erectile function and frequency of sexual contact, with few side-effects. [19,60] Several types of prosthesis are available, including a semi-rigid malleable option or an inflatable two- or three-piece device. [56] Sexual functioning is possible within 6 weeks from surgery and prevention of long term penile deformity and penile length are the goals of treatment, however, changes in sensation and ejaculatory function have been reported. [1] In addition, up to 3% of patients may acquire infections and penile pain relating to prosthesis sizing errors, erosion and/or mechanical failure, so long term management needs to be observed. [1,19]

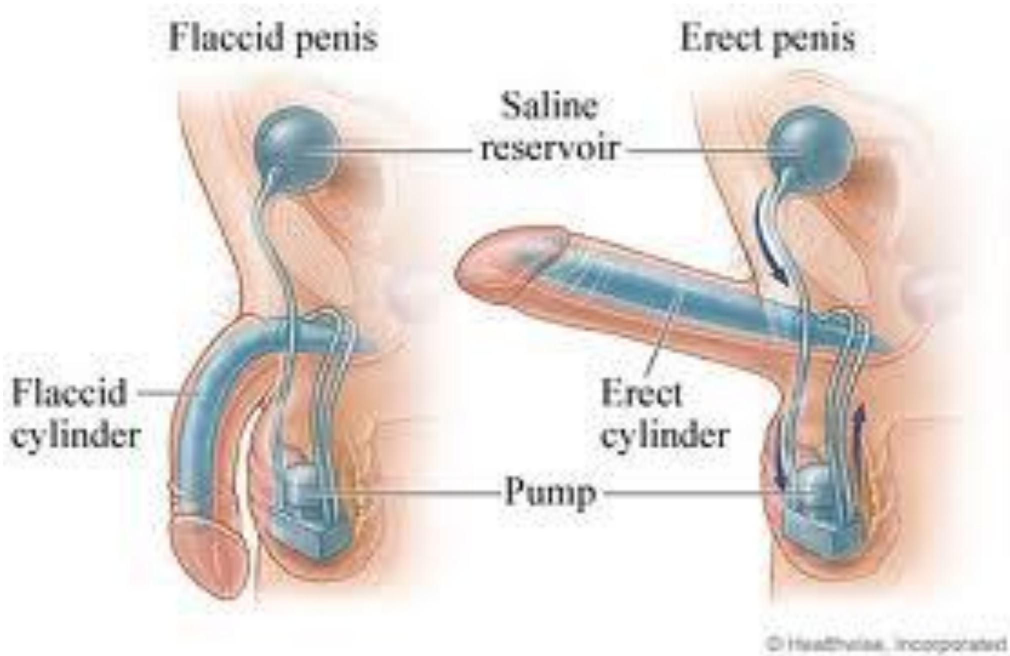


Figure 7.5 Penile implants for erectile dysfunction
(reproduced from *www.healthvista.inc* 25.11.18)

The Role of Pelvic Floor Muscles in Erectile Function

Evidence demonstrating the benefits of PFM training for treating urinary and continence issues in men has received widespread investigation, with significant findings across the literature. Evidence regarding the role of the pelvic floor muscle in sexual function in men has led to the publication of three reviews, by Dorey in 2004, Rosenbaum in 2007 and Rival in 2017. [61,62,63] Each provided evidence of a direct link between PFM strength and increased penile rigidity in the erect penis and authors were able recommend PFM training be considered a first line approach for men seeking resolution of ED. However, just like UI issues, specific protocols for rehabilitation remain elusive.

Historically, observations that contractions of the BC and IC temporarily increase penile rigidity and hardness are over a century old, supported by the 1909 edition of Gray's Anatomy, that labelled the IC as the 'erector penis' muscle. [64,65] In both animal and human studies, the contraction of both IC and BC have been shown to be activated during sexual activity. [61] Contraction of IC participates in the process of erection by inducing suprasystolic intracavernosal pressures and reducing venous return by compressing the roots of the corpora cavernosa as well stabilizing the erect penis. [66,67] Contraction of the BC induces engorgement of the glans penis and corpus spongiosum, increases intraspongiosal pressure and further slows venous drainage of from the corpus cavernosum by compressing the deep dorsal vein of the penis. [68] The capacity for full erection is, thus, dependent on the functional strength, and coordination of the IC and BC working simultaneously to increase maximum inflow pressure within the corpora cavernosal and corpus spongiosum. Voluntary PFM activity has been shown to be more efficient in men with normal erectile function compared to those with ED. [69]

Some of the earliest investigations addressing the role of PFM in erectile function concluded that rehabilitation of PFM function appeared to be beneficial in selected populations, particularly those with mild-to-moderate veno-occlusive function. [70] In a 1993 study investigating 150 men with ED, Claes and Baert found that voluntary contraction of IC potentially provided the necessary increase in intracavernosal pressure to establish or maintain penile hardness sufficient for vaginal penetration. Similarly, in research conducted by Lavoisier, [67] nine men with ED were found to have higher levels of ICP with IC muscle contraction when assessed via needle EMG.

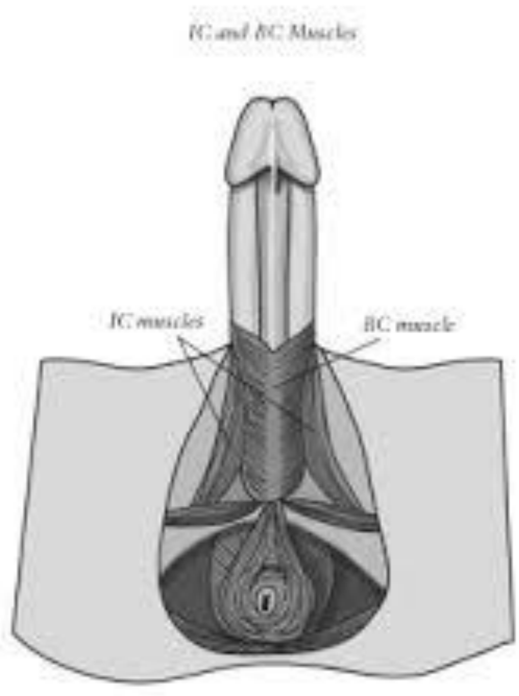


Figure 7.6 Ischiocavernosus (IC) and bulbocavernosus (BC) pelvic floor muscles of erection (reproduced by *www.pelvichealthmelbourne* 26.11.18)

In the comprehensive review by Dorey, the use of physical therapy for men with ED was investigated with nine trials utilizing PFM training. [62] Of these trials, one included electrical stimulation only, three included biofeedback and four included biofeedback plus electrical stimulation. An additional trial used visual erotic stimulation plus electrical stimulation. [71] As many of these studies used only small samples, the evidence provided was limited. Only three of the nine trials included a control group and instructions for performing PFM varied in technique and position performed. Of those described, PFM training protocols varied from three maximal contractions (6-10 s) in sitting, standing and lying, to diverse combinations of short (1 s) and long-lasting contractions (3-10 s) in postures of lying, sitting, crook lying, prone and standing. The number of treatment sessions among these trials also varied from five to 20, with participants assessed initially and at time intervals between 3- and 12-months following intervention. Dorey concluded that whilst results from the nine studies were encouraging, poor methodology was a central concern for most studies. Outcomes suggested, however, that PFM efficacy was higher in potent versus impotent men and that function declines with age, particularly for the impotent patients. PFM targeting BC and IC contractions were linked to improvements in men with mild to moderate ED when venous leakage was the main cause of impotency.

Landmark research by Van Kampen *et al.* investigated 51 men with ED of mixed aetiology who performed PFM training in lying, sitting or standing, in a home-based program of 90 exercises per day. In addition, participants received electrostimulation and anal biofeedback once per week for 4 months via anal or surface electrodes. Of the 42 men who completed the study, 46% reported a cure of ED, while 24% reported improvement, but no control group was included in the study.

RCTs conducted by Sommer [72] and Dorey [73] provided higher levels of evidence, and similar outcomes were achieved. Sommer assessed 124 men with venogenic ED, randomized into three groups: group 1 received 3 x weekly PFM training sessions, group 2 received PDE5i medications and a control group had no intervention. Results indicated the most significant improvements occurred for the PFM training group with 80% erectile function improvement and 46% improved penile rigidity, compared to 74 % improvement in group 2 and 18% improvement in controls. [72] Dorey studied 55 men with ED, randomized to 2 groups; 28 received PFM training, biofeedback and suggestions for lifestyle changes, whilst a control group (n = 27) receiving lifestyle advice. The intervention period was 3 months with participants performing 6 sets per day of 3 maximal contractions (6-10 s) in sitting, standing and lying, and a 50% maximal hold during walking, with advice to 'tighten' the PFM following urination and during sexual activity. At this point, the control group was offered the intervention and the exercise group continued with the original program. After 3 months of intervention and 3 months of PFM exercises, 40% of all participants had attained normal function, 35% had improved and 25% failed to show any change. [73]

Dorey's study was significant in that it was the first to use a validated outcome measure (the IIEF-5) to assess the effectiveness of PFM training enhanced by biofeedback with a clinical improvement of 6.74 after 3 months ($p=0.004$), 9.88 at 6 months in the intervention group, with 10.94 ($p<0.001$) points in the control group at 6 months. Dorey concluded that PFM training was hence a valid, non-invasive option for improving ED in 75% of men undertaking a 3 month intervention. [84]

As knowledge has progressed since these previous studies were conducted, the role of PFM training for sexual dysfunction in other conditions such as premature ejaculation has evolved. Four studies utilized PFM training as the primary intervention in combination with electrical stimulation, over time frames varying from 8 weeks to 3 months. [74-77] Despite differences in interventions and training durations, improvements were reported for all outcome measures, with intra-vaginal ejaculatory latency times improving significantly with reports of cure ranging from 55-82% of participants.

Exploring both ED and premature ejaculation, and utilizing PFM rehabilitation to determine changes in intracavernous pressure in two groups of men (122 with ED and 108 with PE), an observational study by Lavoisier assessed the role of IC muscles in maintaining penile rigidity during erections. [66] Both groups were assigned 20 sessions with 30 minutes of voluntary PFM contractions coupled with electrical stimulation designed to increase IC muscle strength. The maximum change of ICP was assessed from baseline to full erection in both groups and results were significantly higher than in studies by other authors, with 87% having a positive effect in the ED group and 88% in the premature ejaculation group. Lavoisier concluded that, as IC is a skeletal muscle, it responded to strengthening intervention, showed progress during rehabilitation and persisted with improvement beyond the intervention timeframe. His findings suggest that with aging, prolonged ED or following prostate surgery, IC atrophy is likely to occur and, thus, training this PFM is a logical exercise to recommend. [66]

In a different cohort, Mohammed [78] appraised ED in men with chronic obstructive pulmonary disease, assessing the role of PFM training in 44 men who completed a 4-month PFM training intervention. The training protocol consisted of 40 short (1 s) PFM contractions and 50 long-lasting (6-10 s) contractions performed in prone, sitting or standing in three sessions per day. The primary outcome measure was maximal anal pressure via anal manometry. At follow up, 35% reported cure, 40% improvement in EF, with 25% unchanged. [78]

One further population was undertaken by Tibaek *et al.* [79] who investigated the effect of PFM training on sexual function in men with lower urinary tract symptoms (LUTS) after stroke, which affects between 48-62% of sufferers. [80] Participants (n=31) presenting with ED following stroke were randomized into two groups and were provided with a PFM training intervention over 12 weeks (n=15), or no training (control, n=15), then crossed over. The intervention group participants were asked to perform a protocol similar to the MAPS study, in addition to working on endurance and PFM training during activities such as walking, with outcomes assessed by IIEF-5 questionnaires. Results indicated that PFM training was associated with better erectile function in men with LUTS after stroke, although statistical power was low. Adherence to the program was good, there was a low dropout rate and no adverse events were reported. The authors concluded that PFM training may have both short- and long-term effects on sexual function in men with LUTS after stroke. Given, the high rate of stroke in the general population, this is another group who might benefit from PFM training to improve QoL outcomes. [79]

The role of PFM in treating male sexual dysfunction, in conditions such as chronic pelvic pain syndrome (CPPS), has been the focus of several studies with new classifications by the International Continence Society identifying PFM as ‘non-contracting’, ‘non-relaxing’ or a combination of both. [81] Given the role of PFM contraction during the arousal, orgasm and ejaculation phases of the sexual cycle, and the need for relaxation at termination, any impairment of normal PFM function may be identified as a primary factor in ED. [82] In a review paper by Cohen, deficiency of normal penile function and an inability to facilitate and maintain erection was found to be linked to the functional strength and coordination of BC and IC muscle contractions. [64] Abnormally high PFM resting tone, with muscles contracting more often or more strongly than necessary, has been suggested as a possible cause of ED, with spasm potentially causing compression that restricts the lumen of the internal pudendal artery, reducing penile blood inflow. [83] The high prevalence of ED (40-72%) in men with CPPS is thought to interfere with normal physiological processes of corporal veno-occlusive function, which is dependent on sustained smooth muscle relaxation. [64] Hence, strategies to improve EF via PFM relaxation and down-training using a ‘bio-neuromusculoskeletal-pyscho-social’ approach are now recommended in the treatment of male sexual dysfunction and pelvic pain. [64] Research addressing specific PFM rehabilitation strategies in CPPS are not yet developed, however, the links to their role in sexual dysfunction potentially draws parallels to their role in ED post-RP.

The role of PFM in Erectile Function after Radical Prostatectomy

Given the proven benefits for UI in more than 50 studies examining this topic post-RP, it is apparent that far less is known about the comparative benefits of PFM training in ED recovery following RP. Following a thorough review of the existing databases including Medline, Google Scholar and PEDRO, just four previous investigations were found. A clinical case series by Sighnolfi *et al*. in 2009 was the first to assess the potential effectiveness of PFM rehabiltation following RP and provided stimulus for further research.[38] Subsequently, three RCTs by Prota *et al.* [84] (2012), Lin *et al.* [85] (2012) and Geraerts [26] (2015) assessed the impact of PFM training on ED following RP.

Prota's RCT was the first to analyze the effect of PFM training following RP in 33 men by comparing a group who received early pelvic floor biofeedback therapy (PFBT) once per week for 12 weeks versus a control group who received no PFBT or PFM training. [95] The intervention group were provided with a surface electrode inserted into the anus and a reference electrode place on the left lateral malleolus. Patients practiced three series of 10 rapid contractions, then performed three sustained contractions of 5, 7 or 10 s duration, depending on their ability to maintain a contraction. A further 10 contractions during prolonged expiration were completed in supine, with total treatment time of 30 minutes per session. Verbal and written instructions were also used to prompt daily home exercises while lying, sitting and standing. Erectile function was assessed at 1, 3, 6 and 12 months after catheter removal using the IIEF-5 and patients were considered potent when a total IIEF-5 score was higher than 20 out of a possible 25. Prota [95] reported that, at 12 months post-RP, 47% of the intervention group were considered potent compared to only 12% of the control group, with absolute risk reduction in the treatment group 35%. Of the 10 participants who regained potency, 90% also gained full continence recovery. [84] Overall findings of the study included a shorter duration and severity of ED when compared with controls. As both groups were of similar age, with similar rates of pre-operative potency (IIEF-5 scores), similar nerve sparing/neurovascular preservation (70%) and no utilization of PDEi-5 medications, no other factors could be attributed to the positive EF outcomes. [84]

Research undertaken by Lin *et al*. [85] assessed the impact of PFM on sexual dysfunction following RP and consisted of a control group (n=27) commencing PFM training in the third month post-RP versus an intervention group (n=35) who performed PFM training upon catheter removal. Participants were assessed at 1, 3, 6, 9 and 12-month intervals after using the MAPS (man after prostate surgery) PFM training regime of three PFM contractions in three positions, twice per day. Sexual dysfunction was higher in the control group across all time points, with the 12-month data showing most difference (93% of men in the control group versus 66% of men in the inervention group). The authors recommended early PFM training as an effective intervention for sexual dysfunction for RP patients, enabling a faster time course to recovery. [85]

Finally, Garaerts' [86] investigation in 2015 focused on providing PFM training to post-RP patients who displayed persistent ED at a minimum 12 months following surgery. The research assessed the impact of PFM exercise on erectile function recovery and climacturia. Participants (n=33) were randomized to either a treatment group who commenced PFM training at 12 months post-RP, or a control group who delayed PFM training for 3 months. All participants received individual PFM training by a therapist with PFM exercises supported during treatment sessions with electrostimulation of 10 minutes duration once per week for 6 weeks, then once per fortnight for the following 6 weeks. In addition, a home exercise regime of 60 contractions per day aimed at improving strength and endurance of PFMs were combined with dual tasks in varying positions. Unfortunately, specific details on protocols/exercises performed were not provided.

Outcomes were evaluated by the IIEF-EF questionnaire, a visual analogue scale (VAS) assessing erectile quality (hardness, length, elevation and persistence) and a question regarding the incidence of climacturia, pre-operatively and at 12, 15, 18 and 21 months post-RP. Results revealed significant improvement in the intervention group's recovery of EF (4.1) compared to the control group (- 0.2) in the IIEF-EF domain (p=0.025) at 15 months. In addition, the intervention group scored significantly better than the control group on scores of penile hardness, length, elevation and tumescence. This was a very positive outcome given the time delay from surgery. For the nine participants with climacturia in the intervention group, six showed improvement, compared to none from the control group (p=0.004). Of significance, apart from Sighnolfi's 2009 case study series indicating a significant reduction in climacturia with PFM training in just three men following RP [38], Geraerts' investigation was the first RCT to confirm improvement, with 43% of participants reporting a positive change in this larger sample.

Summary

ED is commonly experienced by men during their lifetime, with reduced function expected during the aging process. However, ED experienced by men following RP can be perceived as a sudden and drastic change, with less than 22% regaining their baseline performance levels 2 years out from surgery. The loss of nocturnal erections and ejaculation, alterations in appearance and sensation, and the impact on relationships can greatly impact a man's QoL and self-esteem. Although penile rehabilitation is becoming more commonplace, most of the available options are either invasive or have potential side-effects that may further exacerbate a man's distress. PFM training represents a proven, non-invasive option in the treatment of men with ED and, more recently, for post-RP patients, with no known side-effects.

It was hypothesized that a 'high intensity' PFM training regime commenced pre-operatively, compared to 'usual care', would lead to improved outcomes in erectile function for men undergoing RP. With an intervention period of 12 weeks and a pre-RP lead in time of 5 weeks, the ultimate goal of this study was to evaluate the possible benefit of PFM training on ED, as a potential non-invasive addition to penile rehabilitation. Education about PFM training and its positive relationship to erectile function in the fields of men's health and urology is not widely known. Improved knowledge gained from our investigations could assist in improving the QoL in men in PCa populations.

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CHAPTER 8

Paper 4:

Pelvic floor muscle training and erectile dysfunction in radical prostatectomy: A non-invasive addition to penile rehabilitation.

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Abstract

Objective: Pelvic floor muscle (PFM) training for post-prostatectomy incontinence (PPI) is considered a first line approach to rehabilitation, but PFM training for Erectile Dysfunction (ED) following surgery is less well researched. Commencing pre-operatively, and utilizing both fast and slow twitch fibre training performed in standing postures, new protocols were developed to address clinical presentations with aims to reduce ED and impact on quality of life (QoL). Comparisons to 'usual care' PFM training pre- and post-rehabilitation were also assessed.

Methods: A randomized controlled trial of 97 men undergoing radical prostatectomy (RP) were allocated to either a control group (n=47) performing 'usual care' of 3 sets/day PFM training, or an intervention group (n=50), performing 6 sets/day in standing, commencing 5 weeks prior to RP. Participants were assessed pre-operatively and at 2, 6 and 12 weeks post-RP using EPIC-CP, IIEF-5 and real time ultrasound (RTUS) measurements of PFM function.

Results: The overall QoL main effect for Group was significant ($p < 0.05$), however, post hoc analyses showed the only time point where this difference was significant ($p<0.05$) and clinically relevant was at 2 weeks post-RP, with the intervention group reporting less distress and lower bothersome scores. Secondary measures of EPIC-EF and RTUS PFM function tests demonstrated improvement over all time points in both groups.

Conclusions: Early PFM training reduces early QoL impact for post-prostatectomy ED, with faster return to continence enabling earlier commencement of penile rehabilitation. Whilst our 12-week protocol and sample size was not powerful enough to demonstrate conclusive benefits of early PFM training for ED, PFM intervention post-RP over longer times has been supported by others.

Introduction

Prostate Cancer (PCa) is the most commonly diagnosed cancer in men with more than 1.1 million new cases diagnosed globally. [1] Radical prostatectomy (RP) is the gold standard approach to cure and approximately 97% of men can expect to survive at least 5 years following surgery.[1] Side effects from treatment can, however, greatly impact on the quality of life (QoL) of a man and also his partner. [2,3] These side effects include urinary incontinence (UI), erectile dysfunction (ED) and climacturia (loss of urine with orgasm). [4] More than 70% of men report adverse effects following the diagnosis and treatment of PCa and ED is known to have a greater negative impact on QoL than UI, affecting 26-100% of men [2,3,5,6] with only 16-22% regaining pre-surgery levels of erectile function. [7] This large range reported by various authors is indicative of the challenges of research in this field, with many differing methods of assessment potentially adding to uncertainty post-RP distress. Depression, anxiety and post-traumatic stress occur four times more often in men with PCa, compared to their healthy counterparts [8] and the link with ED is well-established.[9] Strategies to minimize the impact of ED following RP are an important consideration and education from the time of diagnosis should include conservative, evidence-based measures such as pelvic floor muscle (PFM) training [10] and penile rehabilitation [11,12] to enhance recovery.

Many studies have demonstrated the benefits of PFM training for treating UI in men following RP. [13,14] Our recent study utilising high intensity PFM training, pre- and post-RP, to reduce the severity and duration of UI confirmed that the combination of a fast- and slow-twitch muscle contractions performed in functional positions at a high frequency resulted in significantly less leakage and improved QoL outcomes associated with continence when compared to ‘usual care’ patient controls. [15] Previous literature regarding the role of PFM training in addressing sexual dysfunction in men following RP is limited, however, three reviews outling the link between ED and PFM training in normal populations have been published. [16,17-18] This evidence has confirmed a direct link between PFM strength and increased rigidity in the erect penis, and as a result, PFM training is recommended as a first line approach for men seeking resolution of ED. [10]

During RP, the cavernosal nerves that are responsible for erectile function may be damaged or even removed, compromising function.[19] Nerve conductivity problems can ensue, which diminish nitric oxide synthesis required for mediating smooth muscle relaxation and vasodilation in normal penile erection. [20,21] Nerve sparing techniques [22] and penile rehabilitation (PR) utilising medication, vacuum compression pumps, and intra-cavernosal injections are now considered best practice to minimize side effects, given that erectile tissue takes 3-4 months from surgery to recover, and 3-4 years for resolution. [11,12,20] Most of these strategies are invasive, however, and patient compliance to treatment can be poor, with 50-80% discontinuing within one year. [23,24] Since EF is an important survivorship issue among PCa patients, opportunities to pursue and maintain ED treatments may be enhanced by the incorporation of non-invasive methods such as PFM training.

PFM training following RP is a relatively under-studied topic, with only three trials [25-27] and one case study [28] found using multiple online search engines. Furthermore, there have been no published studies regarding the potential impact of pre-operative PFM training (i.e. performed prior to RP) on subsequent ED. Prehabilitation has been recommended for post-RP UI and several recent reviews have confirmed its benefit, with leakage and incontinence lasting for shorter durations. [29,30] In this study we aimed to assess the impact of PFM training on ED and QoL in a prospective study that compared 'usual care' PFM training with an intervention of greater exercise intensity and volume, both beginning approximately 5 weeks prior to RP and continuing for 3 months thereafter.

Methodology

This study was approved by the UWA Human Research Ethics Committee (Ref: RA/4/1/6327) and all participants provided written informed consent. The trial was registered in the Australia New Zealand Clinical Trials Registry and allocated as ACTRN12617001400358. Participants were enlisted from a cohort of patients referred sequentially by their Urologist for pre-prostatectomy PFM training to a single physiotherapy clinic and randomly assigned to a treatment or control ('usual care') group. Patients with pre-existing ED, type 1 diabetes, prior prostate surgery, or a history of receiving radiation or androgen deprivation therapy, were excluded. Both open RP and Robotic-Assisted Laparoscopic Prostatectomy (RALP) surgical types, performed by experienced surgeons operating at two high volume institutions were included, and similar numbers were assigned to each group (Table 1).

Table 1. Participant Characteristics

Characteristics	Control Group (n=47)	Intervention Group (n=50)
Age (y)	63.5 ± 6.8	62.2 ± 6.8
BMI	25.4 ± 2.7	25.3 ± 2.7
Pre-surgery training (weeks)	5.1 ± 3.2	5.2 ± 2.8
Gleason score	7	7
Prostate size (g)	49.5 ± 15.5	50.8 ± 18.6
Operation type	8 Open 39 Robotic-assisted	5 Open 45 Robotic-assisted
Nerve sparing procedure	5 Unilateral 39 Bilateral 4 Nil	12 Unilateral 36 Bilateral 2 Nil
Nerve tissue resected (g)	0.27 ± 0.22	0.32 ± 0.27
Catheter in situ (days)	8.6 ± 3.0	8.1 ± 2.7
Climacturia	17/47 (36%)	17/50 (34%)
(0-5mls leakage)	15/17 (82%)	15/17/ (88%)
(>5ml leakage)	2/17 (12%)	2/17 (12%)
Unsure of leakage	1/17 (6%)	0/17 (0%)
Nil sexual activity	6/47 (12.7%)	1/50 (2%)

Pre-surgery PFM training

Participants in both groups received physiotherapy-directed PFM training over two sessions of 30 minutes duration, approximately 5 weeks prior to RP surgery, with both groups then prescribed a daily PFM training program that differed in mode and intensity. Both groups were provided with active intervention programs as it was deemed unethical to not provide any treatment option, given the body of positive research in this field and the expectations of Urologists referring their patients for prehabilitation. During the PFM training sessions, each participant was given written and verbal instructions on correct PFM exercise technique,[31] to ensure a full contraction and relaxation cycle was implemented with the cue to "stop the flow of urine and shorten the penis while continuing to breathe". [31] Cues to relax abdominal muscles and avoid breathe-holding were also communicated and confirmation of correct technique provided with real time ultrasound (RTUS) assessment as a biofeedback tool. Participants completed a PFM training diary to record the number, type and position of exercises undertaken daily.

In the 5 weeks prior to surgery, members of the control group were directed to perform three sets of PFM exercises per day, with 10 contractions per set, aiming to hold for a duration of 10 s, with an equal rest time, providing a total of 30 contractions per day. Each daily exercise set was to be performed once in supine, sitting and then standing, in accord with previously reported interventions. [32,33] Members of the intervention group were required to perform six sets of PFM exercises per day, with each set comprising 10 fast (1 s duration) and 10 slow (10 s duration) contractions with an equal rest time, providing a total of 120 contractions per day. All sets were performed in standing for this group. Adherence to PFM training programs for members of both groups was assessed via individual diary entries during fortnightly physiotherapy appointments.

Post-surgery PFM training

Post–surgery PFM training was recommenced following removal of the catheter. Members of the control group performing three sets per day of the same exercises performed pre-surgery, while members of the intervention group continued their exercise regime with six sets per day. Both groups exercised in the postures as described above for the pre-surgery period and these protocols were maintained throughout the 12-week assessment period.

Outcome measures

Erectile function was assessed pre-operatively and at 2, 6 and 12 weeks post-RP using the validated IIEF-5 [34] and EPIC-CP [35] questionnaires. Participants completed the questionnaires in a private room at the completion of a scheduled physiotherapy appointment. Secondary measures of PFM function were assessed via real time ultrasound (RTUS) and included the Rapid Response Test (RRT) and Sustained Endurance Test (SET),[36] performed by a single operator for each measurement using a point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China) and were recorded at each post-surgery time point.

Statistical Analysis

Outcome data were entered into SPSS (v22.0, SPSS, Chicago, IL) for subsequent analysis. A series of two-factor, repeated measures ANOVA (Group x Time) were performed and significance was accepted for all analyses at $p<0.05$. Where necessary, post-hoc t-tests for independent samples were performed to determine the time points at which group scores differed.

Our sample size included 101 participants, 97 after dropout, who were randomised to 2 groups (n=50 and 47). Our power calculations was based on the study of Geraerts *et al* [27] as the closest exemplar. They studied 33 patients after RP who were randomised into a PFMT treatment (n=16), or control group (n=17). The outcome measures were IIEF domain scores (their Table 2), similar to the current study.[27] Geraerts *et al.* indicated that a change of 4.1 units (±5.6) in the intervention group, with change of -0.2 (±2.4) in the controls. This difference was statistically significant (P=0.025). Given highly conservative *a priori* assumptions of $\alpha=0.01$, a two-tailed test and a sample size of 40 per group, our study possessed >98% power to detect a similar effect size observed by Geraerts *et al*.[27]

Results

Of the 101 participants recruited to the study, 97 (n = 63±7 y, BMI = 25.4, Gleason 7, Stage T2c) completed the trial, with three participants from the control group (n = 47) and one participant from the intervention group (n = 50) unable to finish the study due to medical complications. These complications included the need for radiation therapy (n = 2) and corrective surgery (n = 2). There were no appreciable group differences between participant characteristics with only a few in each group having open RP versus RALP surgery (Table 1). Prostate size, Gleason score and days of catheterization were also similar between both patient groups, as was rate and type of cavernosal nerve sparing with an average 0.27 g nerve resection achieved in the control group compared with 0.32 g in the intervention group. Missing data were treated using a mean substitution method. Mean data for six participants were substituted at various assessment time points (less than 0.7% of data for analysis) due to several participants reporting ‘not applicable’ for responses to sexual function. In these cases, participants were experiencing significant urinary leakage or had not yet reached a stage of recovery sufficient to attempt sexual activity with confidence.

EPIC-CP QOL outcome scores

The data are presented in Figure 1 for intervention and control patient groups from baseline (pre-surgery) to 12 weeks post-surgery on the EPIC-CP QOL score. The ANOVA results show a significant main effect for Group ($F = 4.607$; $p=0.034$) and Time ($F= 143.364$; $p<0.001$), but not the Group x Time interaction ($F= 1.002$, $p=0.392$). When assessing the effectiveness of the prehabilitation intervention, we note a statistically ($p<0.05$) and clinically relevant difference between groups at the 2-week time point, with the intervention group performing better. The group differences at baseline, and weeks 6 and 12 post-surgery, were only in the order of 2 units and this is not considered clinically relevant. [37]

EPIC-CP-EF erectile function domain

Pre-surgery erectile function scores were similar between groups, and there were no other group differences at any of the post-surgery time points (Figure 2). The ANOVA results show a significant main effect for Time ($F = 129.529$; $p<0.001$), but not for Group ($F= 2.006$; $p=0.160$) or the Group x Time interaction ($F= 1.217$, $p=0.304$).

IIEF erectile function

Pre-surgery scores were similar between groups, and there were no other group differences at any of the post-surgery time points (Figure 3). The ANOVA results show a significant main effect for Time ($F = 159.656$; $p<0.001$), but not for Group ($F= 0.575$; $p=0.450$) or the Group x Time interaction ($F= 1.306$, $p=0.273$).

Pelvic floor muscle function tests

Results for the RRT are shown in Figure 4. Pre-surgery RTUS assessments were not performed so as to avoid any possible training effect for the control group participants. However, at all time points post-RP, the intervention group recorded quicker (i.e. enhanced) RRT scores compared the control group ($p<0.05$). The ANOVA results show significant main effects for Group ($F= 16.132$; $p<0.001$) and Time ($F= 69.790$; $p<0.001$), but not the Group x Time interaction ($F= 2.12$; $p=0.123$).

Finally, Figure 5 provides results for the SET assessment. At all post-surgery time points, the intervention group recorded more sustained (i.e. enhanced) SET scores compared the control group ($p<0.05$). The ANOVA results show significant main effects for Group (F=

12.605; $p=0.001$) and Time ($F= 137.671$; $p<0.001$), but not the Group x Time interaction ($F= 0.679$; $p=0.508$).

Discussion

In our trial, participants were randomized 5 weeks prior to surgery to either a high intensity or 'usual care' PFM training program for the pre-rehabilitation of radical prostatectomy-related erectile dysfunction. Assessments were undertaken at baseline pre-operatively (5 weeks) and at 2, 6- and 12-weeks post-RP surgery, to ascertain the effect on QoL and sexual dysfunction by utilizing the EPIC-CP and IIEF-5 questionnaires. Following RP there was a drastic and immediate reduction in EF in both groups. At all time points there was a significant difference ($p< 0.05$) between groups, however, the only time point where this difference was clinically relevant was at 2 weeks post-RP, with the intervention group reporting less distress in the EPIC-CP QOL outcome. This instrument includes an analysis of urinary bother, urinary leakage and mood domains as well as ED. When assessing the ED domain scores only, there were no group differences across the time points, and IIEF-5 scores were also similar.

Rates of improvement, supported by reductions in EPIC-CP and EPIC-EF scores and increases in IIEF-5 scores, occurred for patients in both groups, at a similar rate across all time points, with no appreciable differences between the two groups. Thus, we were able to confirm that there were no early benefits for EF as a result of pre- and early post-RP PFM high intensity training, and no apparent differences between the control and intervention protocols within the first 3 months following RP. Previous studies, however, have demonstrated improvements in EF scores when utilizing PFM training for 12 weeks post-RP when tracked over a longer follow-up period, with significant outcomes noted at 6 and 12 months post-RP for experimental versus control groups. [25,26] Prota *et al.* for example assessed men who received PFM training with biofeedback, once per week for 12 weeks, and compared these to a control group. [25] The authors reported that 47% of the intervention group were considered potent compared to only 12.5% of the controls. Of the 10 participants who regained potency, 90% regained full continence. [25] Lin *et al.* [26] assessed the impact of PFM training on sexual dysfunction in a control group who commenced PFM training at 3 months post-RP, compared to an intervention group who commenced training soon after catheter removal. Participants were assessed at 1, 3, 6, 9 and 12 months, with rates of sexual function reported as being poorer among the control group participants across all time points. The 12 month data showed the greatest difference, with 92.6% of the control group, versus 65.7% of the intervention group, displaying impotence. [26]

A 3-month PFM training intervention for men with long-term ED greater than 12 months post-RP was undertaken by Geraerts *et al.* to ascertain benefits on both sexual dysfunction and climacturia, following the opportunity for spontaneous recovery. [38] Their results revealed significant improvement in the recovery of erectile function and climacturia within the intervention group compared to the control participants. These results concur with evidence reporting a significant neuropraxic effect in the immediate post-operative time frame, after which erectile tissue begins to recover. [7,20] In this context it is notable that the most commonly utilized first-line treatment, PDE5i medications, provide only 12-17% of men with a response within 6 months of RP. [7] Thus, although our 12 week exercise protocol and sample size were not powerful enough to demonstrate conclusive benefits of ED in this study, PFM training may prove effective with a 6-12 month follow-up, as has been reported by others. [4,26]

In our study, a significant difference in urinary continence rates was observed, with 75% of the intervention group, but only 43% of the control group dry at 3 months. [15] Hence, extending the control group protocol beyond this time was not considered ethical and at 3 months, both groups continued with high intensity PFM training. Prota *et al.* found that a strong association between recovery of continence and potency, with continent patients having a 5.4-fold greater chance of being potent at 12 months post-RP. [25] Similar findings by Kao *et al.* [39] and Burkhard *et al.* [40] further support the relationship between UI and potency following RP, with indications that nerve-sparing and neurovascular bundle preservation may also assist the recovery of both functions. At 2 weeks post-RP there was a significant difference ($p<0.05$) in EPIC-CP scores between our intervention and control groups when UI questions were included in the analysis, indicating QoL at the early stages of RP rehabilitation is most impacted by continence outcomes. As seen clinically, men report distress and embarrassment with loss of urine associated with erectile function. As both climacturia and sexual arousal incontinence [41] occur in 20-40% of men following RP,[42] many men choose to defer sexual activity until continence resolution.

Our secondary measures assessed PFM function utilizing functional tests developed and validated for men and have been previously reported. [36,43] Using RTUS tests that directly visualized and quantified function of the PFM during standardized tests, we were able to demonstrate lower RRT scores across all time points for the intervention versus control group, corresponding to the finding of significantly less leakage at 2 weeks post-surgery and a quicker return to continence for men who undertook the intervention training protocol. [15] Similarly, higher SET scores for the intervention group across post-surgery time points were also reflected in reduced leakage and time to continence for the intervention group. [15] By providing men with an improved PFM training protocol for faster continence resolution, the opportunity to engage in sexual activity earlier is likely to have a positive impact on QoL, as evidenced by EPIC-CP at 2 weeks post-RP in the current study.

Following RP, QoL outcomes are a significant consideration, given the likelihood of long term survival rates. Evidence from a recent study showed that only 16-22% of men return to pre-operative erectile functional capacity at 2 years post-surgery, [44] and just 28% report erections strong enough for intercourse at 5 years. [45] In a qualitative analysis of 27 PCa survivors and their partners by Albaugh, [3] issues of frustration due to changes in sexual function lead to feelings of loss and grief and in several cases, suicidal ideation. Men reported the psychologically devastating effects of feeling abnormal, unnatural and less of a man due to their sexual dysfunction and, in both men and their partners, a sense that this change had a great impact on every aspect of their lives. The importance of education and comprehensive information before and following PCa treatment was considered a significant contributor to reducing distress and for those men who been well prepared for the sexual side effects of treatment, acceptance to the changes were far less devastating. [46]

The opportunity to hasten recovery of EF is the goal of penile rehabilitation, and PFM training potentially offers an adjuvantive strategy. [25,26,47] Whilst we were not able to demonstrate significant impact of high intensity versus ‘usual care’ PFM training on ED in the immediate post-RP period, longer term analysis may have mirrored the results of some previous investigations. However, given the importance of erectile function following treatment for PCa and the expected time frame for spontaneous recovery, the addition of PFM training provides an opportunity for patient driven, positive rehabilitation stratgies from the point of diagnosis.

In conclusion, PFM training has an important role in managing ED and, as demonstrated in the literature, leads to a faster return to continence following surgery for PCa. Previous authors have established the benefits of PFM training and biofeedback in the long-term recovery of erectile function following RP. The opportunity to enhance QoL outcomes following diagnosis and treatment of PCa, through early interventions and education, is well supported in the literature. PFM training, whilst not immediately impacting on improved sexual function, causes no harm, has potential benefits that align with the normal progression of erectile tissue recovery following RP and may be utilised as an additional, non-invasive component of PR.

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Figure 1. Changes in the EPIC-CP quality of life (QOL) scores for patients following radical prostatectomy within the intervention and control groups at baseline, then at 2, 6 and 12 weeks post-surgery, with lower scores indicating better outcomes. * indicates a significant difference ($p<0.05$) between groups at the relevant time points.

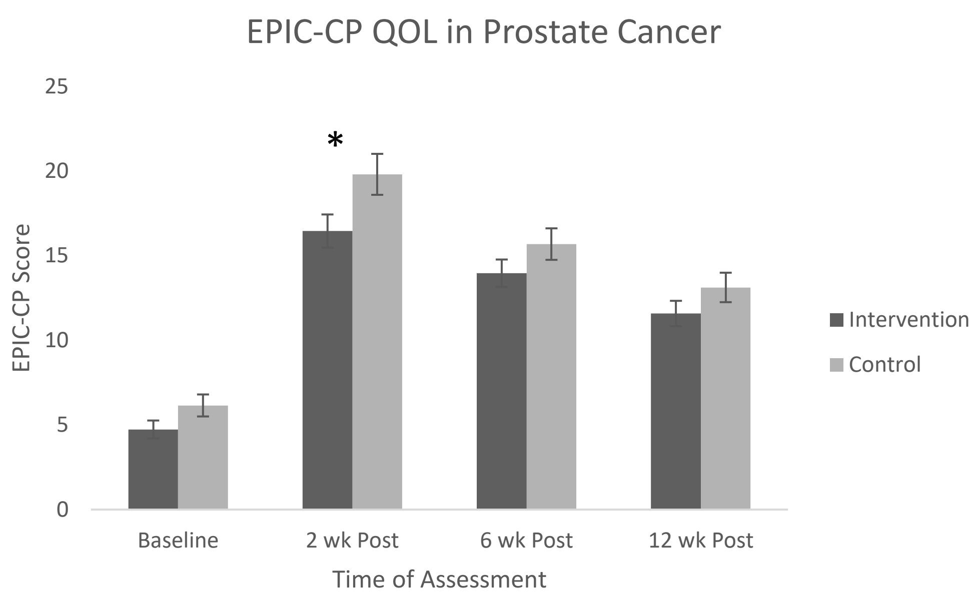


Figure 2. Changes in the EPIC-CP erectile function (EF) domain scores for patients following radical prostatectomy within the intervention and control groups at baseline, then at 2, 6 and 12 weeks post-surgery. The EPIC-CP EF domain (maximum score = 12) assesses self-reported symptoms, with lower scores indicating better outcomes.

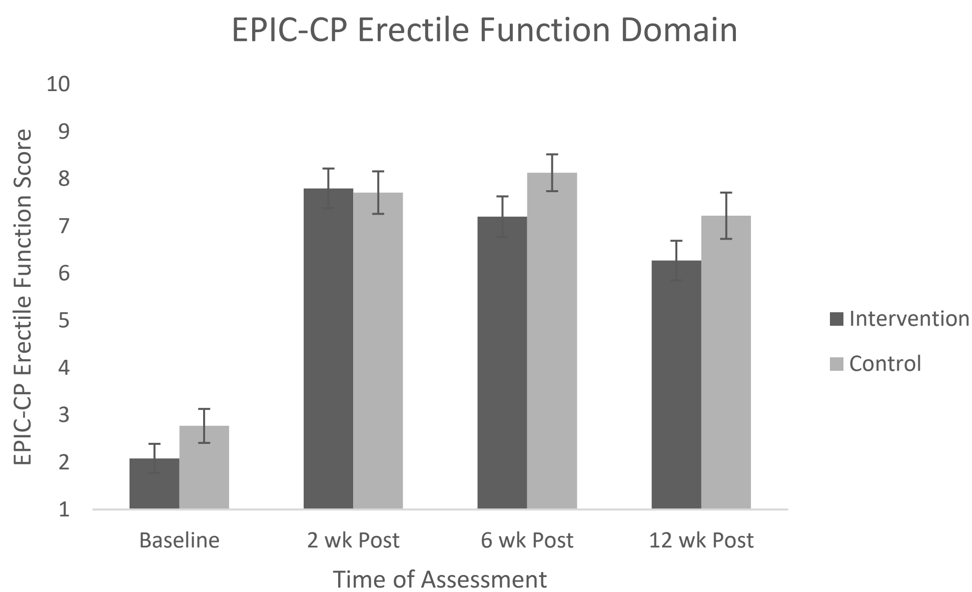


Figure 3. Changes in the IIEF erectile function (EF) scores for patients following radical prostatectomy within the intervention and control groups at baseline, then at 2, 6 and 12 weeks post-surgery. The IIEF EF score assesses self-reported symptoms, with higher scores indicating better outcomes.

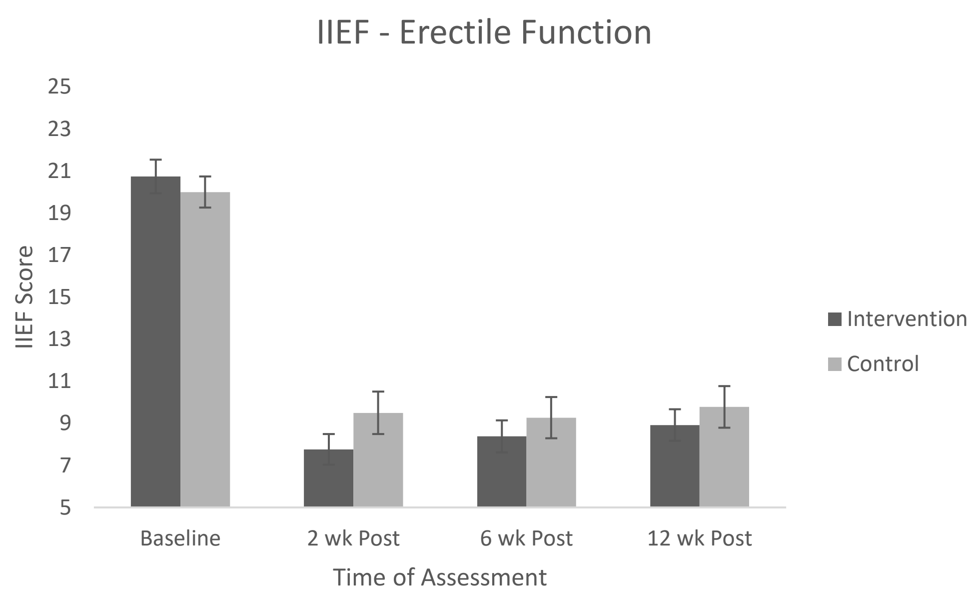


Figure 4. Changes in the Rapid Response Test (RRT) for patients following radical prostatectomy within the intervention and control groups at 2, 6 and 12 weeks post-surgery. The RRT uses real time ultrasound (RTUS) to measure the speed of pelvic floor muscle contractions, with lower scores representing a better outcome. * indicates a significant difference (p<0.05) between groups at the relevant time points.

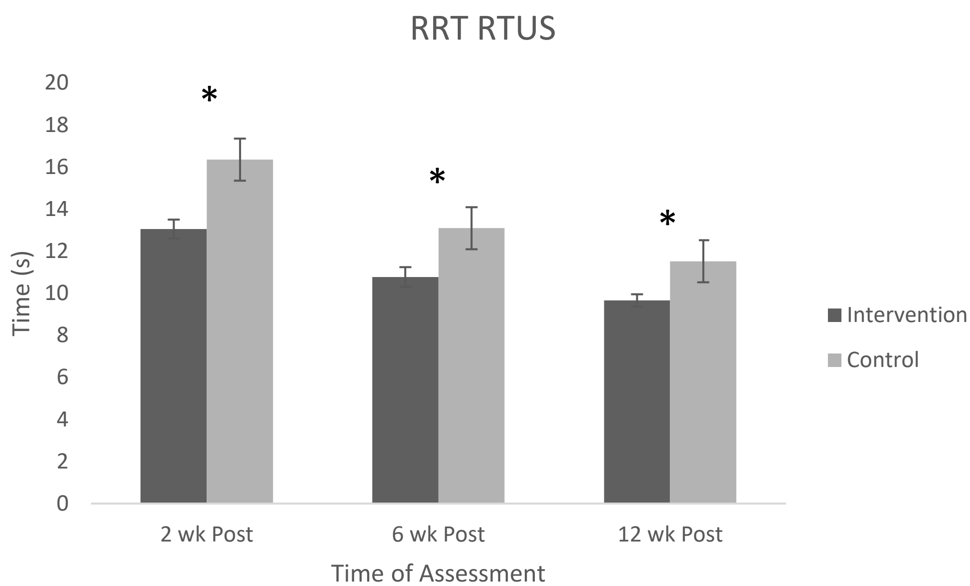
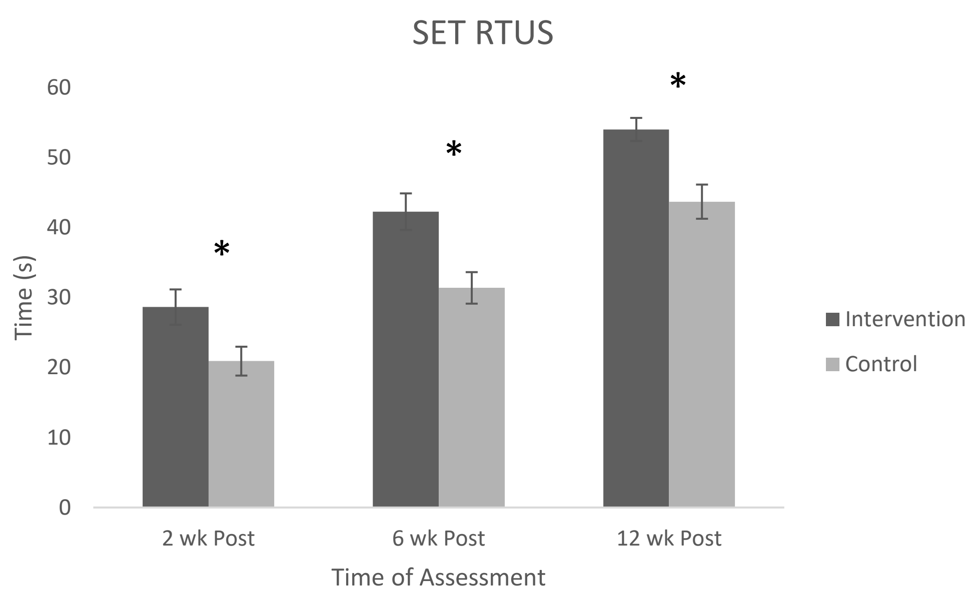


Figure 5. Changes in the Sustained Endurance Test (SET) for patients following radical prostatectomy within the intervention and control groups at 2, 6 and 12 weeks post-surgery. The SET uses real time ultrasound (RTUS) to measure the endurance of pelvic floor musculature to sustain a contraction over time (maximum score = 60 seconds), with higher scores representing a better outcome. * indicates a significant difference (p<0.05) between groups at the relevant time points.



CHAPTER 9

Part 3: Literature Review – Peyronie's Disease

Peyronie's Disease: Background

PD is a symptomatic disorder characterized by a variety of penile symptoms including pain, curvature, shortening, narrowing, indentation, hinge deformity, palpable plaque and erectile dysfunction (ED). [1] Patients with PD develop penile deformity due to the formation of a plaque in the tunica albuginea (TA) of the corpora cavernosa [2] which is believed to occur as a result of aberrant wound healing in physically susceptible individuals (Figure 9.1). [1] Formation of fibrous inelastic plaques within the TA potentially leads to compromised sexual function, with the reduced ability for sexual penetration and consequent psychological and psychosocial distress. [2] With as many as 81% of men with PD reporting emotional difficulties, 48% clinically meaningful depression and 54% relationship difficulties, the impact on individuals and their relationships can be significant. [2] The challenges of PD include alterations in sexual relationships, restrictions in intimacy, socialisation and stigmatisation, along with complete deferment of relationships, which in younger patients may lead to avoidance of fathering and parenthood options. Improved awareness and education about the impact of PD and potential treatment options need further development.

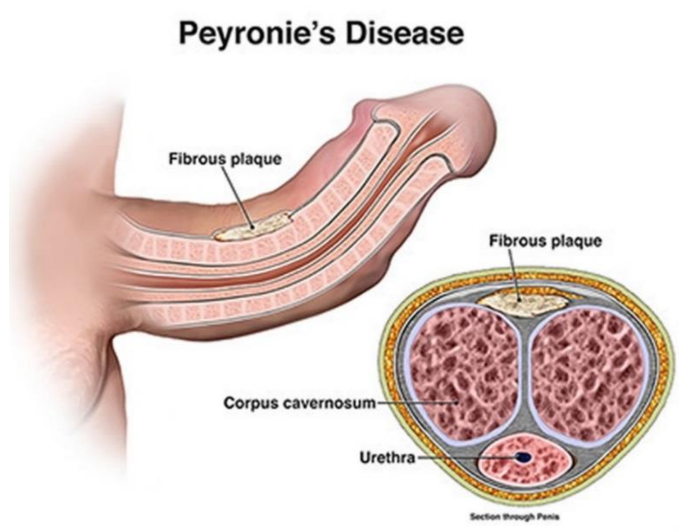


Figure 9.1 Peyronie's disease and plaque formation
(reproduced from *www.jamaicaobsever.com* 27.11.18)

Incidence of Peyronie's Disease

Estimates of the prevalence of PD range from 2-9%, although patient embarrassment may preclude many men from seeking treatment and the incidence may be much higher. [3,4] A recent analysis of 534 men undergoing screening for PCa confirmed 9% of men presented with PD [5] and in sequential autopsy studies by Smith, [6] 22% of men were diagnosed with the condition. The peak incidence of PD is around 55-60 years of age and is known to be associated with ED, diabetes, obesity, hypertension, A-positive blood type, hyperlipidemia, smoking and pelvic surgery. [4] In addition, two thirds of men with PD are likely to exhibit risk factors for arterial disease and are more likely to have disease progression and worsening of ED if left untreated. [1] Dupuytren's contracture (scar tissue formation in the hand) is also prevalent in 39% men with PD compared, with 1.2% of men without PD [7] (Figure 9.2) and, following radical prostatectomy (RP), 16% of patients will also acquire PD. [8] Although the onset of PD might be associated with a history of buckling during sexual activity, an identified history of penile trauma is uncommon and recalled by only 10% of patients older than 40 years. [4,9] A further 10% of PD presentations occur in men under 40 years, with teenagers also known to develop the condition. [10] It is also hypothesized that PD is commonly under-diagnosed in the clinic, especially among men incapable of achieving quality erections, which may preclude the PD-associated deformity to become evident. [8]

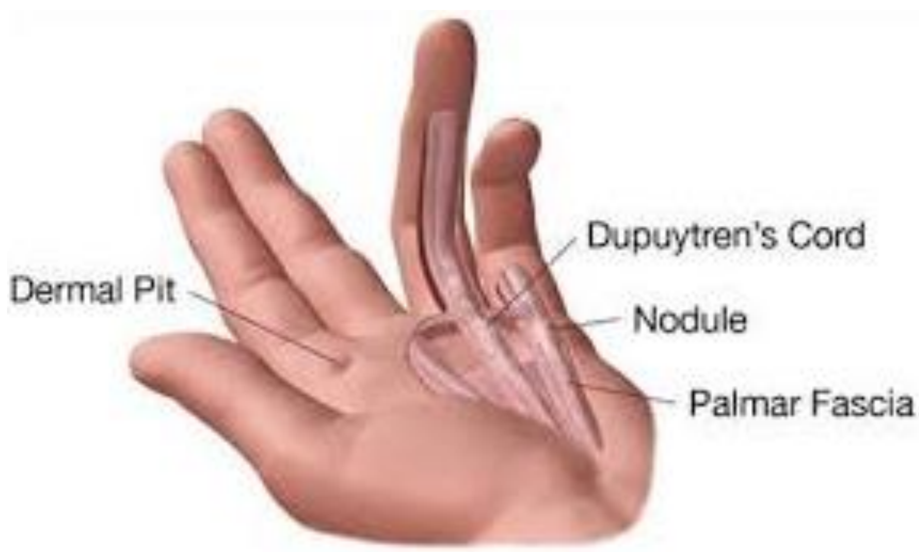


Figure 9.2 Dupuytren's contracture in the hand (reproduced from *www.smna.org* 27.11.18)

Aetiology of Peyronie's Disease

Although the exact aetiology of PD remains unknown, the condition presents as a disorder of wound healing in which an inflammatory response stimulates fibroblast proliferation and collagen accumulation, leading to the production of fibrotic lesions within the structural layers that envelope the penis (the TA) in genetically predisposed men. [11] This is most commonly thought to occur with repeated micro-trauma to the erect penis during sexual activity causing inflammation and disruption of the TA's elastic fibres. [12] The inner layers of the TA contain the cavernosus tissue and are oriented circularly, providing supportive intracavernous pillars which augment the internal septum of the penis during erection, whilst the outer layers are oriented longitudinally. Any damage of the TA resulting in fibrosis physically limits expansion at the site of the plaque during erection (Figure 9.3). [13] Recent studies have suggested that vascular trauma leads to osteoid formation via osteoblast-like cells originating from the vascular lumen, with upregulation of osteoblast specific factor 1 potentially responsible for plaque formation. [12] This transforming growth factor, TGF-β1, is the predominant pro-fibrotic factor in the development of Peyronie's plaques and it is thought to be released in an autocrine manner in genetically susceptible individuals, potentially leading to chronic disease progression and obliteration of normal tissue architecture. [1,14] Another theory for potential explanation of PD is cavernosal hypoxia, which induces collagen deposition and fibrosis, and is possibly responsible for morphological changes and the development of PD following RP. [8]

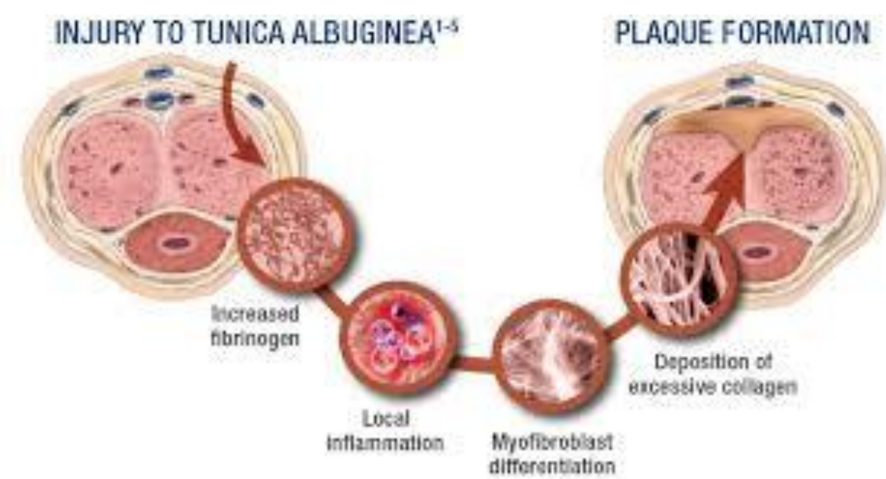


Figure 9.3 Injury to tunica albuginea in Peyronie's Disease
(reproduced from *www.peyroniesdisease-xiaflex.com* 27.11.18)

Pathophysiology: Acute and Chronic Phases in Peyronie's Disease

The natural history of PD remains controversial, however, there are generally two distinct phases; acute and chronic. [1,12] In the initial, acute phase, an inflammatory response is characterized by penile pain, plaque tenderness and the development of penile deformity, including palpable nodules and penile shape changes such as curvature, hinging, hour-glass formation and indentation. [4,12] In the subsequent chronic fibrotic phase, pain may subside and deformity generally stabilizes with stable disease; defined as being clinically unchanged for 3 months based on patient reporting or clinical documentation. [11] By 12-18 months after the onset of PD, nearly all patients are stable and will not spontaneously improve or worsen. However, prolonged inflammation may contribute to an increasing density of plaques and progressing to calcification or ossification, a situation that is considered irreversible and linked to chronic PD, with surgery generally accepted as the only course of action for treatment. [12] Of significance, Mulhall's 2006 investigations of 246 men diagnosed with PD found that 89% had pain that resolved at 1 year, 12% experienced spontaneous improvement in penile curvature, 40% had remained stable and 48% had worsened over 12 months. [15] Thus, most men with the condition will find their penile changes to be permanent.

Diagnosis of Peyronie's Disease

Generally, the diagnosis of PD is based on clinical findings with history and physical examination being satisfactory indicators. Symptoms generally differ according to the phase of the disease, after which medical treatment options are directed. Penile examination includes palpation for nodules or plaques, flaccid stretch length and girth and, if possible, during erection to assess penile length, rigidity, girth and curvature. [16] Curvature direction corresponds with the location of the plaque and, for most patients, the most common presentation is on the dorsal aspect of the mid-shaft of the penis, with lateral and ventral plaques less likely. [4] General examination of the hands and feet is also recommended to detect the possibility of Dupuytren's contracture (Figure 9.2) or Lederhosen scarring of the plantar fascia. [12] Subjective questionnaires recommended for PD include an assessment of erectile function, utilizing the IIEF [17] and the validated Peyronie's Disease Questionnaire (PDQ), a 15-question survey that records penile pain, impact on partner, bothersome scores and patterns of sexual intercourse relating to the presence of PD.[18] The PDQ has recently been recommended as a highly reproducible measure of PD, with recommendations for its use in treatment settings and clinical trials. [19]

For accurate diagnosis of PD, and to assist in counselling patients for prognosis, Penile Duplex Doppler Ultrasonography (PDDU) is the preferred method of examination as it can best determine plaque characteristics (Figure 9.4). [12] Interruptions to cavernosal arterial blood flow and larger plaque size, observed on colour PDDU, have been strongly related to ED during the appraisal of PD. [20] In the clinical setting, digital photographs are often used to assess the degree of curvature in combination with goniometers, or phone applications that measure angles, as evaluation of the flaccid penis is inadequate for evaluating PD deformities. [4] Another option when assessing the angle of curvature is to utilize penile injections, in the form of ICIs, to determine the extent of PD angulation and erectile response. [1,4] Due to the invasive nature of this test, however, it was not utilized in our research.

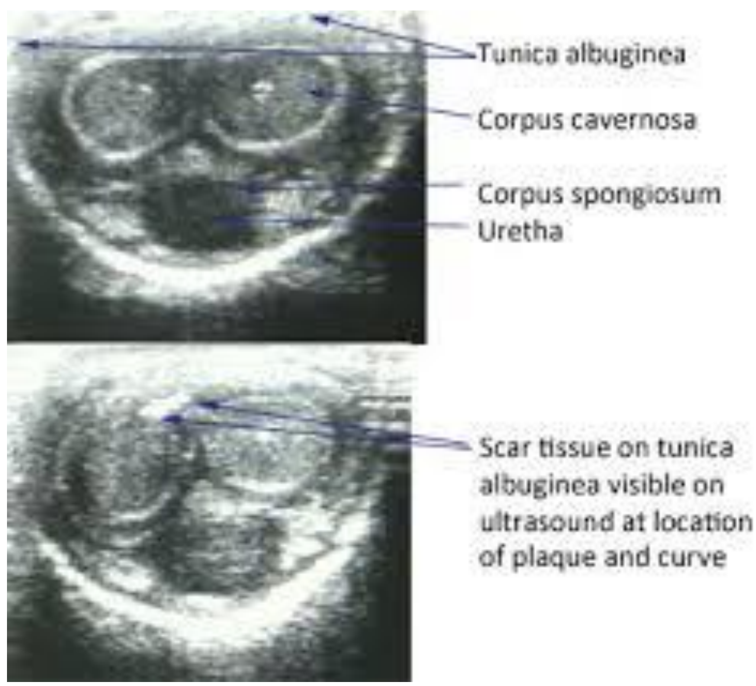


Figure 9.4 Peyronie's disease visible on PDDU
(reproduced from *www.slideshare.com* 27.11.18)

Treatment for Peyronie's Disease

Despite the publication of recommendations and guidelines, there is no consensus on the optimal management of PD. [1,4] Factors such as the potential benefits and risk for adverse events should be openly discussed with patients, given the potential impact on self-esteem, sexual function and QoL. [2] Determining the most appropriate treatment for each individual depends on a variety of factors including the stage of disease, presence of pain, severity and direction of curvature, penile length and the patient's erectile function status. [12] It is widely agreed that optimal patient management requires early detection and onward referral for treatment will achieve maximal functional and psychological outcomes. Treatments are available in the form of non-surgical and surgical options.

Non-surgical treatments target PD at the early stage of diagnosis with aims to decrease penile pain and inflammation, disease progression, penile plaque and deformity. [12] It is also encouraged that treatment may not be necessary if pain and curvature are minimal, and normal sexual function is maintained. [4] Non-surgical options for treatment are highlighted below.

A. Non-surgical options

<u>Oral therapy</u>

There is no oral agent that cures PD and many have been used 'off-label' without efficacy proven in clinical trials. Oral agents that have been used include Vitamin E, Potassium para-aminobenzoate, Tamoxifen, Colchicine and Acetyl esters of carnitine. Pentoxifylline is amongst the most frequently recommended medications and is a non-specific phosphodiesterase inhibitor which appears to improve penile curvature and stabilize the process of mineralisation within the plaques by increasing penile nitic oxide. [16] However, the medication needs to be taken three times per day and has undesirable side-effects of gastrointestinal upset, nausea dizziness and headache. [4] Most recently, phosphodiesterase type-5 inhibitor (PDE5i) drugs are being utilized as a long term pharmacotherapy option and there is a growing body of evidence that they may decrease the ratio of collagen to smooth muscle in the PD-like plaques. However, this has only been trialed in animal studies. [21] Given the body of knowledge developing for the general use of PDE5i for ED, and since the two conditions commonly co-exist, low-dose PDE5i are now part of everyday practice in the urological setting, particularly in the acute stage. [1,4,12] Disadvantages of

PDEi use are that oral agents appear to be effective in less than 40% of cases, and are ineffective in complex deformities. [1]

Intralesional injections

Pharmaceutical agents that are directly injected into PD plaques are currently being investigated, with early clinical results showing promise for improvement as more concentrated pharmacological doses can be administered without the impact of systemic side-effects. [4] Such agents are primarily used in the chronic or stable phase of the disease, however, treatment is effective in less than 40% of patients.[1] The most commonly recommended options include:

i. *Collagenase Clostradial (Xiaflex):* Collagenase acts selectively to break down collagen via the introduction of a purified bacterial enzyme that aims to break down the plaque; smaller plaques were found to be more responsive at earlier stages of the disease. Their use has been the focus of several placebo-controlled RCTs that have demonstrated reduced curvature (up to 37%), plaque size, and physical deformities such as hour-glass presentations. Treatment course consists of four cycles of two injections per cycle, and penile modelling exercises, with 6 weeks between each cycle. However, the treatment is very expensive at approximately A$1200 per dose. Adverse side effects include penile pain, bruising, swelling, redness and itching around the injection site, and is considered to be effective in approximately one third of cases, especially in men with a penile curvature of less than 60^{o}. [12]

ii. *Verapamil:* Verapamil works as a calcium channel blocker which inhibits fibroblast proliferation and may be useful for the acute phase of PD to stabilize disease or reduce penile deformity. [12,22] Some studies have shown Verapamil results in a significantly reduced curvature and reduction in plaque size with best results obtained in men without calcified plaques, curvature less than 30^{o} and disease duration less than 2 years.[23] Minor side-effects have been reported such as nausea and bruising, and its current use is ‘off-label’. [22]

External shock wave therapy (ESWT)

Low intensity ESWT for the treatment of PD has been found, via two studies, to have only limited effectiveness. [24,25] ESWT is thought to inflict damage to the penile plaque to induce remodeling, thus enhancing the vascularity of the area by increasing macrophage activity, plaque destruction and absorption. [12] Although penile pain did reduce significantly in a placebo-controlled trial, no improvement in penile curvature or mean plaque size was noted, so its recommendation for use in PD remains equivocal. [25]

Penile traction therapy

Penile traction therapy (PTT) aims to stretch penile plaques by gradual expansion of tissue to result in the formation of new connective tissue by cellular proliferation. [4] In very compliant patients, 6 months of regular use applying the traction device daily for 8-10 hours has resulted in reductions in penile curvature in the chronic phase of PD. However, application can be difficult and the device cumbersome to wear. [1] In a pilot study of 11 men with PD by Levine *et al.*, improvements were reportedly achieved in penile curvature, stretched penile length and erect girth in all participants without adverse effects or skin complications when a 6-month course was evaluated using PTT for 2-8 hours per day (Figure 9.5). [26]

Figure 9.5 Penile traction therapy (reproduced from *www.slideshare.com* 28.11.18)

More recently, Martinez-Salamanca *et al.* trialed the use of PTT for acute PD in 55 men, reporting a significant reduction in curvature (33-15^{o}), reduced penile pain, improved erectile hardness and an increased ability to achieve sexual penetration (20-62%).[27] These results compared favorably to the control group (n=41) for whom the majority of these measures worsened. Furthermore, PDDU was able to detect a 48% resolution of sonographic plaques in the PTT group and the need for surgery was reduced in 40% of patients who were previously surgical candidates. [27] Although few clinical studies have been undertaken utilizing PTT, there is evidence for its application in compliant patients in both the acute and chronic phases of disease.

Vacuum erection devices (VED)

Similar principles for implementing PTT are the basis of utilizing vacuum therapy in PD. [12] Activation of the VED causes erection by creating a negative pressure around the penis to draw venous and arterial blood into the corpus cavernosum, resulting in tumescence, as recommended for post-RP ED. [28] In animal studies, VED therapy has been demonstrated to preserve erectile function by alleviating tissue hypoxia to help inhibit apoptosis and prevent cavernosal fibrosis. [29] In a recent study of the role of VED to mechanically straighten the penis in 31 patients with PD, Raheem *et al.* [30] reported that, after 12 weeks of twice daily 10 minute sessions, there was a statistically significant and clinically relevant improvement. Reduction in penile curvature occurred in 21 participants (5-25^{o}) in addition to improvement in penile length and reduction in pain. [30]

In a recent development, the 'SOMACorrect' device was introduced to prevent the curved region of the penis hinging or collapsing within the VED cylinder, whilst under vacuum pressure (Figure 9.6). This involves the addition of smaller 'sized-to-fit' cylinders to be placed within the standard vacuum cylinder to mechanically stretch the penile tissues without curvature. A prospective study by Chitale of 26 men diagnosed with PD found encouraging outcomes with reduced penile curvature and pain, improved measurable penile length in both flaccid and erect states, and improvement in IIEF scores, although this evidence was presented at a sexual medicine conference and has not been published. [31] VED is considered to provide positive outcomes for PD patients and may possibly be used in conjunction with other therapies.

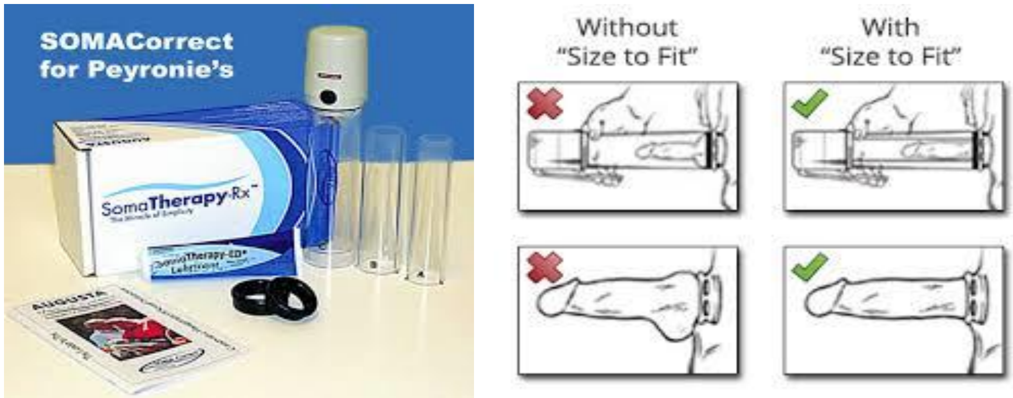


Figure 9.6 The SOMACorrect vacuum erection device
(reproduced from *www.iMed.com* 03.12.18)

B. Surgical options for Peyronie's Disease

Surgery remains the gold standard for correcting penile deformity and is indicated when the patient has had a stable disease for at least 12 months, has difficulty with or an inability to engage in sexual activity because of the deformity, and has a desire for the most rapid and reliable result.[4] The aim of surgery is to create a 'functionally' straight penis (a curvature of $<20^{o}$). Patients require thorough education about the potential risks of surgery as penile shortening, ED, penile numbness, the potential need for circumcision and recurrence of curvature may result.[11] Surgeries for correction of PD include shortening and lengthening procedures.

<u>Penile shortening procedure (Nesbit technique - shortening the 'long side')</u>

The Nesbit technique involves removal of transverse ellipses from the 'longer side' of the TA at the ratio of 1 mm for every 10^{o} of curvature, being generally recommended for men who have a curvature of $<60^{o}$ and adequate pre-operative erectile function and rigidity. Outcomes of the Nesbit procedure are excellent with more than 80% of men gaining complete penile straightening, however an average 1-1.5 cm penile length is lost (Figure 9.7).[32]

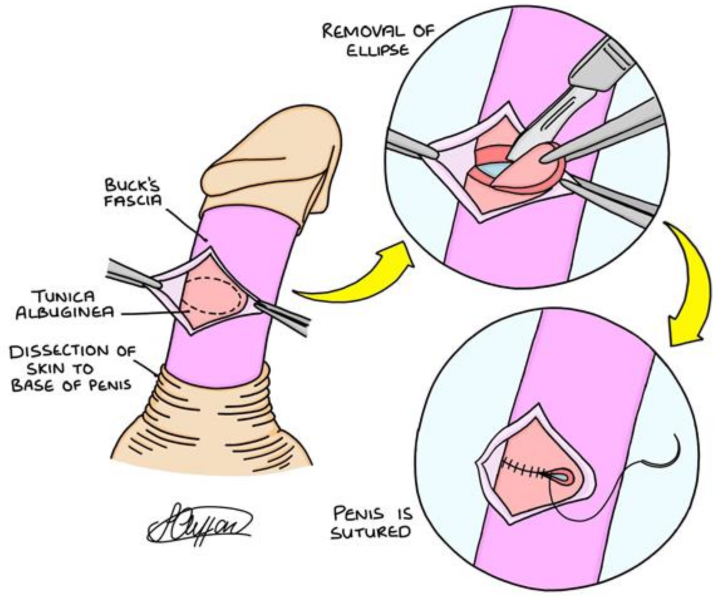


Figure 9.7. Nesbit procedure for Peyronie's disease correction
(reproduced from *www.wessixandrology.com* 03.12.18)

Penile lengthening procedure (Plication - lengthening the 'short side')

For men with a more severe deformity, but satisfactory pre-operative penile rigidity, excision or incision and grafting to lengthen the 'short side' is recommended. This involves making single or multiple longitudinal incisions on the convex side of the penis which are then closed transversely. This procedure may be combined with the removal of calcified plaques, during which a defect is created within the tunica and filled with a graft. [4,12] Post-operative ED is a common side-effect for 25% of patients due to venous leak, while penile shortening is also to be expected, due to potential damage to associated nerve suply. [33]

Penile prosthesis implantation

Penile prosthesis implantation is recommended for patients with poor erectile function or rigidity who are unresponsive to medications and have significant curvature (Figure 9.8). [12] The implant aims to expand tissue and corrects penile curvature over several months in most men, although in more severe cases, additional surgical shortening or lengthening procedures are sometimes necessary. [16] The use of graft material placed over the prosthesis is also a possibility in very complex and severe PD presentations, which may increase the risk of infection. [1,34]

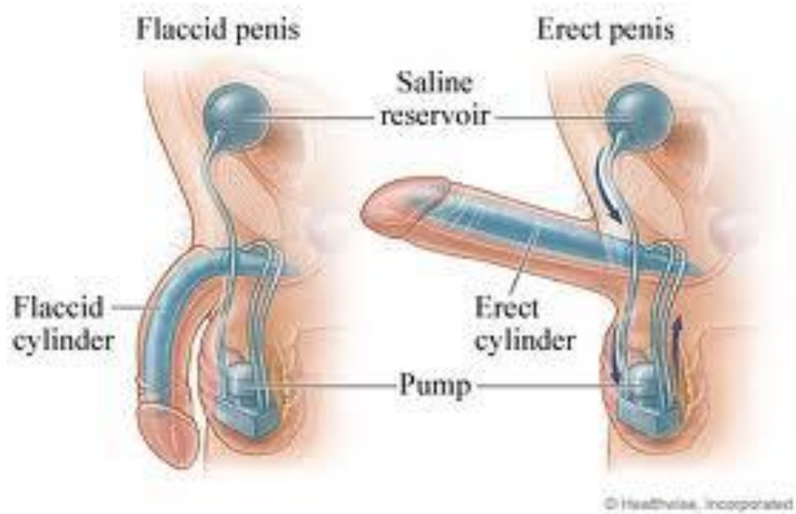


Figure 9.8 Penile prosthesis for Peyronie's Disease
(reproduced from *www.healthvista.inc* 03.12.18)

Impact of Peyronie's Disease on Quality of Life

As PD causes penile deformity, the physical challenge it presents may directly impact a patient's ability to participate in normal sexual activity and can result in sexual dysfunction and psychological distress. Many men have reported that PD negatively affects their masculine image and decreases their sexual confidence and satisfaction, with fear around further injury also impacting on their self-esteem. [2] PD has a substantial negative emotional effect for many (81%) patients and may greatly diminish QoL, with many sufferers avoiding intimacy and withdrawing socially, while 54% report a negative impact on relationships. [35] In an effort to quantify these experiences, Nelson *et al.* recruited 92 men with PD and assessed the level and duration of depression and distress over an 18 month time frame. [36] The results indicated 47% of men had clinically significant, meaningful depression; 21% reported this as being 'severe' and 26% 'moderate'. Furthermore, this impact did not diminish over time, indicating a poor level of patient adjustment to the condition. [36]

In further studies by Terrier *et al.*, depressive symptoms were reported in 50% of men, while more than 80% reporting distress related to PD. [37] This qualitative work also assessed body image and self-esteem with men describing themselves as 'abnormal', 'ugly', 'disgusting', 'like a cripple' and a 'half man', with most also expressing feelings of shame.[37] Many also reported a loss of sexual confidence or ability to initiate sex with a partner, while most reported a decrease in sexual interest. Additionally, men reported a sense of stigmatisation and isolation, leading to difficulties in speaking about their disease with sexual partners or healthcare professionals. [37]

Impact on Partners of Men with Peyronie's Disease

The challenges for partners of men with PD are significant factors when assessing impact on QoL and this was examined for the first time by Davis *et al.* [38] In an analysis of 44 heterosexual couples, partners of men with PD were found to have decreased sexual function, sexual satisfaction and reduced mood when compared with population norms. [38] The degree of physical deformity and level of penile pain experienced was found to impact on the ability to penetrate and availability of sexual positions. As seen clinically, female partners often report that the altered penile shape and size in PD may make penetration uncomfortable or impossible, causing further relationship distress. Indeed, the degree of sexual interference as reported in Davis' study, was associated with lower sexual function, and satisfaction correlated inversely with higher levels of PD induced-sexual interference.[38] In addition, the psychological repercussions on self-image in the PD patient may lead to further relationship discord and social isolation, with subsequent declines in intimacy. [2] Partners of individuals may then respond with a sense of hurt and rejection, to further compound the emotional withdrawal experienced by men with PD. [2] Similar findings were also reported in 23 homosexual men with PD when compared to 200 heterosexual men, however, there was no statistical difference between these groups, with both reporting high distress and negative impact on intimate relationships. [39] Finally, men without partners have also been under-represented in studies and may completely avoid relationships.

Peyronie's Disease in Prostate Cancer Patients

Following diagnosis and treatment for PCa, the possibility of acquiring PD is not usually discussed in the clinical setting as a potential side-effect. Although sparse, the research that has been undertaken in this area reliably confirms that PD is prevalent following both surgical and radiation approaches in PCa. Education for prospective patients should now include this in the general information provided for the sake of full transparency.

PCa and PD are prevalent in men from the fifth decade of life and Tal, Teloken and Mulhall *et al.* were able to define the incidence of PD in men who had RP, and to determine possible predictors of PD development after surgery. [8] Utilizing a prospectively built, sexual medicine database from 2002-2008, 1011 participants were identified to form a group that developed PD within 3 years of RP and were compared to a group that did not. Following multivariate analysis, younger age (odds ratio =1.3, for 5-year decrease in age) and white race (odds ratio =4.1 vs non-white) were found to be significant, independent risk factors. [8] In the 16% of participants diagnosed, nerve-sparing status showed only marginal statistical significance ($p=0.049$) and the role of cardiovascular comorbidities such as hypertension, hypercholesterolemia, ischemic heart disease and peripheral vascular disease were found to be unrelated to incidence of PD post-RP. [8]This is in contrast to findings by others.[4]

A comparative study by Ciancio *et al.* calculated fibrotic penile changes indicating PD in 11% of the 409 patients assessed for PD following RP. [40] The authors were unable to find any statistically significant predictors, despite additional factors being investigated, such as the use of VED, ICIs, tobacco use, duration of surgery, estimated blood loss, tumour grade and stage and post-operative anastomotic strictures. [40] The authors remarked, however, that patients with poor nerve-sparing were at increased risk of severe refractory ED and may be less likely to notice a PD curvature due to poorer sexual function generally. [8,40] Time, they proposed, may also play a part, with the mean time for PD onset following RP reported at 13.9 months with variations of 8% at 1 year, 14% at 2 years and 16% at 3 years. [8] Other factors, such as low sexual interest, shame and embarrassment, infrequent sexual activity, PD manifestations that do not affect sexual function, or concerns about seeking treatment, were also considered to potentially reduce the incidence, with under-representation in this patient population acknowledged.

Despite extensive searching, the incidence of PD following other forms of treatment for PCa including EBRT, brachytherapy and ADT proved extremely challenging to source. Whilst it is acknowledged that ED occurs in these populations, it seems apparent that there is far less emphasis on penile rehabilitation in these groups, possibly due to the higher grade of cancers in some, and a greater incidence of pre-existing comorbidities preventing surgery being possible in others. Whilst it is known that the rates of ED following RP and radiation groups are similar, the onset of ED is often later in patients treated with radiation therapy and continues to develop for up to 3 years following treatment (Figure 9.10). [41,42] In addition, there has been confirmation that ADT alone, or in combination with EBRT, significantly increases the risk of ED. [43] Delay in structural changes to associated soft tissues of the penis, relating to underlying corporal cavernosal smooth muscle hypoxia from treatment, may preclude patients from seeking treatment, particularly when other side-effects may be of higher priority.

In the final search for this gap in evidence, a recent publication in the *Journal of Sexual Medicine* in 2017 shed light on the prevalence and predicting factors for commonly neglected sexual side-effects from EBRT for PCa. [44] This included analysis of 109 patients, of whom 12% reported an altered curvature in their penis after EBRT. [44] A further 24% reported anorgasmia, 44% decreased intensity of orgasms, 42% penile length loss of >1 cm, 40% delayed orgasm , 27% decreased sensitivity of the penis, 15% orgasm-associated pain, 11% on ejaculation, 6% painful erections, 4% climacturia, 2% paresthesia and 2% reported a cold sensation. [44] Increasing time since final EBRT treatment (median time was 50 months) increased the risk of penile sensory disturbance, [44] to mirror earlier research conclusions. [42] This paper therefore represents the first and only study to quantify the incidence of PD following radiation therapy for PCa and the authors concluded that patients should be properly informed of the occurrence of such side-effects before deciding which treatment to pursue. [44]

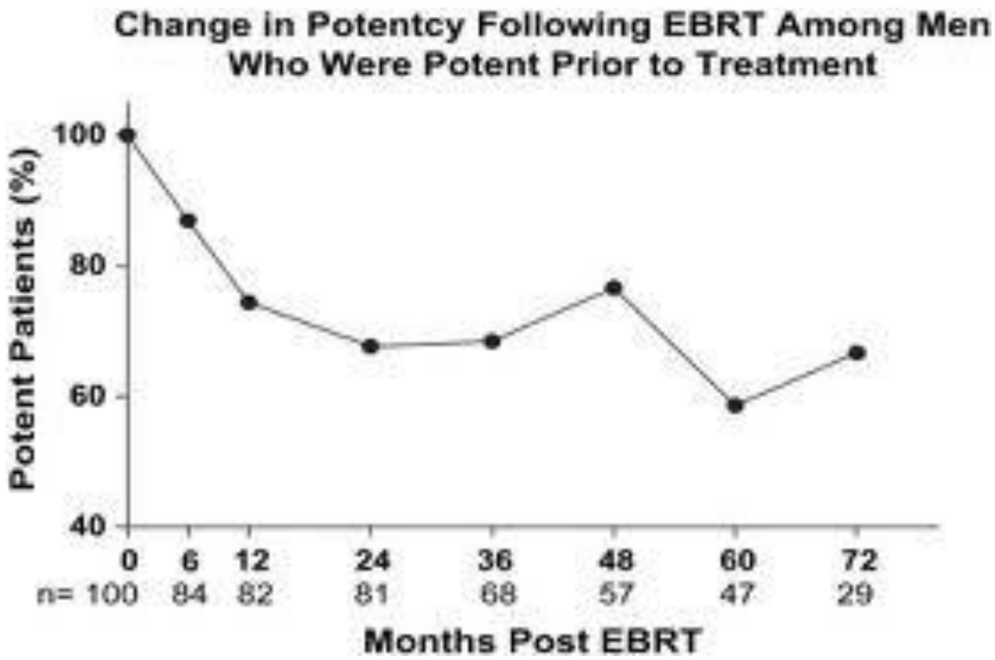


Figure 9.10 Impact of time for EBRT and potency following treatment for prostate cancer (reproduced from *www.slideshare.com.au* 10.12.18)

In my own research experience, when recruiting for Chapter 10 in this thesis, of the 43 men completing the study, a subset series of 10 participants (23%) with PD (diagnosed from PDDU) had a prior history of treatment for PCa, with eight (19%) undergoing RP and two EBRT (5%). The mean time from treatment to PD onset was 15.8 months for both groups with a wide variation of development from 4-48 months following PCa treatment. This research was presented at the Asia-Pacific Prostate Cancer (APCC) in October 2018 and the poster [45] and podium presentation are included in the Appendices.

Strategies for Management of Peyronie's Disease

Strategies to minimize the impact of PD need further research. Enhanced awareness and education regarding early detection are necessary for effective therapeutic options. [2] Members of the community may be unaware of the possibility for treatment in the acute phases and the psychological impact PD can present over long-time frames. The embarrassment and shame encountered by men with PD may also delay initial access to medical investigations, potentially leading to more severe presentations. Similarly, it has been established that physicians may underestimate the prevalence and pathology of PD, sometimes providing incorrect information about PD progression, thereby limiting patient access to non-surgical options for treatment. [46] Clinicians experienced in PD management believe favorable outcomes are best achieved for patients when both the physical and psychological functions of each individual are individually and comprehensively assessed. [2] By commencing physical therapies, it is possible for the psychological and psychosocial issues to improve or resolve completely. Additional psychological support for men and their partners may greatly assist recovery and provide strategies to minimize isolation, gaps in communication, withdrawal from intimacy and relationship breakdown. [2,38] Finally, access to non-invasive treatment options to assist in the stabilization and potential recovery of PD is the final primary ambition of the author, having discovered unexpected improvements with therapeutic ultrasound (TUS) in a clinical setting.

A Role for Ultrasound Therapy?

Use of therapeutic ultrasound (TUS) in the treatment of soft tissue injuries has origins in the early 1930’s, employing high frequency sound waves that utilize mechanical vibration to stimulate tissue repair. [47] TUS works by emitting longitudinal sound waves that cause an oscillation of particles in a particular area to increase molecular vibration, resulting in a generation of energy. Electrical energy is converted to acoustic energy through mechanical deformation of a piezo-electric crystal located within a transducer, which causes a progressive loss of energy intensity via tissue attenuation due to absorption, wave scattering and dispersion. [47]

Frequencies used for a therapeutic effect are typically activated between 1.0-3.0 MHz. Low- frequency ultrasound waves have greater depth penetration, but are less focused and, at 1.0 MHz frequency, are absorbed at a depth of 3-5 cm. These frequencies are recommended for deeper injuries and in patients with more subcutaneous fat. [48] For superficial lesions at a depth of 1-2 cm, 3.0 MHz frequency is recommended. Typically, a hand-held transducer is applied with a coupling media, which is used to prevent reflection of soundwaves and moved in a circular motion over an injured area. [49] Transmission gel is the most commonly used media with few air bubbles and enabling the transducer to glide over the skin surface. [50] The dose of TUS can also be varied by altering wave amplitude and intensity. In addition, TUS can be used in pulsed form which has on/off cycles, or a continuous form which has a greater heating effect, with 40-45^{o} estimated as the tissue temperature rise for optimal treatment. [47]

Thermal effects include increased blood flow, reduction in muscle spasm, increased extensibility of collagen fibres, reduction in pain and a proinflammatory response. [47] Although the level of clinical benefit to the patient from TUS treatments remains uncertain, and research supporting it has had recent criticism, [49,51] the modest level of efficacy and patient benefit, together with a low level of risk were encouraging points to consider when designing the final study. After extensive consultation with colleagues, sexual health physicians and urologists, it was agreed that minimal harm was likely if the TUS treatment was applied for PD with appropriate protocols and precautions. Given these combinations of factors, it was felt that providing TUS to men with PD and utilizing the known benefits for soft tissue injury, could potentially provide a non-invasive approach to treatment (Figure 9.11). Subsequent investigation led to the confirmation of TUS applications for PD used previously, with encouraging results reported.

Figure 9.11 Application of therapeutic ultrasound in Peyronie's Disease.

Previous Studies of Therapeutic Ultrasound in Peyronie's Disease

Since the 1950's there has been some experimental studies utilizing TUS for patients with PD, however, given the lack of RCTs and biological data collected in these studies, it has not evolved as a mainstream treatment option. Dugois's 1951 publication was the first to report the treatment of PD with TUS and, in a series of 20 cases, he was able to recommend a minimum of 20 treatment sessions per patient for a successful outcome. [52] However, the data collected was based on observations over 8 years of clinical experience, rather than the rigour afforded by a structured RCT. In addition, an active ingredient (a-chymotrypsin), was also utilized and so the efficacy of TUS alone was not able to be determined. A smaller investigation by Heslop *et al.* in 1967 reported of the nine patients to receive TUS for PD, all had reduced pain, while four had a complete resolution of palpable plaques. [53] Similarly, Liakhovitski applied TUS to 67 patients and noted a decrease in penile pain in almost all patients after 3-5 sessions, and absence or marked decrease in 52 patients after 20-25 TUS applications. [54] Improvements in penile curvature and palpable plaque size were also reported, but to a lesser degree. In both series no adverse side-effects were reported.

Building on these optimistic results, urologist W.W. Scott commenced a trial in 25 successive patients who presented with symptomatic PD, over an 11-year epoch, from 1959-1970. [55] Patients were provided with a variable number of treatment sessions, 5 days per week for 5 minutes duration at an intensity of 1.5 W/cm^2. The number of treatment sessions was determined by the patient's response to TUS. Subjective improvements were noted in 23 of 25 participants (92%), which included "*a decrease in chordae, improved filling with erection and more satisfactory intercourse with relief of erectile pain"* from clinical notes. The size of the plaque was considered to have reduced in 19 cases and was described as "*difficult to find*" in three further cases. No sign of increase in plaque size was noted in any of the 25 cases. Given the positive outcomes, the authors recommended patients be provided with 12 TUS sessions, at which point, if no improvement occurred, further therapy should be indicated. However, although a rapid response to treatment was noted, with some patients improving within 3-5 sessions, evaluation of results was considered difficult as all outcomes were reported subjectively. Variability in treatment number and the lack of objective findings in this study may have also reduced its impact and validity.

More recent research to assess the impact of TUS on PD was published by Miller *et al.* in 1983 and included a cohort of 30 men receiving TUS over a period of 5 years from 1977-1982. [56] Participants received a variable number of treatments, designed around 2-week courses of daily TUS, with a range of 1-6 courses. A standard dose of 1.5 W/cm^2 for 5 minutes was the prescribed treatment protocol, with participants self-regulating the frequency of courses over the 5-year period. In addition, a hydrocortisone ointment was used as the conducting agent for each session, based on evidence produced by Griffin *et al.* in earlier investigations advocating its benefits in combination with TUS for reducing inflammation. [57] Of the 25 men who completed treatment, 19 reported improvement with 16 reporting reduced plaque size, four reporting resolution of plaque, nine reporting reduced pain and four reporting reduced penile deviation. Miller [56] concluded that treatment benefit was most likely with earlier presentations of PD, although a positive effect was still seen in cases >1 year duration. Given these observations, TUS was recommended as a non-invasive treatment option, which was repeatable and led to softer more flexible plaques, which were less deforming, less prominent and less painful. [56]

The most recent publication exploring the use of TUS in PD by Kos *et al.*, explored the case of a 49 year old patient who received 90 sessions over an 18-month period (protocols - 2.0 W/cm^2 for 8 minutes per session). Assessment methods included the IIEF-5, the Visual Analogue Scale and measurement of plaque volume via PDDU, with outcomes showing significant improvement in all parameters. Interestingly, the particular medical facility that produced this paper, the University Medical Centre of Ljubljana in Slovenia, reported that patients with PD had been treated with TUS at their institution for almost 30 years, with empirically good results, despite the lack of objectivity in outcome measures.

Pilot Study

Whilst the papers above report generally positive observations utilizing TUS in the treatment of PD, the limited reporting of objective results may have impeded its translation to mainstream clinical practice. Evidence recording biological data has been lacking and this, combined with the recently designed and validated PDQ [18], may now provide a better opportunity to properly quantify outcomes. Moreover, previous investigators have utilized quite low frequencies at 1.5 W/cm^2 and relatively short treatment time of 5 minutes, which may have limited efficacy. In the clinical practice of the author, an opportunity recently presented to provide one patient with TUS treatment, with his approval and that of his physician. A PDDU confirmed the presence of multi-focal calcifications and two plaques measuring 7 mm, with three foci calcifications, each measuring 0.5 mm.

Upon receiving 12 sessions of TUS at 3.0 W/cm^2 with a 10 minute continuous mode dose over 4 weeks, the patient was re-scanned via PDDU. Complete resolution of the both the plaque and foci calcifications had occurred. This was considered by the ultrasonographer to be “*highly unusual”* given his 25 years clinical practice in assessing PD. Subjectively, the patient also improved with resolution of pain, greatly improved penile curvature from 75^{o} to 20^{o} (Figure 9.12), and resumed sexual intercourse. Repeat pilot testing in three subsequent patients with PD, provided similar outcomes, which set in motion plans for the final study of this thesis.

Figure 9.12 Peyronie’s disease pre- and post-therapeutic ultrasound of patient ‘PB’

Summary

PD is a common condition that can affect men of all ages and was presented unexpectedly in a post-RP patient, which formed the impetus for Study 5. Equally unexpected was the link between RP and the potential onset of fibrosis following damage sustained to the nerve bundles affecting penile blood flow. Furthermore, the one in eight risk for men to experience PD following EBRT was not anticipated, but has been confirmed in recent scientific studies.

Treatment for PD has proven difficult with much research invested in phramaceutical and physical strategies, which are often highly invasive and with outcomes similar to placebo; only surgery provides more optimistic results. Given the distress experienced by men diagnosed with PD and the resultant impact on relationships, when the advice is simply to ‘wait and see’ over the next 12 months before stabilization, they can be even more psychologically affected by inaction. As PD is expected to have both ‘acute’ and ‘chronic’ phases, our investigation sought to provide treatment options before disease progression and the need for surgical intervention.

The opportunity to provide TUS in the first clinical case led to a pilot study and the subsequent development of an RCT to assess its effectiveness in a larger cohort. We hypothesized that, based on evidence identified from earlier case studies, meshed with today’s improved diagnostic technology, patients would experience benefit from TUS. Thus, the first RCT investigating the utilization of TUS in PD was designed and delivered, with a total of 43 participants, of whom 10 had recently received treatment for PCa.

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CHAPTER 10

Paper 5:

A randomized controlled trial using therapeutic ultrasound as a non-invasive treatment for Peyronie's disease.

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Abstract

Objective: Peyronie's Disease (PD) is an acquired connective tissue disorder affecting the tunica albuginea (TA) of the corpus cavernosum, causing physical and psychological burden in at least 50% of affected men. PD arises due to the formation of inelastic scar tissue, creating plaques in genetically susceptible individuals or following microtrauma. Following treatment for prostate cancer (PCa), 16% of men will acquire PD and a further 12% following radiation therapy, often associated with pain and curvature of the penis. Therapeutic Ultrasound (TUS) is a non-invasive treatment for soft tissue injuries, however, research in PD patients is limited.

Methods: Forty-six men with PD were recruited into a randomized controlled study that assessed the effectiveness of TUS (n = 23 intervention, n = 20 control). Each participant underwent Penile Duplex Doppler Ultrasound (PDDU) pre- and post-trial to assess PD, TA fibrosis and plaque formation. All completed the Peyronie's Disease Questionnaire (PDQ) and IIEF-5. Photographic based measurement of the angle of penile deformity was also assessed. In the intervention group, 12 TUS sessions were provided over 4 weeks utilizing 1.5-2.5 W/cm^2, 3 MHz x 10 min/session after which all outcome measured were re-assessed. The control group participants had a 4-week delayed entry into the intervention and were re-assessed at this time.

Results: Forty-three participants (59 ± 11 y, BMI = 26.3 ± 11 $kg.m^{-2}$, duration of PD = 17 ± months) completed the trial. The intervention group showed significant ($p < 0.05$) improvements in PDDU, penile deformity and IIEF-5 scores from pre- to post-trial. There was also a trend ($p=0.05$) for improvement in the PDQ in this group. No changes were recorded for patients in the control group.

Conclusions: TUS offered an effective first line, non-invasive approach to treatment for PD as confirmed on PDDU, penile angle, erectile function and subjective reporting. Previous studies utilizing TUS on PD have relied on case study reports, this is the first randomized controlled trial to be undertaken in this field.

Introduction

Peyronie's Disease (PD) is a physically and psychologically challenging disorder that affects at least 9% of the male population and can have an impact on male self-esteem, relationships and erectile function. [1-3] PD arises due to the formation of inelastic scar tissue, creating plaques in the tunica albuginea (TA) of the penis in genetically susceptible individuals or following micro trauma. [4] The plaque results in palpable penile scar tissue in the flaccid state and may cause pain, penile deformities, penile curvature, hinging, narrowing and penile shortening that are generally only seen in the erect state. [5]

Probable causes of PD include infection, autoimmune diseases, local manifestation of a general fibromatosis and generalized arterial disease. [6,7] The peak incidence of PD occurs around 55-60 years of age and is known to be associated with erectile dysfunction (ED), diabetes, obesity, hypertension, A-positive blood group, hyperlipidemia, smoking and following pelvic surgery. [8] Two-thirds of men with PD possess risk factors for arterial disease and this group are more likely to have disease progression and worsening of ED if left untreated. [4] A family history of PD exists in 2% of patients and an association with Dupuytren's palmar fibromatosis is apparent in 20-39% suggest that patients may have an inherited predisposition to this disease. [9,10] Although the onset of PD might be associated with a history of buckling during sexual activity, an identified history of penile trauma is uncommon and recalled by only 10% of patients older than 40 years. [8,11] A further 10% of PD presentations occur in men under 40 years, with teenagers also known to develop the condition. [12] Finally, PD is a side-effect from treatment for prostate cancer (PCa) and this is thought to occur due to injury of the cavernosal nerves and adjacent neurovascular bundles that supply erectile blood flow during radical prostatectomy (RP) and External Beam Radiation Therapy (EBRT). [13] Recent evidence confirms 16% of men undergoing RP will experience PD, at an average 13.9 months following surgery [14,15] and an additional 12% of men following EBRT. [16]

Current treatment options for PD are generally invasive with penile injections, vacuum pumps, traction devices and surgery the most common approaches. [4] As PD has an 'acute phase' that may last 12-18 months before stability (the 'chronic phase'), physicians are generally reluctant to introduce treatments too early and often recommend a 'watch and wait approach'. [4,5] In the clinical setting, however, many patients are distressed by the lack of action and greatly fear the condition worsening over time. Supporting this is Mulhall's 2006 investigations of 246 men diagnosed with PD, finding that 12% experienced spontaneous improvement in penile curvature, 40% remained stable and 48% worsened over 12 months. [17] Thus, most men with the condition will find their penile changes to be permanent, which may greatly impact on their quality of life. [18] Furthermore, embarrassment, fear of stigmatization and of treatment options may also mean the true incidence of PD is unknown, with serial autopsy studies by Smith *et al.* confirming that 22% of men at death had PD. [19]

At present, there is no known cure for PD and most current non-surgical treatments only offer an approximate 30% improvement.[4] Non-invasive treatment options to assist in the rehabilitation of PD therefore warrant investigation, with the aim to translate findings into clinical practice. Therapeutic Ultrasound (TUS) has had a role in treating soft tissue injuries since the 1930's, but its application to PD has had limited investigation.[20] Early reports, stemming from the 1950's did show promising findings in case studies, however, no randomized controlled trials utilizing TUS have been conducted in this population. [21-23] Significantly, since this time, technological advancements including the use of Penile Duplex Doppler Ultrasound (PDDU) scans have also become available, and are considered the 'gold standard' approach for the diagnosis of PD. [24] We hypothesized that men receiving TUS would show positive treatments outcomes with reduced pain, reduced penile deformity (including angle of curvature), reduced plaque size on PDDU scans and reduced scores in the PDQ.

Methodology

This study was approved by the UWA Human Research Ethics Committee (Reference: RA/4/1/8089) and all participants provided written informed consent. The trial was registered in the Australia New Zealand Clinical Trials Registry and allocated as ACTRN12617001415392.

Over a 2-year period from June 2016-18, 43 participants with PD were enlisted from a cohort of men referred sequentially by their Urologist, GP or radiological clinic following confirmation on PDDU. Men with diabetes, taking PDE5i or other PD medications, smokers and those undergoing radiation therapy were ineligible to join the study.

Sequential '1:1' randomization was performed as each participant attended a single high volume physiotherapy clinic following diagnosis of PD. Patients were allocated to either a 'delayed entry' or 'intervention' group based on the date of initial attendance and receipt of sequentially numbered pre-set information folders (generated by one of the authors). Once consent was provided, enrolment and the randomized intervention commenced. Relevant notes were recorded in participant medical files, which were collated over the trial duration, with results subsequently analysed by a blinded, independent statistician.

<u>Medical history</u>

Prior to the trial, a full medical history pertaining to timing and probable cause of PD onset was recorded. This included the participant's recollection of specific injury, pain, bruising or his initial awareness of a penile deformity. If no known incident was recalled, relevant medical background such as a family history of PD, cardiovascular disease, Dupuytren's contracture, treatment for PCa or previous pelvic surgery was ascertained. All participants were physically examined via palpation of their penis in the flaccid state by the gloved hand of the therapist. The presence of penile plaques was noted with the location confirmed by both the participant and the PDDU report and recorded.

<u>Intervention: therapeutic ultrasound</u>

Over a 4-6 week period, an intervention group (n= 23) attended private medical rooms to receive therapeutic ultrasound 2-3 times per week for 10 min for 12 sessions in total. TUS dose ranged from 1.5 W/cm^2 to 2.5 W/cm^2, continuous mode, utilizing 3 MHz with a 2 cm diameter soundhead (Model: Chatoonga Intelect mobile Model 2776 SN T29173). A second, 'control' group (n=20) had a 4-week delayed entry to the intervention, then completed the same intervention over 4-6 weeks for a total of 12 sessions. Questionnaires were completed prior to the first session of TUS and following completion of the 12th TUS session. During the TUS sessions, aqueous transmission gel was applied directly to the TUS soundhead, which was then covered with a latex condom for infection control and second layer of transmission gel was applied to the external surface of the condom. Each surface was disinfected prior to and following each TUS application. Participants were then provided with the following verbal warning, *"The ultrasound treatment should be maintained at a mild, comfortable warmth and at no time should there be any pain or* *discomfort. Please let me know if you experience any unpleasant sensations and I will cease the TUS immediately"*.

Twelve TUS sessions of 10 minutes duration were provided directly to the penile plaque with each participant positioned in the supine position, with towels available for draping and participant comfort. TUS intensity dose commenced at 1.5 W/cm^2 initially, with a gradual increase to 2.5 W/cm^2 over subsequent sessions, as tolerated. At any time point, participants were advised to provide verbal feedback to reduce the TUS intensity if desired. At the conclusion of each treatment, participants were provided with sterile wipes to remove excess transmission gel and instructed to wash their hands with disinfectant and warm soapy water.

Outcome measures

The primary outcome measure, the PDDU, confirmed the size (mm), number, position of penile plaques and presence of calcification. [5] The measurement of the TA (mm) and plaque presentation were considered the most significant primary outcomes. All PDDU measurements were made by an ultrasonographer with 25 years' experience in PD and then reported by a radiologist, both of whom were blinded to the treatment provided.

Secondary outcomes included angle of penile deformity, completion of the International Index of Erectile Function (IIEF-5) [25] and the Peyronie's Disease Questionnaire (PDQ).[26,27] All participants were asked to provide photographic evidence of their penile curvature or deformity, prior to, and following the trial period, taken within one week of the first and final TUS treatment sessions. A standard clinical goniometer was applied to the photographic image to record the degree of curvature, with the axis taken from the base of the penis to the midline, in line with the urethral meatus.

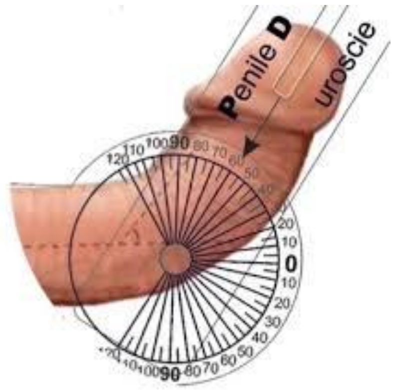

Figure 1. Goniometry measurement of penile curvature in Peyronie's disease

Statistical analysis

Outcome data were entered into SPSS (v25.0, SPSS, Chicago, IL) for analysis. A series of two-factor, repeated measures ANOVA (Group x Time) were performed and significance was accepted for all analyses at $p<0.05$. We could not find a previous study in which PDDU was used as a primary outcome measure in response to TUS in PD. We therefore based our power tests on penile curvature studies. There has also not been an RCT that utilised TUS as a treatment modality for PD. The closet exemplar that we found was the study by Ralph *et al.* (J Sex Med 14: 1430-1437, 2017)[28] who studied the impact of combined collagenase and vacuum pump therapy on penile curvature in 30 subjects with PD. Improvement in penile curvature was 23.5±9.0˚. Our sample size included 46 participants, 43 after dropout, who were randomised to 2 groups (n=20 and 23). Given highly conservative *a priori* assumptions of $\alpha=0.01$, a two-tailed test and a sample size of 20 per group, our study possessed >99% power to detect a similar effect size to that observed by Ralph *et al*.

Results

Of the 46 participants recruited to the study, 43 completed the study (Age = 59 ± 11 y, BMI= 26.3 ± 11 $kg.m^{-2}$, duration PD = 19 months), with two participants from the control group (n = 20) and one participant from the intervention group (n = 23) unable to finish due to medical illness or relocation due to work, respectively. Participants were recruited over a

12-month period with follow up over a subsequent 12 months, when sufficient participant numbers were achieved. There were no appreciable differences in baseline characteristics between the groups (Table 1).

Participants in our study (n = 43) derived PD from a range of aetiologies, with a sub-group of 10 men being treated for PCa (n = 8 following surgery, n = 2 following EBRT). PD resulting from trauma occurred in three cases, pelvic surgery precipitated PD in two participants, and another two had a confirmed diagnosis of Chronic Pelvic Pain Syndrome (CPPS) which has been associated with sexual dysfunction and reduced blood flow due to hypertonic pelvic floor muscles. [35] One patient presented with the triple combination of PD, Dupuytren’s contracture and Lederhosen Disease (hard lumps of connective tissue in the plantar aspect of the foot), and another six participants in the total cohort had confirmed Dupuytren’s contracture. One patient reported PD following a combination of chemotherapy and EBRT for pelvic cancer, while all other cases had no specific trigger. This represents a total of 58% of the cohort having an established link to identified causes, with the remaining 42% not able to pinpoint a triggering event or co-existing pathology.

Table 1: Participant characteristics at baseline (mean ± SD scores). T-test for independent samples scores showed no between-group differences ($p<0.05$) prior to treatment.

Characteristics	Intervention Group (n = 23)	Control Group (n = 20)
Age (years)	56.8 ± 10	57.7 ± 17
BMI ($kg.m^{-2}$)	26.5 ± 4.7	26.1 ± 5.1
Duration of Peyronie’s disease (months)	23 ± 33	16 ± 13
Angle of deformity (degrees)	37 ± 22	37 ± 21
PDDU - size of plaque (mm)	2.05 ± 0.66	1.96 ± 0.67
Number of calcifications >0.5 mm	6	5
IIEF-5	16 ± 8	17 ± 6
Peyronie’s Disease Questionnaire	14 ± 11	15 ± 10

Primary outcome - PDDU measures

Results are presented in Figure 2 for intervention and control group patients from baseline (pre-treatment) to completion of 12 TUS sessions for the assessment of penile plaques (PDDU score). The ANOVA results show no significant main effect for Group ($F = 0.416$; $p = 0.523$) or Time ($F = 2.35$; $p = 0.133$), however the Group x Time interaction ($F = 4.702$; $p = 0.036$) was significant. When assessing the effectiveness of the TUS intervention, we note a difference between groups in PDDU measures, with only the intervention group having a reduction in PDDU scores.

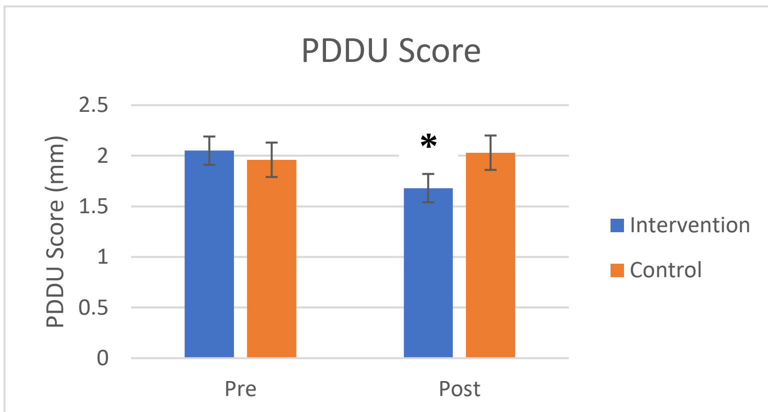

Figure 2. Changes in penile plaque size (mean ± SE) for intervention and control group patients from baseline (Pre) to completion of 12 TUS sessions (Post). Measures used Penile Duplex Doppler Ultrasound (PDDU) and were recorded as the length of the plaque (mm). * indicates a significant ($p<0.05$) change from baseline.

Secondary outcomes

1. Angle of deformity

The data for angle of penile deformity are presented in Figure 3 for intervention and control groups. The ANOVA results show a significant main effect for Time ($F = 16.762$; $p < 0.001$) and the Group x Time interaction ($F = 16.762$; $p < 0.001$), but not for Group ($F = 2.200$; $p = 0.146$). Thus, there was a reduction in angle of 17^{o} (38%) over time for the intervention group only.

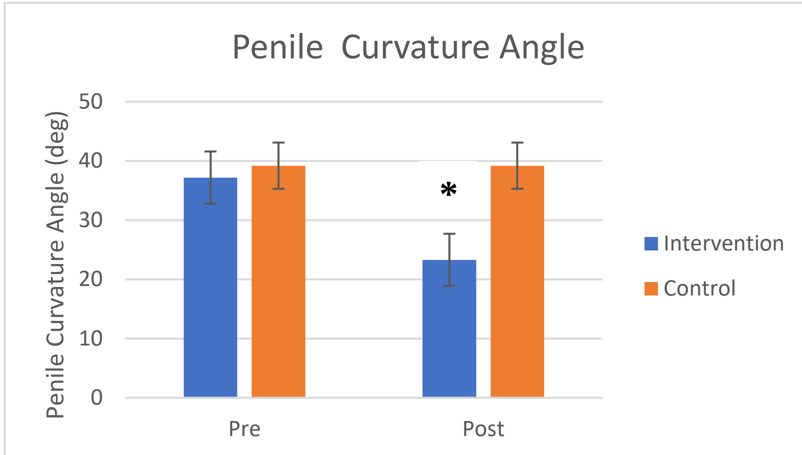

Figure 3. Changes in the angle of penile deformity for intervention and control group patients from baseline (Pre) to completion of 12 TUS sessions (Post). This was measured as the angle of deformity using photographic evidence and goniometry, and recorded in degrees. * indicates a significant ($p<0.05$) change from baseline.

2. IIEF-5 scores

The data for IIEF-5 scores are presented in Figure 4 for intervention and control patient groups. The ANOVA results show no significant main effects for Group (F = 0.016; p = 0.900) or Time (F = 2.198; p = 0.146), but the Group x Time interaction was significant (F = 4.752; p = 0.035). Following similar scores at baseline between groups, only the intervention group improved over time.

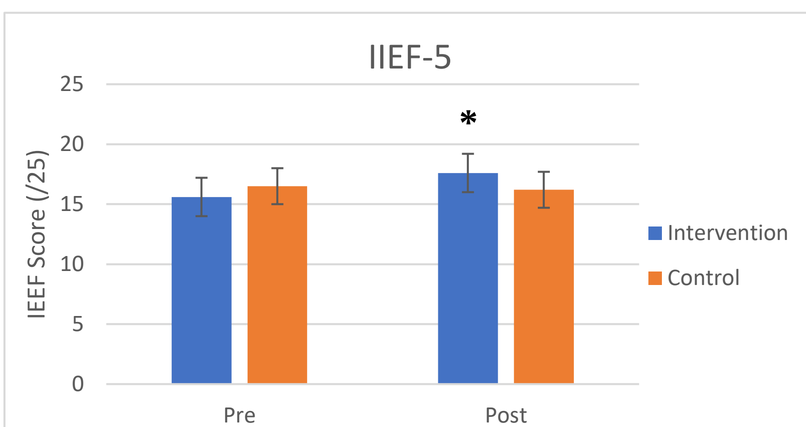

Figure 4. Changes in IIEF-5 scores, indicating erectile function rated by participants from baseline (Pre) to completion of 12 TUS sessions (Post). Higher scores indicate better function. * indicates a significant ($p<0.05$) change from baseline.

3. PDQ

The data are presented in Figure 5 for subjective responses to PD via the PDQ. When data from both groups were pooled, the main effect for Time just failed to reach significance ($F = 4.102$; $p = 0.050$). The ANOVA results also revealed no significant main effect for Group ($F = 0.842$: $p=0.365$), or the Group x Time interaction ($F = 1.918$; $p = 0.175$). However, upon inspection of Figure 5, it would appear that there was a drop in PDQ scores for the intervention group, but our sample was insufficient to provide the statistical power needed to show the impact of this intervention.

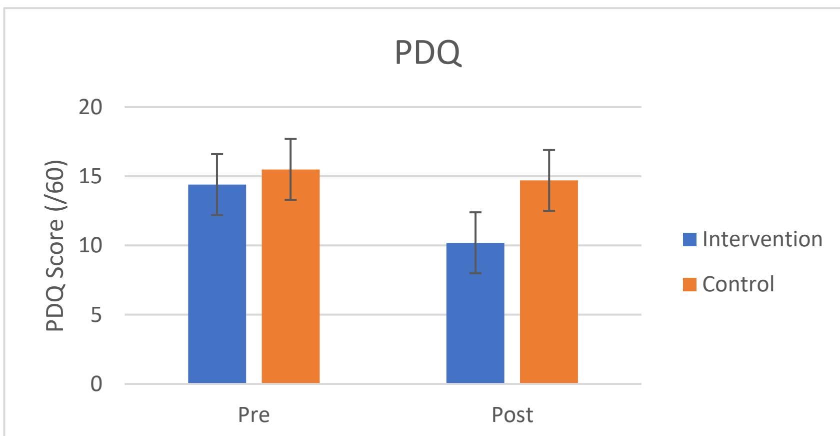

Figure 5. Changes in responses to the Peyronie's Disease Questionnaire (PDQ) for intervention and control group patients from baseline (Pre) to completion of 12 TUS sessions (Post). Lower PDQ scores indicate better outcomes and are also reflective of the impact on participants' partners.

Discussion

With as many as 81% of men with PD reporting emotional difficulties, 48% clinically meaningful depression and 54% relationship difficulties, the impact of PD on individuals and their partners can be clinically significant. [2,3,29] The challenges of PD include alterations in sexual relationships, restrictions in intimacy, socialization and stigmatization, along with complete deferment of relationships, which in younger patients may lead to avoidance of fathering and parenthood options. [30] Improved awareness and education about the impact of PD, and potential treatment options, need further development. Our study aimed to address a gap in the availability of effective, non-invasive protocols using TUS, particularly in the acute stage of pathogenesis.

Use of TUS in the treatment of soft tissue injuries has origins that stem from the early 1930's. TUS uses high frequency sound waves that induce mechanical vibration to stimulate tissue repair. [20] Frequencies used for a therapeutic effect are typically between 1.0-3.0 MHz. Low- frequency ultrasound waves have greater tissue penetration, but are less focused. Sound waves at 1.0 MHz frequency are absorbed at a depth of 3-5 cm and are recommended for deeper injuries and for patients with substantial subcutaneous fat. [31] For more superficial lesions at a depth of 1-2 cm, 3.0 MHz frequency is recommended and, therefore, was used in this study. The dose of TUS can also be varied by altering wave amplitude and intensity, and can be used in pulsed or a continuous form. The latter form has a greater heating effect, with 40-45^{o} the estimated tissue temperature rise for optimal treatment. [20] Thermal effects include increased blood flow, reduction in muscle spasm, increased extensibility of collagen fibres, reduction in pain and a pro-inflammatory response. [20] After reviewing previously used protocols, [21-3] a continuous TUS at 1.5-2.5 W/cm^2 was selected as our treatment dose.

Our main outcome measure, based on PDDU scans, is the 'gold standard' for assessing changes to penile tissue. PDDU is the preferred method of examination as it can best determine plaque characteristics, [32] and was employed as the primary outcome measure in this study. This measure has the advantage of being able to demonstrate objective changes in biological tissue, without the bias of subjective reporting. Of significance, the normal tissue size of the TA is 1.0-1.2 mm and this was measured both pre- and post-intervention. The average reduction in TA was 0.37 mm indicating a treatment effect not seen in the control group patients. Reductions in plaque size from PDDU were mirrored by participant reports of reduction in size and hardness of plaques, improved malleability of the penis and satisfactory improvements in curvature and physical deformities. Importantly, participants displaying calcified plaques >0.5 mm at baseline tended not to respond to TUS, however, several individuals with 'foci' plaque formation of <0.5 mm had complete resolution of this presentation. This is an important consideration for the selection of patients for future treatment.

Improvement in the angle of deformity is possibly the most important outcome for patients, given the potential impacts on self-esteem, sexual function and relationships. The intervention group reported an average 17^o (38%) reduction in curvature. Several participants, who had other penile deformities such as indentations and hour-glass formations, observed improvements in penis shape and appearance (both elements of the 'bothersome' score). In these individual cases, PDQ scores were greatly improved, reflecting positive outcomes psychologically. In particular, all participants reported a resolution of pain and this is a significant QOL outcome, having positive translation to the re-engagement or improvement of sexual activity and frequency.

Examination of erectile function via the IIEF-5 questionnaire, which is often closely related to PD, was the third outcome measure. The intervention group displayed improvement in scores, indicating a treatment effect when compared to the control group. The average improvement in IIEF-5 scores was 3 points which is clinically relevant, representing a shift in category from 'mild to moderate ED' to 'mild ED'. [25]

The PDQ score provided an opportunity to assess the psychological impact of PD on both the individual and his relationships. Although our analysis was not able to show significance ($p = 0.175$; trend only), those individuals who were most improved in other measures, tended to show similar improvements in PDQ scores over time. The PDQ was seen as an important measure in the clinical setting in this study and has been recommended by others as being a valid assessment tool. [27]

Since the 1950's there has been some experimental studies utilizing TUS for PD, however, given the lack of controlled trials and employment of patient reported outcomes in previous studies, TUS has not evolved as a mainstream treatment option. Dugois's 1951 publication was the first to report the treatment of PD with TUS and, in a series of 20 cases, he was able to recommend a minimum of 20 sessions per patient for the successful treatment of PD. [21] However, the data collected was based on observation over 8 years of clinical experience. In addition, an active ingredient a-chymotrypsin, was also utilized and the efficacy of TUS alone could not be ascertained. A smaller investigation by Heslop *et al.* in 1967 reported on nine patients who received TUS for PD, all of whom had a reduction in pain and four reported complete resolution of palpable plaques. [22] Similarly, Liakhovitskii applied TUS to 67 patients and noted a decrease in penile pain in almost all patients after three to five sessions, and the absence or marked decrease in 52 patients after 20-25 TUS applications. [33] Improvements in penile curvature and palpable plaque size were also reported, but to a lesser degree. In both series no adverse side effects were reported.

More recent research to assess the impact of TUS on PD involved a case series published by Miller *et al.* in 1983, which included a cohort of 30 men receiving TUS over a period of 5 years from 1977 to 1982. [34] Participants received a variable number of treatments, designed around 2 week courses of daily TUS, with a range of one to six courses undertaken. A standard dose of 1.5 W/cm^2 for 5 minutes was the prescribed treatment protocol, with participants self-regulating the frequency of courses over the 5-year period of assessment. In addition, a hydrocortisone ointment was used as the conducting agent for each session, based on evidence produced by Griffin *et al.* in earlier investigations advocating its benefits in combination with TUS for reducing inflammation.[35] Of the 25 men who completed treatment, 19 reported improvement with 16 reporting reduced plaque size, four reporting resolution of plaque, nine reporting reduced pain and four reporting reduced penile deviation. Miller and colleagues concluded that treatment benefit was most effective with earlier presentations of PD, although a positive effect was still seen in cases who presented after 1 year. Given these observations, TUS was recommended as a non-invasive treatment option, which was repeatable and led to softer, more flexible plaques that were less deforming, less prominent and less painful.[34] The variability in treatment frequency, however, makes the comparison of results between studies challenging, despite the generally positive outcomes from each study.

However, none of these previous studies were randomized controlled trials, hence a lack of control groups not exposed. As the first randomized controlled trial to assess the impact of TUS on PD , a treatment effect was confirmed in the intervention group compared to the control group. The TUS protocols utilized afforded clinically relevant reductions in plaques of the TA, penile curvature, and pain, with improvement in IIEF-5 scores. A younger patient (33 years of age with a 13-year history of PD), however, achieved excellent score reductions in PDDU (from 2.4 to 1.2 mm) and penile curvature (from 40^o-10^o). Furthermore, in our RCT, individuals who did not respond to TUS had confirmed calcification of plaques larger than 0.5 mm, with smaller areas of foci calcifications typically responding to TUS and resolving.

Given the large range of TUS sessions/participant (3-25) reported in the aforementioned studies, it is encouraging to note that the 12 TUS sessions undertaken in our study were able to produce significant, positive outcomes. This also identifies a possible limitation in our results. Had this number been increased to 20-25 sessions, results may have been more impactful. However, our aim was to provide a clinical treatment that could be reviewed after 12 sessions, with the time and financial cost to patients minimized. This baseline provides clinicians with an option to continue therapy if only partial TA reduction was noted, or to cease TUS if no improvement or a complete resolution of PD is noted. As found in our cohort, the presence of calcified plaques >0.5 mm may also assist patient selection, as TUS appears to be ineffective for these patients. Also, a longer follow up may have been beneficial to assess the long term impact of TUS on PD.

Conclusion

In conclusion, we present a non-invasive treatment option for PD patients, utilizing experience gained from previously published clinical case series. TUS appears to be particularly useful when the calcification of plaques, as confirmed by PDDU scans, has been eliminated. Given the potential psychological distress for men with PD, our findings indicate that treatment with TUS, especially in the early phases of PD, reduced penile pain, improved penile deformity and increased erectile function. TUS may represent an effective, inexpensive treatment option for men suffering with this difficult to treat affliction. It causes no harm and can be provided by any qualified physiotherapist. Further independent studies in larger cohorts are encouraged to confirm our promising findings.

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CHAPTER 11

Thesis Summary and Discussion

Chapter 1 introduced the current status of men's health with a particular focus on prostate cancer (PCa) and male attitudes towards health. As PCa is the most common cancer diagnosed in men, issues relating to side-effects from treatment were highlighted and gaps in clinical care identified. In particular, the field of physiotherapy has recently evolved with a much greater awareness of many of these men's health issues, but knowledge and experience remains undeveloped. Fortunately, global physiotherapy organisations are now changing the names of their special interest groups, from just women's health to now including both genders. This was first instigated by New Zealand in 2016, then Australia in 2017, with international peak bodies not far behind. Co-chairing a World Confederation of Physical Therapy (WCPT) focused symposium entitled *'Men's health: A new frontier in physiotherapy'* in Cape Town in 2017 allowed me to facilitate men's health physiotherapy as a discipline, and a grounding for future development was established. Specific areas highlighted at that symposium included new approaches to pelvic floor muscle (PFM) assessment, chronic pelvic pain syndrome in men and the role of physiotherapy in PCa, with wide gaps in services noted between nations.

This thesis was separated into three components, in accordance with my clinical interests across the disciplines in men's health. The first section focused on the development of new tests of PFM function utilizing real-time ultrasound (RTUS) in a prostatectomy population. Building on the foundation of others who had validated both transabdominal (TrA) and transperineal (TrP) approaches, I developed two novel bed-side RTUS-based tests of PFM function. The Rapid Response Test (RRT) and the Sustained Endurance Test (SET) were based on the physiological stimulation of fast and slow twitch fibres. I compared the effectiveness of both tests with respect to traditional invasive *per rectal* approaches (incorporating digital rectal examination and perineometry measures). This was done in an effort to establish physiologically relevant functional measures and to reduce the need for invasive assessment.

The results outlined in Papers 1 and 2 demonstrated a modest correlation between the *per rectal* assessment of squeeze pressure and objective perineometer measures assessments, however, these were found to be unrelated to the novel RTUS tests. This effectively minimises the need for *per rectal* PFM assessment in prostatectomy patients. The RRT and SET assessments were able to be immediately translated to clinical practice. Additionally, strong agreement was found for both the RRT and SET when they were performed using either TrA or TrP approaches, in either supine or standing postures. These papers also reported the tests as having excellent inter- and intra-observer reliability (in contrast to *per rectal* assessments). A final analysis determined the relationship between RRT and SET scores versus 24-hr pad weight as a measure of urinary continence (UI), with moderate to high correlations between pad weight and the tests performed both in standing and supine postures. Indeed, there was no significant difference ($p>0.05$) between the two postures for RRT and SET tests using either RTUS methods. This effectively means that physiotherapists now have an objective, clinical, evidence-based, non-invasive, bed-side test applicable to men with PFM dysfunction performed in postures of clinical significance. We were also able to show that men leak more in upright postures and that this is primarily caused by PFM fatigue, which can be measured and used as a baseline for treatment strategies. Chapters 3 and 4 consisted of published articles in the *Australian & New Zealand Continence Journal*, highlighting relevance to clinical practice.

Part 2 of the thesis focused on PFM training programs for men affected by PCa who, as a result of radical prostatectomy (RP), experience UI and erectile dysfunction (ED). Chapter 5 reviewed the published literature and provided the background and conceptual thinking on PFM exercise training for minimising incontinence severity and duration. Although it is recognized that physiotherapists currently offer PFM training strategies for these patients, the supporting evidence was found to be equivocal. A randomized controlled trial of a novel ‘high intensity’ PFM training strategy was designed, implemented and compared to ‘usual care’(low intensity) PFM training, in an effort to reduce the most common clinical presentation of UI, with most leakage occurring in upright postures. Although the severity of leakage is unique to each man, the general clinical picture is reasonably homogenous, with most men attaining continence in supine positions (at night initially), before developing gradual improvement across the day. Patients typically complain of UI volumes being related to the number of hours spent vertical, with worsening incontinence as the day progresses and ‘afternoon fatigue’ resulting in increased urinary frequency, urgency and leakage. Measurement of this phenomenon, attributed to PFM fatigue, was the foundation for developing the RRT and SET tests described above.

The next goal was to provide men diagnosed with PCa a PFM intervention that aimed to improve PFM strength, endurance, hypertrophy and reflex responses, to better equip them for the typical post-RP incontinence scenario. Incorporation of recently described and more anatomically correct instructions to focus on the anterior PFM component, versus the more traditional *per rectal* approaches, [1-3] was also an important element of the RCT protocols. The 'high intensity' intervention consisted of both fast and slow twitch muscle fibre training exercises. Outcomes were compared to a group of men who performed a 'usual care' exercise protocol targeting only slow twitch muscle fibres, with one set each performed in supine, sitting and standing. The results indicated that at 2, 6 and 12 weeks post-surgery, the percentage of dry participants was greater across all time points in the 'high intensity' intervention group, compared to the 'usual care' group, with the former demonstrating a faster return to continence. At 2 weeks post-surgery, 14% of the intervention group participants, compared to 4% of the control group, were dry. At 6 weeks, this percentage increased to 32% and 11% respectively, then 74% and 43% by 12 weeks post-surgery. QoL questionnaires, pad weights and PFM function tests showed significantly better outcomes for the intervention group across all time points. In conclusion, 3.5 times more men were dry in the intervention group from the outset compared to 'usual care', with severity and duration of leakage approximately 50% less across all post-surgery time points. Thus, in the absence of extant evidence-based guidelines for management of PCa patients with exercise, this thesis supports a new protocol appropriate for the management of UI in men following RP. This formed the basis of Paper 3, which is currently in review with BMC Urology and is presented as Chapter 6 in the thesis.

Another aim of Part 2 was to investigate ED outcomes for patients undertaking PFM training following RP. In clinical practice, continence recovery and cancer clearance are the main focus of Urological surgeons performing RP. However, in reality, men are also concerned with their potency and the potential impact on their feelings of manhood, masculinity, relationships and self-worth. As highlighted in the literature review in Chapter 7, although well behind research for continence outcomes, there have been three published RCTs on the topic of ED and PFM training, with each showing improved erectile function with PFM training at 6-12 months following RP. We aimed to reduce this time, in an effort to reduce the burden of surgery and promote a faster return to satisfactory QoL. Hence, our RCT compared 'high intensity' versus 'usual care' PFM training on ED outcome scores and utilized the same design and methodology as for Paper 3. Although no statistically significant difference was found between the training groups within the 12-week training protocol when assessing erectile function, this was in line with previous studies that demonstrated a minimum 3-4 months was required for resolution of neuropraxia resulting from intra-operative tissue damage. When assessing QoL measures, however, the 'high intensity' training group displayed significantly improved and clinically relevant outcomes for overall EPIC-CP scores at 2 weeks post-RP. Outcome scores included erectile function and quality of life domains. This result enabled the intervention group participants to engage in penile rehabilitation and sexual activity earlier post-RP than the 'usual care' group, which reflected in a higher QoL. Importantly, these results indicate an earlier return to continence for post-RP patients in the intervention group, resulting in an expedited pathway to sexual rehabilitation, and possibly a reduction in psychological distress. Chapter 8 comprises a manuscript (Paper 4) on these findings and offers a role for new protocols in PFM training for the management of ED in men following RP, as an adjunct to penile rehabilitation.

The final section of this thesis was not initially planned. However, when I reviewed a patient following RP whose UI had resolved within a month of surgery and EF was improving, he was concerned that the PCa had returned as he could feel a hard, painful lump in his penis. I confirmed that this was most likely a condition known as Peyronie's disease (PD) and assured him I would investigate. Chapter 9 is a literature review of the published evidence on PD and the subsequent investigation of therapies commonly used in the treatment of this affliction. PD is far more prevalent than generally acknowledged, with 9% of all men affected, 16% following RP, 12% following EBRT and 22% on autopsy. Subsequent physiotherapy clinic experiences also revealed a 'silent' group for which there is no known cause. These patients do not appear to be genetically predisposed (e.g. Dupuytren's contracture), have no past history of trauma, ED, cardiovascular disease or senescence, but have pain, curvature and altered sensation and appearance of their penis.

Research published by Dornan[4] in 2012 and Cohen[5] in 2016, focusing on pudendal neuralgia and chronic pelvic pain syndrome (CPPS), highlighted musculoskeletal aspects that may compromise sexual function in men, leading to hypertonicity in PFMs, reduced blood flow and the potential development of penile fibrosis. This is reflective of a gap in medical understanding, as men who are routinely diagnosed with 'prostatitis' for any affliction in their pelvis causing unidentified pain and dysfunction, are usually treated with antibiotics, despite only 3% resolving. The remaining 97% remain distressed with complex medical histories and a sequalae of bowel, bladder and sexual health issues. Currently, there is limited help for the 1 in 9 men who will fall into this category in their lifetime, as PD represents the most common urological disease in men under 50 years, with an average of 87 months duration before diagnosis.[6] Further research is required in this group and measuring elasticity and vascularity of PFMs is now a research aim beyond this thesis.

Chapter 10 represents a RCT that investigated the use of therapeutic ultrasound (TUS) for the treatment of PD. As revealed in Chapter 9, TUS had been utilized in a number of case studies for the treatment of PD from 1951-1983 with generally positive, albeit anecdotal findings. A pilot study was undertaken and the TUS intervention resulted in a drastic reduction in penile curvature, complete resolution of pain, return to sexual activity and resolution of 2.6 mm fibrosis and foci calcifications reported upon follow up with penile duplex Doppler ultrasound (PDDU). The subsequent RCT aimed to develop and assess the efficacy of a non-invasive approach to the treatment of PD with administration of TUS compared to 'usual care'. Assessment of penile plaques via the PDDU score was the primary outcome measure with only the intervention group showing improved scores. There was also a reduction in penile curvature angle of 17^{o} (38%) over time for the intervention group only. Following similar scores at baseline between groups, only the intervention group improved erectile function (IIEF-5 scores) over time, however, the sample was not sufficiently large to provide the statistical power needed to show the QoL impact of this intervention. Clearly, TUS has a place in the treatment of acute and chronic PD when calcifications greater than 5 mm are not present. This treatment may potentially reduce the distress experienced by men with PD, and offers a non-invasive, easy to administer, cheap and effective intervention that has the potential to make improvements for approximately 70% of men with the condition. The TUS treatment has no known harmful side-effects and can be delivered by any physiotherapist with minimal training, effectively making it translatable immediately. Although only 12 sessions were applied in my investigations, previous authors performed up to 25 TUS sessions, so further research may help to better quantify what is best practice.

Future Directions

By establishing novel non-invasive methods of PFM assessment utilizing RTUS, the need for intrusive, per rectal testing in men is now not necessary and this may potentially reduce reluctance by men to attend physiotherapy services. It would be helpful if the RRT and SET tests could be assessed and translated to other populations including children, the elderly, women under 18 years of age, victims of sexual abuse or those reluctant to have internal PFM assessments. Further research is, therefore, required to address this gap in clinical care. Additionally, the use of TUS as a non-invasive treatment for PD fills a gap in the treatment of men newly diagnosed with penile deformities and offers opportunities for improved clinical care for this vulnerable population. Further RCTs utilizing PFM exercise training and/or vacuum pump therapy in comparison to TUS could further explore the role of physiotherapy in men’s health.

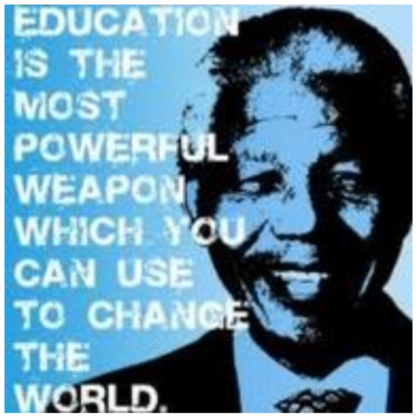
By providing men with the opportunity to learn a high intensity PFM exercise training program prior to RP and with the focus on correct anatomical structures, this thesis offers the first RCT to challenge multiple Cochrane review findings, which at this stage, do not recommend PFM training in prostate surgery patients. Incorporation of fast and slow twitch fibre training in standing postures addresses the clinical presentations of men post-RP with a 5-week prehabilitation program strongly supporting reduced leakage and improved QoL outcomes immediately post-op compared to usual care. With publication of these findings, a new benchmark could be set for men and the 1.3 million diagnosed with PCa annually.

Limitations of this thesis include the fact that there was no ‘third arm’ control group in the PFM RCT, to form a cohort that did not receive any PFM training. This was considered unethical, since the research was conducted in a private clinic setting, with urologists already routinely referring patients for pre-RP PFM physiotherapy. It was also felt that it was highly unlikely that any man undergoing RP would not seek information and try some form of exercise therapy, making it almost impossible to have a compliant control group for comparison. In addition, with the sample group limited to one practitioner performing most assessments and training, some bias may have occurred. Other limitations include a sample that was not quite large enough to register significant outcomes in the impact of high intensity PFM training on ED, aside from improved QoL scores from 2 weeks post-RP. Hence, the recruitment of larger cohorts, over a longer PFM training time would be encouraged. Also, many men reported climacturia and arousal leakage, a distressing combination of both urinary and erectile dysfunction following RP, that had a negative impact on their self-esteem and relationships. There are currently no validated instruments to assess the prevalence and severity of this condition, which restricted my ability to analyze a neglected QoL outcome for men in this population.

Finally, it is evident that a large group of men diagnosed with PCa are not provided with any physiotherapy care in relation to their potential for experiencing UI, ED and faecal incontinence. This includes those men who are on active surveillance and those undergoing radiation, hormone treatment (ADT) and chemotherapies. Currently, it is acknowledged that men who receive EBRT, for example, do not generally experience incontinence and ED initially with treatment, but rather experience it 2-3 years post-treatment, due to ongoing fibrosis and vascular damage. As this group makes up approximately 50% of all men diagnosed with PCa, the opportunity to translate the knowledge gained for men undergoing RP could be easily transferred, then investigated in the remaining population. With one-in-six men at risk of developing PCa and up to one-in-four by the age of 85 years, PFM training could potentially provide a beneficial tool for all men to become familiar with.

Conclusion

My aim in this thesis was to address critical gaps observed in men's health research and clinical practice, with a desire to lessen the QoL burden for men following diagnosis and treatment of PCa. The clinical treatment and experiences of patients were highly variable at the outset of my studies. It was upsetting to witness the huge variation in results for patients between those referred for 'pre- and post-RP' physiotherapy versus 'post-RP' only, and the positive impact of PFM preparation. It bothered me that the education was so far behind in men's, compared to women's health. Moving forward, there is still much work to do, but I feel many of my goals were achieved and that this body of work offers new techniques and strategies that can be immediately translated to clinical care and for patient benefit in both the physiotherapy and medical settings. The opportunity to share this knowledge in the community is my next challenge, for my patients have taught me most of what I now understand and, for me, that matter the most. For, as the great Rolichcha Delubunga (Nelson Mandela) once said,



(Please see the appendix for a list of educational and community endeavours completed throughout the duration of this thesis. PROST!)

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Appendix 1: Thesis Documents and Publications

1. Ethics approval: Pelvic floor muscle training in radical prostatectomy study
2. Patient Information form : Pelvic floor muscle training in radical prostatectomy study
3. Consent form: Pelvic floor muscle training in radical prostatectomy study
4. Ethics approval: Therapeutic ultrasound in Peyronie's disease
5. Patient information form: Therapeutic ultrasound in Peyronie's disease
6. Consent form: Therapeutic ultrasound in Peyronie's disease
7. Paper 1 published ANZ Cont Journal Summer 2018
8. Paper 2 published ANZ Cint Journal Autumn 2019
9. Poster 1 APCC 2014 'Stop giving your patients the finger'
10. Poster 2 WCPT 2017 South Africa " Is there a role for therapeutic ultrasound in Peyronie's disease: 3 case studies?'
11. Poster 3 APCC 2018 'New protocols for a faster return to continence and quality of life following radical prostatectomy
12. Poster 4 APCC 2018 " Therapeutic Ultrasound- A non-invasive approach to treatment for Peyronie's disease'
13. Publication: APA In Motion Magazine article 2018 'A bend in the men's health learning curve'.
14. APA GP Fact Sheet**:** Men's Pelvic Floor Health: Pelvic Floor Muscle Dysfunction in Men

THE UNIVERSITY OF WESTERN AUSTRALIA
Achieving International Excellence

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Our Ref: RA/4/1/6372

22 October 2013

Winthrop Professor Daniel Green
School of Sport Science, Exercise & Health
MBDP: M408

Dear Professor Green

HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA

Pelvic Floor Muscle Exercise Training in Prostatectomy Patients

Student(s): Joanne Milios - PhD - 18906151

Ethics approval for the above project has been granted in accordance with the requirements of the *National Statement on Ethical Conduct in Human Research* (National Statement) and the policies and procedures of The University of Western Australia. Please note that the period of ethics approval for this project is five (5) years from the date of this notification. However, ethics approval is conditional upon the submission of satisfactory progress reports by the designated renewal date. Therefore inital approval has been granted from 22 October 2013 to 01 November 2014.

You are reminded of the following requirements:

1. The application and all supporting documentation form the basis of the ethics approval and you must not depart from the research protocol that has been approved.
2. The Human Research Ethics Office must be approached for approval in advance for any requested amendments to the approved research protocol.
3. The Chief Investigator is required to report immediately to the Human Research Ethics Office any adverse or unexpected event or any other event that may impact on the ethics approval for the project.
4. The Chief Investigator must inform the Human Research Ethics Office as soon as practicable if a research project is discontinued before the expected date of completion, providing reasons.

Any conditions of ethics approval that have been imposed are listed below:

Special Conditions

None specified

The University of Western Australia is bound by the National Statement to monitor the progress of all approved projects until completion to ensure continued compliance with ethical standards and requirements.

The Human Research Ethics Office will forward a request for a Progress Report approximately 60 days before the due date. A further reminder will be forwarded approximately 30 days before the due date.

If your progress report is not received by the due date for renewal of ethics approval, **your ethics approval will expire**, requiring that all research activities involving human participants cease immediately.

If you have any queries please contact the HREO at hreo-research@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/6372 – and the associated project title in all future correspondence.

Yours sincerely

[redacted]

Dr Mark Dixon
Associate Director, Research Ethics and Biosafety

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PARTICIPANT INFORMATION SHEET

Pelvic Floor Muscle Exercise Training in Prostatectomy Patients

Chief Investigator: W/Professor Danny Green Email: jomilios22@gmail.com
Student Investigator: Jo Milios Telephone: 0408022950

The following information relates to a research study in which you may choose to participate. Please take the time to read all the information so that you understand what the study involves. Should any additional information be required, contact details are provided above.

Purpose of the Project:

The main aim of this study is to assess the effects of pelvic floor muscle (PFM) exercise training on measures of erectile function, post-prostatectomy urinary incontinence(PPI) and Health Related Quality of Life (HRQL) issues in men who have undergone a prostatectomy.

Eligibility

We wish to recruit patients who are undergoing a radical prostatectomy with intent for nerve sparing. Regular smokers, patients with uncontrolled diabetes, significant cardiovascular disease and those consuming >21 units of alcohol/week will be excluded from participation. Regular medications for pre-existing risk factors will be monitored. No information from this screening will be shared and your data will be de-identified, securely stored and destroyed after the study has terminated.

What will happen if I take part?

If eligible, you will be randomized to undertake 3 months of pelvic floor muscle (PFM) exercise training of either usual care or high intensity. All participants will be required to attend the University of Western Australia or a Physiotherapy clinic for 1.5 hours of experimental testing (described in detail below). These sessions will happen 4 times over a 12 month period: once before prostatectomy, soon after prostatectomy, 3 months after starting PFM exercise (or usual care) and finally after 12 months.

Pelvic Floor Muscle Exercise Training

You will be able to complete these tasks at home or during your typical working day with no need to attend UWA at a specific time or place. However you will be required to complete a diary to ensure that PFM exercise tasks were completed. PFM exercise will be initially taught and supervised by a physiotherapist.

Usual Care
If randomly assigned to this group, you will receive usual clinical care and follow-up after prostatectomy. This will consist of education on pelvic floor and bladder training, plus a regime of low intensity pelvic floor exercises.

High Intensity
If randomly assigned to this group, you will receive usual clinical care and follow-up after prostatectomy. This will consist of education on pelvic floor and bladder training, plus a regime of high intensity pelvic floor exercises.

Experimental Measurements (repeated on 4 occasions across ~12 months):
Each session 1 – (~1.5 hrs.)

Erectile function, urinary incontinence & health related quality of life (HRQoL)
You will complete a number of questionnaires to assess erectile function, urinary incontinence (PPI) and health related quality of life issues. You will be asked to answer a number of questions regarding continence pad use and the weight of such pads will be assessed. Your pelvic floor muscle strength will also be assessed by completing pelvic floor contractions under real time ultrasound. This technique is safe painless, non-invasive and has no known side effects. An ambulatory penile tumescence monitor for testing erectile dysfunction will also be provided to assess nocturnal erectile events over 12 hours to record volumetric changes within the penis in a small sub group of subjects. This is safe to use, painless and has no known side effects. In addition, a Duplex Ultrasound to assess penile blood flow will be performed to provide a 'picture' via sound waves of the erectile function in another small sub-group.

Risks and benefits
There are no known biological side effects of ultrasound.
Benefits of the current study include an improved knowledge of the impact of specific pelvic floor muscle activity on symptoms following prostatectomy. Similarly, this study may reveal a potential avenue to effectively improve urinary continence, erectile function and QoL following prostatectomy.

SUBJECT RIGHTS AND WITHDRAWAL
Participation in this research is voluntary and you are free to withdraw from the study at any time without prejudice. You can withdraw for any reason and you do not need to justify your decision. If you withdraw from the study and you are an employee or student at the University of Western Australia (UWA) this will not prejudice your status and rights as an employee or student of UWA. If you withdraw from the study and are a patient recruited from one of the affiliated clinics your treatment will not be prejudiced or affected in any way. If you do withdraw we may wish to retain the data that we have recorded from you but only if you agree, otherwise your records will be destroyed. Your participation in this study does not prejudice any right to compensation that you may have under statute of common law.
If you have any questions concerning the research at any time please feel free to ask the researcher who has contacted you, about your concerns. Further information regarding this study may be

obtained from Jo Milios (completephysiotherapy@gmail.com), W/Professor Daniel Green (danny.green@uwa.edu.au)

"Approval to conduct this research has been provided by The University of Western Australia, in accordance with its ethics review and approval procedures. Any person considering participation in this research project, or agreeing to participate, may raise any questions or issues with the researchers at any time. In addition, any person not satisfied with the response of researchers may raise ethics issues or concerns, and may make any complaints about this research project by contacting the Human Research Ethics Office at The University of Western Australia on (08) 6488 3703 or by emailing to hreo-research@uwa.edu.au. All research participants are entitled to retain a copy of any Participant Information For and/or Participant Consent Form relating to this research project."

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PARTICIPANT CONSENT FORM

Pelvic floor muscle exercise training in Prostatectomy patients.

Chief Investigator: W/Professor Daniel Green

Email: jomilios22@gmail.com

Student Investigator: Jo Milios Telephone: 0408 022 950

1. I…………………………………..confirm that I have read and understand the information provided for this study and that any questions I have asked have been answered to my satisfaction I agree to participate in this study.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect any treatment that I am receiving or may receive, nor my legal rights.

3. I understand that all identifiable information that I provide is treated as strictly confidential and will not be released by the investigator in any form that may identify me. The only exception to this principle it documents are required by law.

4. I have been advised as to what data is being collected, the purpose for collecting the data and what will be done with the data upon completion of the research.

5. I agree that research data gathered for the study may be published provided my name or other identifiable information is not used.

______________________________ ____________________

PARTICIPANT *DATE*

"Approval to conduct this research has been provided by The University of Western Australia, in accordance with its ethics review and approval procedures. Any person considering participation in this research project, or agreeing to participate, may raise any questions or issues with the researchers at any time.
In addition, any person not satisfied with the response of researchers may raise ethics issues or concerns, and may make any complaints about this research project by contacting the Human Research Ethics Office at The University of Western Australia on (08) 6488 3703 or by emailing to hreo-research@uwa.edu.au
All research participants are entitles to retain a copy of any Participant Information For and/or Participant Consent Form relating to this research project."

Human Ethics

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Our Ref: RA/4/1/8089

03 May 2016

Winthrop Professor Daniel Green
School of Sport Science, Exercise and Health
MBDP: M408

Dear Professor Green

HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA

Ultrasound therapy for Peyronie's Disease: A novel, non-invasive treatment approach.

Student(s): Joanne Milios - PhD - 18906151

Ethics approval for the above project has been granted in accordance with the requirements of the *National Statement on Ethical Conduct in Human Research* (National Statement) and the policies and procedures of The University of Western Australia. Please note that the period of ethics approval for this project is five (5) years from the date of this notification. However, ethics approval is conditional upon the submission of satisfactory progress reports by the designated renewal date. Therefore initial approval has been granted from 03 May 2016 to 02 May 2017.

You are reminded of the following requirements:

1. The application and all supporting documentation form the basis of the ethics approval and you must not depart from the research protocol that has been approved.
2. The Human Ethics office must be approached for approval in advance for any requested amendments to the approved research protocol.
3. The Chief Investigator is required to report immediately to the Human Ethics office any adverse or unexpected event or any other event that may impact on the ethics approval for the project.
4. The Chief Investigator must submit a final report upon project completion, even if a research project is discontinued before the anticipated date of completion.

Any conditions of ethics approval that have been imposed are listed below:

Special Conditions

None specified

The University of Western Australia is bound by the *National Statement* to monitor the progress of all approved projects until completion to ensure continued compliance with ethical principles.

The Human Ethics office will forward a request for a Progress Report approximately 30 days before the due date.

If you have any queries please contact the Human Ethics office at humanethics@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/8089 – and the associated project title in all future correspondence.

Yours sincerely

[redacted]

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CRICOS Provider Code: 00126G

PARTICIPANT INFORMATION FORM

Project Title: Ultrasound Therapy in Peyronie's Disease: a non-invasive treatment.
Investigators: Joanne Milios, Professor Daniel Green, Dr. Patrick Teloken, Dr Neil Palmer Professor Timothy Ackland

Study Purpose

Thank you for your interest in participating in this research study conducted by researchers from the School of Sport Science, Exercise & Health (SSEH) at the University Of Western Australia (UWA). This study forms part of a PhD being undertaken by Joanne Milios under the supervision of Prof Daniel Green, Prof Timothy Ackland and Professor Loiuse Naylor. The focus of the PhD is to assess Quality of Life measures in men who undergo a radical prostatectomy for prostate cancer.

The main aim of the study is to assess the effectiveness of therapeutic ultrasound in men with Peyronie's disease (PD). Peyronie's disease is a build-up of hard, fibrotic plaques within the penis as a result of decreased blood flow and can result in shortening, pain and curvature of the penis.

PD is common in diabetes, cardio-vascular disease, ageing and occurs in 16-19% of men following radical prostatectomy. Therapeutic ultrasound involves the non-invasive local application of sound waves that can soften fibrotic tissue. We plan to determine whether ultrasound is beneficial in PD.

Procedures

Prior to commencing the study, we will ask you to attend the Cardiovascular Research Laboratory at UWA to ensure you meet some eligibility criteria. This will involve the collection of your medical history and physical measures such as height, weight and BMI. On the same day, if eligible, you will then complete two questionnaires which give you the opportunity answer questions on how Peyronie's Disease affects your quality of life.

Experimental Outline: This study involves an initial penile Doppler Scan to be completed at SKG Radiology, Hollywood Hospital under the care of Dr Alar Kaard,. The scan will determine the presence of fibrotic plaques and measurements can then be taken of their size. Flaccid penile length and diameter will also be measured. There are costs for participants for Doppler scans.

Following these measures, you will attend private medical rooms to receive therapeutic ultrasound 3 times per week for 4 weeks. The dose of ultrasound will gradually increase from 1.5W/cm^2 to 3.0W/cm^2 over 4 weeks. A second group will receive sham intervention over 4 weeks. This means that a control group will receive ultrasound that does not emit ultrasound waves as a comparison with participants that do. This is to ensure a control group forms part of the study, so that experimental design may lead to more accurate results. A follow up Doppler Scan with Dr Kaard will then occur at the end of the 4-week intervention period and the same measurements of plaques and penile length will be recorded. This will take place at SKG Radiology at Hollywood Hospital. If allocated to the sham group and the true intervention can be shown to be effective, then these participants will be offered treatment for a one month period. In addition , a small subset group of the sham group (n=10) will receive both therapeutic ultrasound at the same rate and at the same time as using a SOMACorrect Vaccum Compression Device (VCD), especially designed for Peyronie's Disease. This will be used for 10 minutes/ day 5 days/week during the period of receiving ultrasound therapy. A follow up Doppler Scan with Dr Kaard will then occur at the end of the 4-week intervention period and the same measurements of plaques and penile length will be recorded. This will take place at SKG Radiology at Hollywood Hospital.

Explanation of therapeutic ultrasound:
Ultrasound (US) is applied using a round-headed probe that is put into direct contact with the patient's skin. Ultrasound gel is used on all surfaces to reduce friction and assist in the transmission of ultrasonic waves. In this experiment, ultrasound will be used in the frequency range of 1.5-3.0W/cm^2, gradually increasing over a 4 week intervention. The ultrasonic waves that are generated cause a vibration of crystals within the head of the probe. This vibration can cause a deep local heating, which treats the area of fibrosis. Generically, therapeutic ultrasound has been shown to cause deep tissue relaxation, improve local blood flow and cause scar tissue breakdown, although it has not previously been used widely for the treatment of PD.

Explanation of Vacuum Compression Pump:
Vaccum Compression Pumps (VCP)s can provide stretching and straightening of collagen fibres that make up scar tissue and fibrotic plaques that develop in Peyronies Disease. It is theorised that a recently released VCD, the SOMAcorrect will help to reshape the fibrotic plaque, thereby reducing its contractile impact and the degree of penile curvature. The new pump comes with size adapted cylinders that induce a series of 'straight' erections over a 10 minute period. Traditionally VCP's have been used in erectile dysfunction in men by increasing local penile blood flow and stretching the corpus cavernosal and spongiosum tissues.

Risks
There are minimal risks associated with participation in this study. The Doppler ultrasound tests are safe and use a machine similar to that involved in foetal scanning. There are no known side effects of the penile Doppler ultrasound assessment and no radiation involved.
Therapeutic ultrasound is contraindicated if there are metal implants, local acute infection or areas of malignancy, but is a local heat treatment only. Patients will be screened for these and excluded from the study if any concerns are raised. Vacuum Compression Pumps have been widely utilised for male erectile dysfunction without risk. Instruction will be provided to all participants. A penile ring –which if used longer than 30 minutes may cause harm, will not be used in this study as it is not required for therapy and is used only if sexual activity is desired.

Benefits
The results of this study will be novel and aim to provide evidence for the non-invasive treatment of Peyronie's Disease. Currently, there is no gold standard treatment for PD and most procedures involve experimental medication or surgery, both of which have potential side effects.

Confidentiality
The participants confidentially will be maintained throughout the study. Data collected, which includes images of the ultrasonography, will be securely stored on a password-protected laptop. Only research personnel will have access to the passwords for the laptop.

Subject Rights and Withdrawal

Participation in this research is voluntary and you are free to withdraw from the study at any time without prejudice. You can withdraw for any reason and you do not need to justify your decision. If you do withdraw we may wish to retain the data that we have recorded from you but only if you agree, otherwise your records will be destroyed. Your participation in this study does not prejudice any right to compensation that you may have under statute of common law.

If you have any questions concerning the research at any time please feel free to ask the researcher who has contacted you about your concerns. Further information regarding this study may be obtained from Jo Milios 0408 022 950 or E:completephysiotherapy@gmail.com) or Professor Daniel Green, 6488 5609 or E:danny.green@uwa.edu.au

The Human Research Ethics Committee at the University of Western Australia requires that all participants are informed that, if they have any complaint regarding the manner, in which a research project is conducted, it may be given to the researcher or, alternatively to the Secretary, Human Research Ethics Committee, Registrar's Office, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009 (telephone number 6488-3703). All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

Thank you for considering participating in this research project.

Pelvic floor muscle assessment in men post prostatectomy: comparing digital rectal examination and real-time ultrasound approaches

ABSTRACT

This paper reports three studies. Study 1 assessed the degree of association between traditionally used digital rectal measures, and real-time ultrasound assessments of pelvic floor muscle function in men who report incontinence following prostatectomy. Study 2 compared transabdominal and transperineal approaches to view the pelvic floor using real-time ultrasound. Study 3 explored inter- and intra-observer reliability of two functional tests using real-time ultrasound: a rapid response test requiring participants to perform 10 rapid pelvic floor muscle contractions with elapsed time recorded, and a sustained endurance test wherein participants performed a single sustained pelvic floor muscle contraction with task failure visually confirmed and elapsed time recorded. A modest correlation was observed between the rectal assessment of squeeze pressure and objective perineometer measures ($r=0.51$, $p<0.05$). Rapid response test ($r=0.18$, $p=0.36$) and sustained endurance test ($r=0.18$, $p=0.36$) assessments were unrelated to pelvic floor muscle squeeze pressure measured by perineometry. Strong agreement was found using Bland-Altman analysis for both the rapid response and sustained endurance tests when they were performed using transabdominal and transperineal approaches, or when determining inter- and intra-observer reliability. The two simple functional tests using real-time ultrasound provide objective, non-invasive and reproducible assessment of pelvic floor muscle function that is more acceptable to men than rectal approaches.

Keywords: Men's health, pelvic floor muscle, prostate cancer, prostatectomy, physiotherapy, real-time ultrasound.

INTRODUCTION

Prostate cancer (PCa) is a global health problem and the second most commonly diagnosed cancer among men[1]. Radical prostatectomy (RP), involving complete removal of the prostate, is a standard surgical treatment performed via retropubic, perineal laparoscopy or robotic-assisted laparoscopic techniques[2,3]. After radical prostatectomy men report a high prevalence of urinary incontinence (UI) and erectile dysfunction (ED)[4-6], and compromised function of the pelvic floor musculature (PFM) is one of several contributing causes. Post-operative rehabilitative therapy includes strategies to improve PFM function, to address issues such as UI[7] and ED[8] that impact on quality of life. The objective of this three-part study was to assess tests of PFM function using real-time ultrasound (RTUS) to further enhance clinical practice.

The standard approach to assessing PFM function in men has involved digital rectal examination (DRE) and scoring of "squeezing" pressure on an ordinal scale (for example, Modified Oxford Scale)[8-11]. However, this approach only provides ordinal data and is described as physically invasive, psychologically challenging[12-17], possessing poor inter-observer reliability and lacking universal standardisation (studies predominantly undertaken in women)[18]. Aversion to this method of assessment is supported by research indicating the procedure induces a sense of shame and men are reluctant to receive DREs due to it being personally invasive[19,20]. In addition, rectal PFM strength assessment in men has been shown to be largely unrelated to male

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Competing interest statement:
All authors declare they have no relevant relationships or circumstances that present actual or potential conflicts of interest.

urinary function[21,22]. The muscles assessed during a DRE can include those related to anal sphincter function (external and internal anal sphincter and puborectalis).

Using RTUS assessment of PFM, function is observed as elevation at the base of the bladder during a PFM contraction and relaxation cycle[14]. Transabdominal real-time ultrasound (TrA RTUS) is a valid and reliable method for use in both men and women, although specific components of PFM that are associated with continence cannot be assessed individually[21,23,24]. An alternative approach involves transperineal real-time ultrasound (TrP RTUS), which uses the pubic symphysis as a bony landmark and enables simultaneous visualisation of all three striated muscles (the striated urethral sphincter, the bulbocavernosous and the puborectalis) that control male urinary continence via a complex "horseshoe action"[25,26]. No research to date has compared TrA versus TrP RTUS measures in men.

The PFM comprises two broad types of skeletal muscle fibres, with each responsible for different functions. Slow twitch (type 1) endurance fibres make up approximately 80% of the PFM[27,28] and are capable of long-lasting but relatively weak contractions[29]. These fibres are activated to maintain bladder and bowel continence, assist in upright posture and help maintain PFM tone during rest or activity[29,30]. The remaining ~20% of PFM fibres are fast twitch (type 2)[11,28], which are adapted for strong, rapid contractions, required for both reflex occlusion of the urethra and for voluntary retention of urine[29]. Although they fatigue faster than type 1 fibres, type 2 fibres are primarily responsible for preventing urinary leakage during sudden actions such as coughing and sneezing[31,32]. In these scenarios, reflex reactions are required to compress the urethral wall during periods of increased abdominal pressure[29,33]. To assess the different functional capacities of the pelvic floor in men, we used two tests; the rapid response test (RRT) and sustained endurance test (SET), involving RTUS visualisation of PFM function.

The results of three studies are reported in this paper. Study 1 investigated the relationship between muscle function measured via traditional rectal examination approaches versus RTUS methods. Study 2 compared RTUS TrA and TrP approaches and study 3 assessed intra- and inter-tester reliability for the RRT and SET tests seen on RTUS.

METHODS

This study was approved by the University of Western Australia, Human Research Ethics Committee (Ref RA/4/1/6265) and the participants provided written informed consent.

Description of studies

Participants in study 1 were enlisted from a cohort of patients referred sequentially by their urologist for pre-prostatectomy PFM training to a single physiotherapy clinic. No specific inclusion or exclusion criteria were applied. Each participant underwent rectal perineometry assessment and a rectal squeeze pressure assessment by DRE. The Modified Oxford Scale[9] was used to assess PFM squeeze pressure in the lateral decubitus (side-lying) posture by a clinician experienced in PFM dysfunction. Prior to each examination, instructions were provided on correct PFM exercise technique[34], to ensure a full contraction and relaxation cycle was implemented with the cue given to "stop the flow of urine and shorten the penis while continuing to breathe"[34]. Cues to relax abdominal muscles and avoid breath holding were also given. The DRE was performed with palpation beyond the external anal sphincter (EAS) to assess the pelvic floor musculature approximately 3–4cm within the anal canal, to minimise contamination of EAS contraction. The use of a perineometer (Peritron A PRTN-1-1-1301135, Ontario) was to provide an objective measure of PFM squeeze pressure. The covered probe was inserted beyond the EAS, such that the hilt of the probe was adjacent to the anus, in keeping with the guidelines provided in the Peritron A instruction manual. Whilst we cannot exclude the possibility that anal sphincter pressure affected the probe reading, the pressure-sensitive component of the perineometer lies on the shaft of the device, distal to the hilt, and it is therefore likely that our measurement approximated the PFM assessment described for the manual DRE approach[35]. This test was also performed in the lateral decubitus posture. On a separate day within one week of their initial clinic visit, these participants also underwent SET and RRT testing using the TrA approach. The TrP approach was not used at this stage of the experiment, with subsequent testing used to directly compare these two approaches (study 2).

Participants in study 2 were also enlisted from a cohort of patients sequentially referred by their urologist and were all assessed between two weeks and six months post-surgery. Participants were assessed (in random order) for the RRT and SET tests in the supine posture during two consecutive testing sessions, by the same tester, one week apart to determine intra-tester reliability. For each measurement, participants underwent both TrP and TrA RTUS assessments using a commercially available point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China).

In a third study, to determine inter-tester reliability, the RTUS tests were repeated by a second experienced observer within one week of the original test (at the same time of day) on a sub-sample of participants, with instructions between testers and participants standardised. To standardise bladder volume, each participant voided their bladders and then drank 500 ml of water, and were instructed not to void again prior to testing.

Description of pelvic floor muscle function tests

Participants were assessed for PFM function in the crook lying position (the 'supine' posture) with a pillow underneath the head, and hips and knees flexed at 60 degrees and with the lumbar spine positioned in neutral.

Cues to relax abdominal muscles and avoid breath holding were also given. Instruction was provided on correct PFM exercise technique[34], to ensure a full contraction and relaxation cycle was implemented with the cue given to *"stop the flow of urine and shorten the penis while continuing to breathe"*[21,34]. Participants were allowed one 'practice' contraction prior to the test in order to provide feedback for both tester and participant, and to avoid poor technique.

For the RRT, participants were instructed to *"perform 10 maximal PFM contractions and relaxations as fast as possible"*, with the elapsed time recorded as the outcome measure. In the SET participants were instructed to *"hold a maximal contraction for as long as possible, whilst continuing to breathe"*. The time to task failure was recorded (with a maximum time of 60 seconds), where task failure was defined as the descent of the bladder base (TrA) or bladder neck (TrP).

Transperineal RTUS assessments

Prior to the TrP RTUS, each participant was asked to disrobe in private and to drape a towel around their waist, before reaching under and gently moving their genitals to one side with their hand. Standard infection control measures were observed. After applying a layer of transmission gel, TrP RTUS was performed by placing the covered probe on the perineum in the mid-sagittal location, midway between the base of the penis and the anus, with the transducer orientated to obtain sagittal images, and then the participant removed his hand. To optimise the images, the pubic symphysis (SYMP) was used as the bony reference point, with the urethra (U), bladder (BL), bladder neck (BN) and anorectal angle (ARA) visible simultaneously (Figure 1). Using screen calipers, a measure of the position of the bladder neck was taken at rest 'x' and the change from the resting position in a vertical direction was observed. In this study any cranial movement of the bladder neck was noted as a correct action, whereas no cranial movement or any caudal movement of the bladder neck was noted as incorrect action, as with previous guidelines[21]. During SET assessments, an arrow was placed at the bladder neck as a visual marker to determine whether changes in amplitude were indicative of task failure.

Any participant unable to perform the PFM contraction correctly (that is, cranially versus caudally), was given the opportunity to rest to allow for PFM recovery. Cues to contract and relax the pelvic floor were repeated and, with the benefit of visual feedback, all participants were able to correct their technique. This approach was also adopted during the transabdominal procedure if initial contractions were incorrect.

Transabdominal RTUS assessments

Assessment via the TrA RTUS approach was performed by placing the probe suprapubically on the lower abdomen at a mid-sagittal location with the transducer probe orientated to obtain transverse images and angled in a caudal/posterior direction such that a clear image of the inferior-posterior aspect of the bladder was obtained (Figure 1). Standard infection control measures were observed and a layer of gel was placed over the head of the probe. Screen calipers were used to place a mark 'x' on the bladder base (BB) at rest where any elevation of the BB was noted as a correct action and any depression of the BB was noted as incorrect action in accordance with previous guidelines[14,24]. As per TrP RTUS assessments, during SET measures, an arrow was placed at the bladder neck as a visual marker to determine whether changes in amplitude were indicative of task failure.

Statistical analysis

Data for the DRE, perineometer, SET and RRT tests were entered into SPSS (v22.0, SPSS, Chicago, IL) for subsequent analysis and significance was accepted for all analyses at $p<0.05$. The association between scores from DRE and perineometer measurements was analysed using a Pearson's correlation with linear regression performed to characterise association

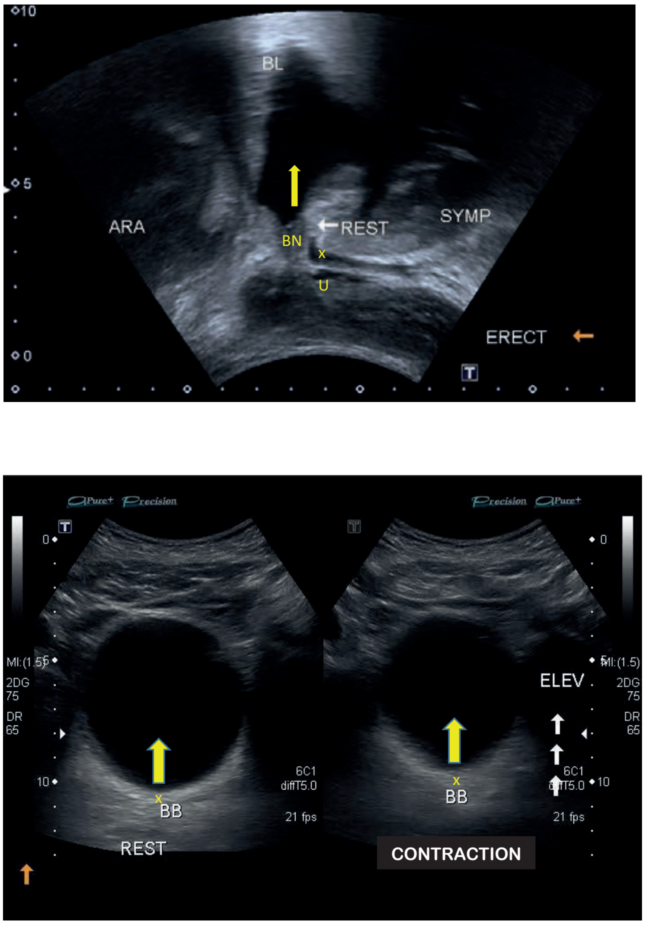

Figure 1: Upper panel: Transperineal real time ultrasound image (RTUS) used to assess pelvic floor muscular (PFM) function utilising screen calipers to determine correct PFM action during the rapid response test (RRT) and sustained endurance test (SET). Movement should be in a cranial direction as indicated by the arrow. BL = bladder, BN = bladder neck seen in relation to SYMP = symphysis pubis, U = urethra, ARA = anorectal angle and bladder. Lower panel: Transabdominal (TrA) RTUS images used to assess PFM action during the RRT and SET (left image = at rest; right image = whilst contracting). BB= base of bladder and arrows indicate direction of pelvic floor muscles.

between these variables. For this paper we defined the strength of correlation as follows:[36]

- r= 0.25–0.50 weak to moderate
- r=0.5–0.75 moderate to good
- r> 0.75 good to excellent

Bland-Altman analyses and plots were used to determine the limits of agreement for:

- the relationship between RRT and SET outcome scores using TrP versus TrA approaches with patients in the supine posture
- inter-observer reliability for SET and RRT tests conducted using TrA RTUS with patients in the supine posture
- intra-observer reliability for SET and RRT tests conducted using TrA RTUS with patients in the supine posture.

RESULTS

Study 1: Relationship between rectal examination approaches and RTUS tests

Test scores for 27 post-prostatectomy patients (63±7y, 170.0±18.3cm, 76.2±16.3kg, all Gleason 7) averaged 3.0 ± 0.8 on the Modified Oxford Scale and 44.3±22.2 cmH_2O by perineometry. DRE results were only moderately correlated with the more objective perineometry measurements (r=0.5, *p*<0.05).

RRT (r=0.18, *p*=0.36) and SET (r=0.18, *p*=0.36) assessments were unrelated to perineometry-based PFM squeezing pressure. Correlations between the digital rectal squeeze pressure and the SET (r=0.02, *p*=0.94) and RRT (r=0.04, *p*=0.86) were also not correlated.

Study 2: Comparison of RTUS TRA and TrP approaches

Of the 100 patients recruited to Study 2, five were excluded from analysis due to post-surgery complications involving the bladder neck, which required further surgical intervention (n=95, 63±11y, 172.0±15.2cm, 72.9±16.9kg, all Gleason 7), with ± referring to the mean ± standard deviation.

The limits of agreement for each of the RRT and SET assessments, performed using TrP and TrA methods, are presented as Bland-Altman plots in Figure 2. These data show no significant difference (*p*>0.05) between the assessment methods. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between both methods being close to 0 and the standard deviation for difference scores low (0.9 seconds for RRT and 4.1 seconds for SET).

Study 3: Intra- and inter-tester reliability for the RRT and SET tests seen on RTUS

This sub-sample of participants were recruited from the cohort of men in study 2, who were able to attend two consecutive appointments within one week (n=47, 63±12y, 171.0±14.9cm, 76.1±17.2kg). The limits of agreement for each of the RRT and SET assessments, performed on the same participants by two operators, are presented as Bland-Altman plots in Figure 3. These data show no significant difference (*p*>0.05) between operators. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between operators being close to 0 and the standard deviation for difference scores low (2.0 seconds for RRT and 2.7 seconds for SET).

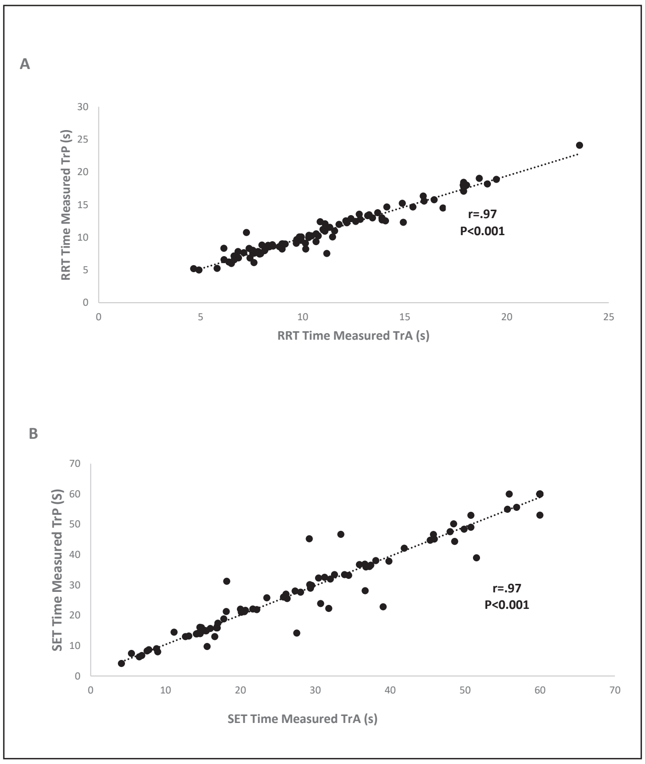

Figure 2: Bland-Altman plots presenting the limits of agreement for PFM function assessed by transabdominal (TrA) and transperineal (TrP) ultrasound for the rapid response test (RRT) in the upper panel, and the sustained endurance test (SET) in the lower panel — all tests were conducted in the supine posture.

Similarly, limits of agreement for each of the RRT and SET assessments, performed by the same operator on two occasions, one week apart, are presented as Bland-Altman plots in Figure 4. These data show no significant difference (*p*>0.05) between test sessions. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference in scores between both test sessions being close to 0 and the standard deviation for difference scores very low (0.4 seconds for RRT and 0.5 seconds for SET).

DISCUSSION

In the present study we observed a moderate correlation between the traditional DRE approach to PFM assessment, compared to more objective perineometry. Conversely, strong agreement was found for both RRT and SET when tests were performed

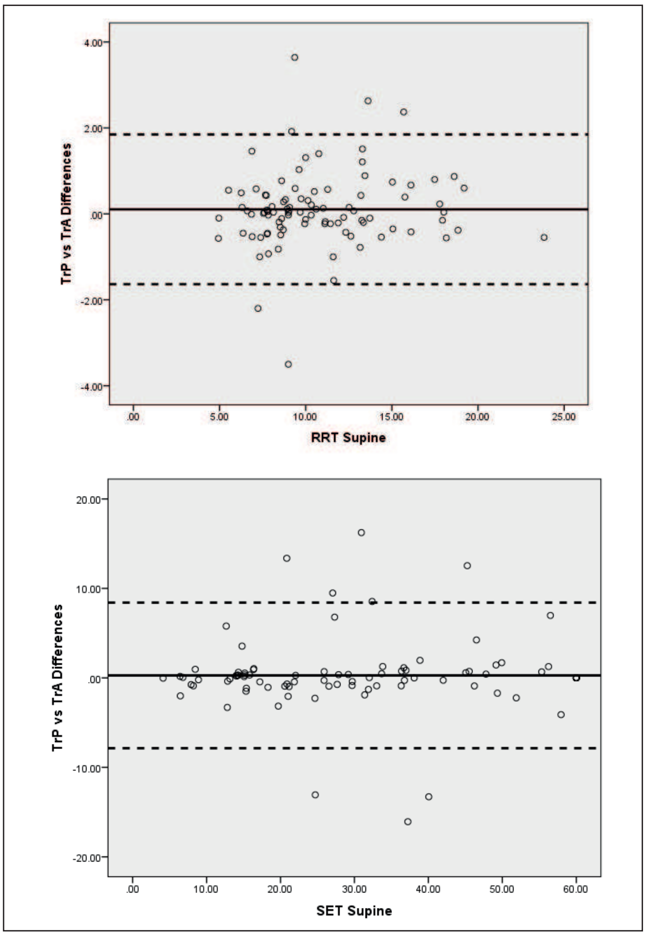

Figure 3: Bland-Altman plots presenting the limits of agreement for two assessors measuring the same patients on the rapid response test (RRT) in the upper panel, and the sustained endurance test (SET) in the lower panel — all tests were conducted using transabdominal real-time ultrasound images with patients in the supine posture.

Figure 4

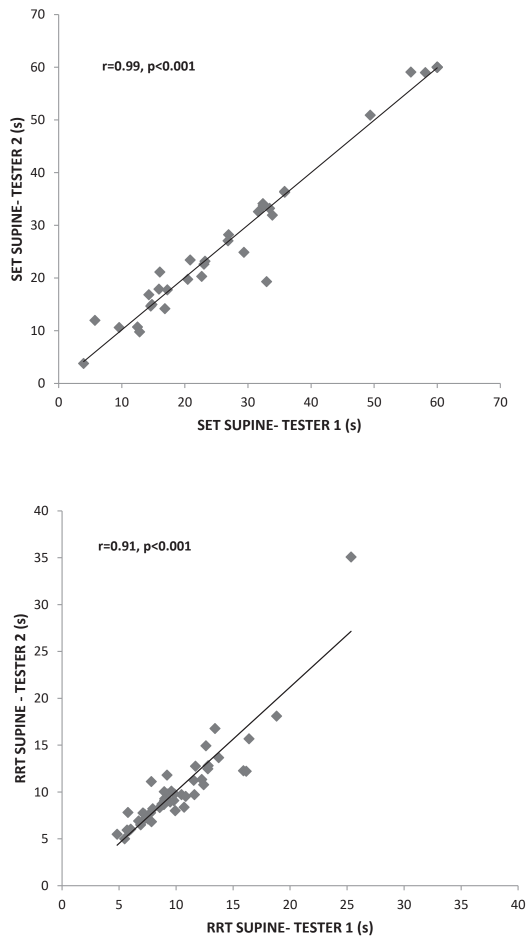

Figure 4: Bland-Altman plots presenting the limits of agreement for a single assessor measuring patients on two occasions, one week apart, on the rapid response test (RRT) in the upper panel, and the sustained endurance test (SET) in the lower panel — all tests were conducted using transabdominal real time ultrasound images with patients in the supine posture.

using TrA and TrP protocols, and when determining inter- and intra-observer reliability.

Study 1: Traditional versus RTUS assessment of pelvic floor muscle function

Our findings indicate that digital rectal squeeze pressure scores correlated only moderately with an objective pressure measurement technique. In addition, PFM strength grading was poorly correlated with our RTUS tests of function (both RRT and SET). This finding is broadly consistent with previous studies in women[12,19,37] which report poor correlations between digital strength grading and ultrasound measures. Sherburn and colleagues[16], in particular, found no significant relationship between ultrasound measures and digital palpation[12]. In contrast, recent investigations by Arab and colleagues[38] comparing TrA RTUS versus digital palpation in females[39] reported a positive correlation if RTUS assessments were performed simultaneously with PFM contraction. These differences in study outcomes are likely due to earlier studies performing the assessments separately and the variability in per rectal methodologies. Hence, our findings concur with previous studies, mostly performed in women, and we conclude that different aspects of PFM function were assessed using the per rectal and RTUS tests. The latter are simple to administer, clinically relevant[14], non-invasive, well-tolerated and provide direct visualisation of PFM contraction[24,40].

Study 2: Transabdominal versus transperineal approaches

While TrA and TrP RTUS approaches for PFM assessment in men are validated, there is no previous direct analysis to compare these approaches[14,25]. Similar investigations in women[23,24,41] confirmed the reliability of TrA RTUS as 'excellent' and comparable to TrP for measuring pelvic floor movement during PFM contraction. The TrP approach was found to be more reliable for inter-patient comparisons as it measured from a fixed bony landmark, although the increased complexity of evaluation and increased time of assessment in a clinical setting has been noted[24]. In comparison, the TrA RTUS approach is minimally invasive, quick to perform, does not require the person to undress and is relatively easy to learn[24]. This approach can be particularly helpful for the clinician who is working with men who wear continence pads, those unwilling to undergo perineal assessment due to culture or ethnicity, survivors of sexual abuse, those who are anxious, or children and the elderly who need PFM evaluation.

We were able to demonstrate that during PFM contraction, a strong association exists for scores derived using both the TrP and TrA approaches. This confirms that either option may be used and that clinical evaluations designed for patients can be individualised, particularly when PFM digital palpation may not be appropriate.

Of course, studies in which the assessment of individual muscle groups within the pelvic floor is an imperative should favour the TrP approach. Although not encountered in our investigations, should there be clinical presentations such as complete incontinence, whereby any holding of bladder volume is limited, the TrP RTUS option may be more appropriate, since a full bladder is not required. Obesity, scar tissue and previous abdominal surgery may also impact on the quality of imaging in TrA RTUS. Therefore, having two approaches available is helpful clinically for optimal assessment and rehabilitation.

Study 3: Inter- and intra-tester reliability of RTUS tests

The inter- and intra-tester reliability of the SET and RRT tests were high, with strong associations observed between the sets of scores. By contrast, coefficients of variation reported for repeated assessment of the Modified Oxford Scale squeeze pressure test[9], as previously assessed in women, are >20% and the correlation for repeated assessment is substantially lower than that observed for the SET and RRT in our study[19]. In the analysis of Bland-Altman plots, the relatively small range of the 95% confidence intervals indicates that both the RRT and SET tests have good intra- and inter-tester reliability. However, the limits of agreement for the inter-tester SET test results were slightly higher than expected, which possibly relates to a difference in skill and level of experience between testers. This emphasises the importance of training for clinicians so that a narrower confidence interval may be achieved. Across all Bland-Altman plots, the difference between tests seems consistent across a large baseline of values. These data suggest that the measures we present in this paper are reliable and mostly immune to the effects of different observers.

There are several limitations of the current study. There is no universally accepted “gold-standard” measure of PFM function in men. The DRE derived measures used in study 1 were not intended as a basis for comparing to a gold standard. Such DRE measures remain, however, widely used and considered by some to be the best currently available. The criteria used for task failure could be more objective if, for example, automatic edge detection and wall tracking software were developed. The posture used to perform the DRE-based tests (lateral decubitus) was selected as instructed for use in the Peritron A manual, and because it was the preference of the physician who undertook these tests. It is a posture commonly used in routine clinical DRE examination in men. It differed from the posture used to undertake the SET and RRT tests (crook lying) and the lack of correlation between DRE and RTUS tests we observed in study 1 may be partly explained by this postural difference. The results of the RRT and SET tests can be affected by the technical difficulty of the selected approach. It is relevant in this regard that, whilst the TrP technique is more technically demanding, the TrA and TrP tests are highly correlated. While the SET and RRT data are specific to this study, the objective and timed nature of these tests should make the collation of normative data sets possible in larger cohorts in future. Prospective outcomes, related to performance that is scaled by normative comparison, should also be possible.

CONCLUSIONS

Both TrP and TrA approaches to RTUS of the pelvic floor had high inter- and intra-tester reliability and appear to have advantages over the DRE and/or perineometry, which are only moderately correlated and have poor inter-tester reliability. Similar scores were observed if measurements were performed by either TrA or TrP approaches, with TrA assessment potentially less problematic for those uncomfortable with the TrP approach. Future studies are needed to investigate whether the RRT and SET RTUS tests are posture-dependent or relate to clinical outcomes such as post prostatectomy incontinence (pad weight).

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Application of two pelvic floor muscle function tests in men following radical prostatectomy: relationship to urinary incontinence

ABSTRACT

This study examines the impact of posture and measures of urinary incontinence relating to two non-invasive, real-time, ultrasound-based tests. Using real-time ultrasound with transperineal and transabdominal approaches, we previously assessed pelvic floor muscle function in men and found the rapid response and sustained endurance tests possessed strong reliability in both supine and standing postures, and for both ultrasound approaches. However, questions remained pertaining to the relationship of the tests to other outcome variables, including measures of urinary incontinence. Participants (n=95) undergoing radical prostatectomy were assessed to determine the relationship between incontinence and pelvic floor muscle function, as seen on ultrasound. The presence and severity of incontinence was measured via 24-hour pad weight. When related to pad weight, the transabdominal protocol produced weak to moderate correlations between the rapid response test in standing (r=0.43) and supine (r=0.46), and the sustained endurance test in standing (r= –0.56) and supine (r=–0.56). Similar results were found using the transperineal approach. All Bland-Altman analyses showed no significant difference (p>0.05) between the two postures, for either test or scan approach. While the plots also demonstrate no heteroscedasticity or proportional bias, with the bias being close to 0, the magnitude of variation in difference scores suggests different outcomes for tests performed in standing compared to supine postures. We present two simple tests that provide objective, non-invasive, and reproducible assessment of pelvic floor muscle function in men that relate to the clinical outcome of urinary leakage.

Keywords: Men's health, real-time ultrasound, physiotherapy, urinary incontinence, prostate cancer, pelvic floor muscle.

INTRODUCTION

Urinary incontinence (UI) is often associated with compromised function of the pelvic floor muscles (PFM) and while most studies regarding this association have involved women, there is a high prevalence of UI in men following radical prostatectomy (RP)[1,2]. It is estimated that more than one million new cases of prostate cancer (PCa) are diagnosed annually[3], and RP is considered the gold standard surgical approach to treatment. Current opinion states that strategies to enhance PFM function may improve continence outcomes in men who undergo RP[4,5]. However, researchers have been hampered by the lack of a reliable and practical test of PFM function in men.

Post-prostatectomy incontinence (PPI) is one of the most distressing side effects following RP treatment, with up to 91%[6] of men reporting urinary leakage initially and 30–76%[7,8] continuing to experience it one year following RP[7]. Incontinence is mostly caused by damage to the internal urethral sphincter affecting autonomic function, coupled with an increased demand on the PFM following complete removal of the

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Competing interest statement: All authors declare they have no relevant relationships or circumstances that present actual or potential conflicts of interest.

prostate[1,9]. Evidence currently supporting the benefits of PFM training in men[8,10] is inconclusive and this may be due to most PFM research (both assessment and treatment) being focused on female PFM dysfunction and translating knowledge across the sexes may be difficult, particularly in the implementation of rehabilitation strategies.

Men are typically continent in supine positions following RP. In contrast, upright posture and actions such as sitting and sit-to-stand cause increased intra-abdominal pressure that leads to stress UI[2,11], a problem also seen in women[12]. For men with PPI the condition can worsen as the amount of time in the upright position increases over a day, particularly in association with physical activities such as walking[11]. The existing evidence does not address these incontinence issues in recovery following RP and validation of a reliable test to meet clinical presentation may help bridge this gap.

The study reported here is of two objective, real-time ultrasound (RTUS) tests, that are specific to sustained and rapid demands placed on the pelvic floor muscles. The sustained endurance test (SET) and rapid response test (RRT) of PFM function used in the current study are non-invasive and avoid the need for rectal assessment of the pelvic floor[13]. The aim was to determine the extent to which the SET and RRT may be posture-dependent and whether they relate to clinical outcomes such as PPI. To determine the severity of UI, 24-hour pad weight was assessed and compared to performance on the RRT and SET assessments. We chose 24-hour pad weight as our criterion measure of PPI, since pad number can be influenced by the variety of pads used and individual differences in hygiene management. In addition, 24-hour weight has been described as the most reliable non-invasive method of quantifying the severity of urine leakage over longer time frames than the previously utilised 20-minute and 1-hour tests[14,15]. In 2012, Mungovan and colleagues determined that in men most PPI episodes occur in the upright posture[11], and so we performed the dynamic tests of PFM function in supine and standing for comparison.

METHODS

This study was approved by the University of Western Australia HREC (Ref RA/4/1/6265). Participants received written information about the study and provided written consent. Participants were enlisted from a cohort referred sequentially by their urologist for pre-prostatectomy PFM training. Following surgery, participants were reviewed between two weeks and six months post urinary indwelling catheter removal and assessed in random order for the RRT and SET assessments in both supine and standing postures.

For each measurement, a commercially available point-of-care ultrasound machine (3.5 MHz sector probe, Mindray DP-30 Ultrasound, 6U-42000440, China) was used. To standardise bladder volume for the TrA approach, each participant voided their bladder and then drank 500 ml of water, 1 hour prior to testing and were instructed not to void. A full bladder is not required routinely for TrP assessments. To assess severity of incontinence, pad weight was calculated by the collection of continence pads across a 24-hour period, on the day testing was completed[16,17]. All participants wore pads and applied their first pad of the day after their first morning void. All pads were placed in a single plastic bag and stored in a refrigerator to avoid evaporation. The net weight was calculated by deducting dry pad weight, using a single standardised digital scale[11]. Any positive net weight, recorded in grams (g), was deemed indicative of incontinence, with 'zero' weight assessed as no leakage and full continence. Participants were assessed for PFM function in the crook lying position (supine) with a pillow underneath the head and hips and knees flexed at 60 degrees and with the lumbar spine positioned in neutral. They were also assessed when standing in the anatomical position (standing). Cues to relax abdominal muscles and avoid breath holding were also given. Verbal instruction was provided on correct PFM exercise technique, as per Stafford and colleague's 2016 study[18], to ensure a full contraction and relaxation cycle was implemented with the cue given to "stop the flow of urine and shorten the penis while continuing to breathe"[18,19]. Participants had one 'practice' contraction prior to the test, while in view of the screen, in order to provide feedback for both tester and participant, and to promote good technique.

For the RRT, participants were instructed to "perform 10 maximal PFM contractions and relaxations as fast as possible", with the elapsed time recorded as the outcome measure. In the SET, participants were instructed to "hold a maximal contraction for as long as possible, and continue to breathe". The time to task failure was recorded (with a maximum time of 60 seconds), where task failure was defined as being the onset of descent of the bladder base (TrA approach) or bladder neck (TrP approach).

Transperineal RTUS assessments

Prior to the test using the TrP approach, RTUS participants were invited to disrobe in private and to drape a towel around their waist, before reaching under and gently moving their genitals to one side with their hand. Standard infection control measures were observed. After applying a layer of transmission gel, TrP RTUS was performed by placing the covered probe on the perineum in the mid-sagittal location, midway between the base of the penis and the anus, with the transducer orientated to obtain sagittal images, after which the participant removed his hand. To optimise the images, the symphysis pubis was used as the bony reference point, with the urethra, bladder, bladder neck and anorectal angle visible simultaneously[13]. Using screen callipers, a measure of the position of the bladder neck was taken at rest ('x') and the change from this resting position in a vertical direction was observed. Any cranial movement of the bladder neck was interpreted as a correct action; whereas, no cranial movement or any caudal movement of the bladder neck was noted as an incorrect action, in accord with previous guidelines[19]. During SET assessments, an arrow was placed at the bladder neck as a visual marker to determine the elapsed time (seconds) at which task failure, defined as the moment of descent toward the resting position of the bladder neck ('x'), was observed.

Transabdominal RTUS assessments

For tests using the TrA approach, ultrasound assessment was performed by placing the covered probe suprapubically on the lower abdomen at a mid-sagittal location with the transducer probe orientated to obtain transverse images and angled in a caudal/posterior direction to achieve a clear image of the inferior-posterior aspect of the bladder. Standard infection control measures were observed and a layer of gel was placed over the head of the probe. Screen callipers were used to place a mark ('x') on the bladder base at rest where any elevation of the bladder base was interpreted as a correct action and any depression of the bladder base was noted as an incorrect action in accordance with previous guidelines[20,21]. As per the TrP approach, during SET assessments, an arrow was placed at the bladder base as a visual marker to determine the elapsed time (seconds) at which task failure, defined as the moment of descent towards the resting position of the bladder base ('x'), was observed. Any participant unable to perform the PFM contraction correctly (that is, cranially versus caudally), was given the opportunity to rest and repeat the test.

Statistical analysis

Data for the SET and RRT assessments and pad weight were entered into SPSS (v22.0, SPSS, Chicago, IL) for subsequent analysis and significance was accepted for all analyses at $p<0.05$. To determine whether two scores were related, we performed correlations. For example, the association between SET and RRT (in both standing and supine postures) versus pad weight scores was determined using Pearson's correlation. For this paper we defined the strength of all correlations as follows[22]:

- r = 0.25–0.50 weak to moderate
- r =0.50–0.75 moderate to good
- r > 0.75 good to excellent

To assess agreement, Bland-Altman analysis and plots were performed. For example, the level of agreement between tests performed in supine versus standing postures was assessed with a series of Bland-Altman plots for the SET and RRT assessments created using both TrA and TrP RTUS.

RESULTS

Participants in the study were 95 men, average age 63 years (range 52 to 74 years). All participants were in a healthy weight range (height 172.0±15.2 cm, body weight 72.9±16.9 kg, all Gleason 7).

Relationship between RTUS tests and pad weight

The range of pad weights, for the pads collected from all 95 subjects, was 0 to 98 g. Pad weight averaged 46.0 g (±52.2 g). Weak to moderate, though statistically significant, correlations were evident between 24-hour pad weight and both the SET and the RRT scores in all combinations of posture and probe position. The relationships between pad weight and RRT via TrA RTUS performed in standing ($r=0.43$, $p<0.001$) and supine ($r=0.46$, $p<0.001$) were moderate, and moderate to good for the SET in standing TrA ($r=-0.56$, $p<0.001$) and supine ($r=-0.56$, $p<0.001$). The relationships between pad weight and pelvic floor function was assessed via TrP RTUS, RRT in standing ($r=0.52$, $p<0.001$) and supine ($r=0.51$, $p<0.001$) were moderate with similar results for SET via TrP in standing ($r=-0.58$, $p<0.001$) and supine ($r=-0.54$, $p<0.001$).

Supine versus standing measurements

The limits of agreement for each of the RRT and SET assessments, performed using TrP and TrA approaches in both standing and supine postures, are presented as Bland-Altman plots in Figure 1. The results for all analyses show no significant difference ($p>0.05$) between the two postures for RRT and SET assessments using each RTUS scan approach. The plots also demonstrate no heteroscedasticity or proportional bias, with the mean difference (bias) in scores between postures being close to 0 (RRT: TrA = –0.15 s, TrP = –0.16 s; SET: TrA = 1.59 s, TrP = 1.26 s). However, the magnitude of variation in difference scores (an average 1.8 s for RRT and an average 9.5 s for SET) suggests different outcomes for tests performed in standing compared to supine postures, especially for the SET.

DISCUSSION

In this study, we compared PFM function measured by SET and RRT scores with the severity of incontinence assessed using 24-hour pad weight. Moderate correlations were observed between RTUS assessments and this widely accepted clinical measure of continence[23]. Lower RRT times related to good PFM function and, therefore, mild incontinence. For example, a patient performing the RRT in 15 seconds, has more PPI (that is, a higher pad weight) than one who performed the test in 7 seconds, with speed of contraction being the significant functional difference. An inverse relationship was noted for the SET, with lower scores relating to higher levels of incontinence. For example, a patient maintaining a contraction for 15 seconds had more PPI (higher pad weight) than one contracting for 45 seconds, with most who achieved a contraction for 60 seconds having full continence. Similar results were obtained between supine and standing postures for both the RRT and SET outcomes. In the same way, TrA and TrP approaches to assessment were very similar for both tests. These findings provide evidence that the non-invasive measures we have introduced are clinically valid and reliable for assessing PFM function, as it may relate to urinary leakage in PPI. Traditionally,

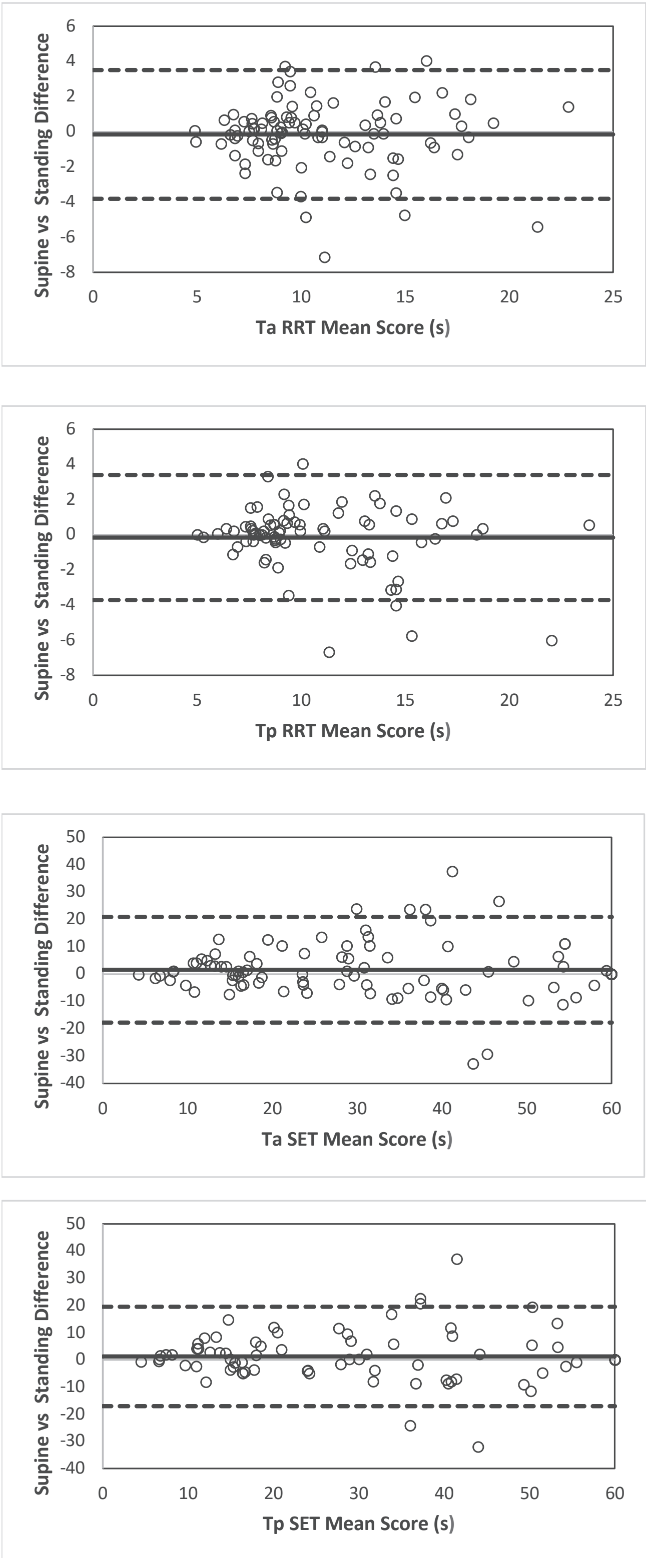

Figure 1: Bland-Altman plots presenting the limits of agreement for PFM function with tests conducted in the standing versus supine postures. The rapid response test (RRT) results are shown for transabdominal assessment in Panel A, and for transperineal assessment in Panel B. The sustained endurance test (SET) results are shown for transabdominal assessment in Panel C, and for transperineal assessment in Panel D.
Solid line = mean difference
Dotted line = limits of agreement

assessments of PFM function are performed in the supine or lateral decubitus positions[12]. The purpose of performing tests in the standing posture in this study was to account for the clinical presentation of PPI, which is often gravity-dependent[11]. Our results suggest that posture does have an impact on PFM function, with some variation in scores noted for SET measured in supine versus standing. These findings suggest that increased skeletal muscle activation in upright postures may be associated with incontinence. RTUS testing can be performed using whichever posture is specific to individual patient symptomatology; however, we would suggest default assessment in the standing position as this corresponds with the posture and loading conditions under which PPI typically occurs[1,8,26]. In addition, an individual's RRT and SET results can be used in a clinical setting to provide guidance to both the clinician and patient, for baseline assessment and training purposes.

While outcomes regarding the prediction of pad weight, based on RTUS tests, were moderate, they were not excellent (that is, correlations of 0.75 or greater). This is perhaps not surprising, given that many factors other than PFM function can contribute to PPI. These may include surgical experience, operative approach, associated damage to the internal urethral sphincter and the degree of nerve sparing[9,24,25]. We did not limit our recruitment according to these factors and it is conceivable that a study stratified by surgical outcome may have produced stronger associations. It may also be possible to further improve these correlations by refining the technical approaches we used. For example, our SET and RRT measures, while reproducible[13], may be more sensitive if edge detection algorithms had been used to better detect movement of the bladder base. In an attempt to obtain ecological validity, we did not control for factors such as measurement time of day or 24-hour fluid intake; however, such controls may have enhanced the relationships we observed. Equally, while pad weight is an accepted and simple assessment of incontinence, it may be possible in future to correlate our functional outcomes with more recently adopted and sophisticated assessments, such as MRI-derived measures of membranous urethral length[2]. In addition, although we did not use it in this study, the three-day, 24-hour pad weight method introduced by Malik in 2016 may have provided more variability in pad weight scores, given ranges that may occur with physical activity levels in individuals over subsequent days[16].

CONCLUSIONS

In post-radical prostatectomy patients the outcomes of our RRT and SET assessments were associated with the severity of UI. These tests can be used to design personalised treatment plans. Correlations performed between PFM tests and pad weight varied according to whether the SET and RRT assessments were performed in standing versus supine, but not with respect to the TrP versus TrA approach. This indicates that factors specific to the individual patient, such as the presentation of gravity-dependent PPI, or sensitivity regarding perineal assessment, can be taken into account when selecting the preferred test. Based on our experience, we suggest performing tests in the standing position. One advantage of the TrP approach for the very incontinent patient is the removal of the requirement to have a full bladder, compared with the TrA approach which requires bladder volume for optimal imaging. This further enhances our findings that either TrA or TrP are appropriate options, depending on patient presentation. In conclusion, our studies indicate that the RRT and SET assessments are minimally-invasive, objective, and may be of use in a clinical setting. Further research is needed to ascertain whether spontaneous recovery is impaired following surgery, or to introduce a treat-to-target approach to rehabilitation.

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☝ Stop giving your patient the finger ☝

Assessing pelvic floor muscle function(PFM) in prostate cancer. Using non-invasive tests to replace the DRE.

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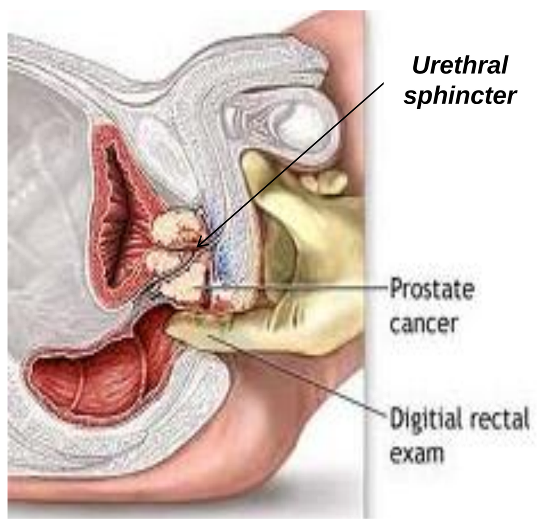
background:

Digital rectal examination (DRE) to assess pelvic floor muscle (PFM) function, the "Brink" test[1], has several limitations:

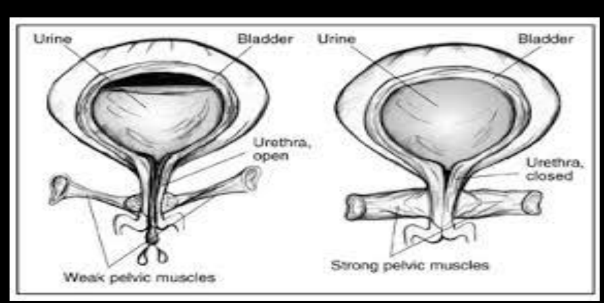
- Invasive
- Subjective
- Confronting for patients
- Sometimes painful
- Poor reliability
- Clinical reticence



Its validity is also questionable as:

- it involves a subjective measure of global 'strength', is anatomically distant from the urethral sphincter & does not address fatigue[2] or endurance of PFMs[3]
- the 0-5 ordinate scale is subjective, arbitrary & has poor inter- and intra-tester reliability[4]
- it ignores the physiology of the pelvic floor muscles, which contain both fast (~20%; rapid contractile) and slow twitch (~80%; endurance) fibre types[5]
- DRE is performed in supine or lateral side lying which is unrelated to clinical symptomatology

New, patient friendly non-invasive objective tests of Pelvic Floor Muscle Function are required



aims:

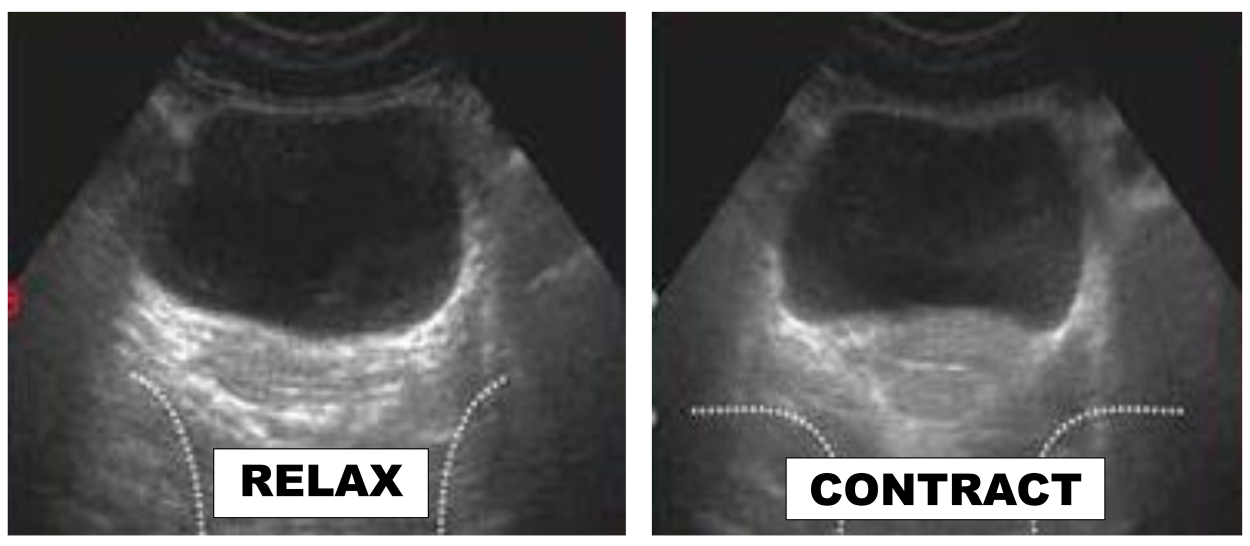
To develop novel tests of pelvic floor muscle (PFM) function which:

- are non-invasive
- accepted and well tolerated
- objective, easily and quickly administered
- performed in postures consistent with clinical signs & symptoms
- assess fast and slow twitch muscle function, relating to stress urinary incontinence, bladder holding capacity & sexual function
- valid and reproducible within and between clinicians

Our novel tests are based on PFM physiology: fast & slow twitch fibre function are assessed during quick and endurance activities

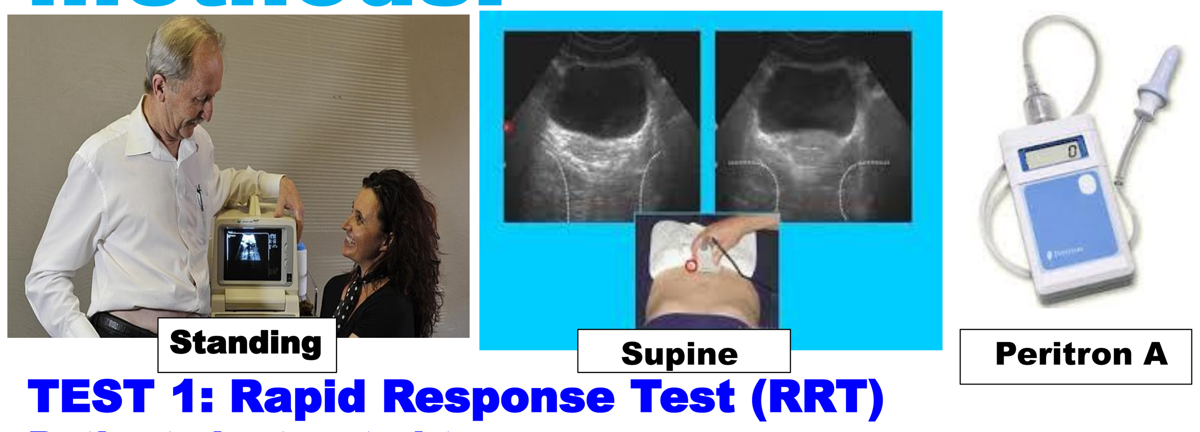
novel tests

We developed two novel PFM function tests utilising trans-abdominal real time ultrasound (RTUS)[6] and a stop watch



The "rapid response test" (RRT) and "sustained endurance test" (SET) were performed supine and standing to assess effects of posture, PFM fatigue and symptomology as per clinical presentation

methods:



TEST 1: Rapid Response Test (RRT)

Patients instructed to:

"perform 10 maximal PFM contractions "as fast as possible"

- RRT assesses *fast twitch* muscle function ~20% pelvic floor is fast twitch
- elapsed time recorded (10 sec = 1.0sec/lift)
- relevant to cough, sneeze, sit-stand, lifting

TEST 2: Sustained Endurance Test (SET)

Patients instructed to:

"hold maximal contraction as long as possible, whilst breathing normally"

- SET assesses *slow twitch* muscle function ~80% pelvic floor is slow twitch
- time to task failure recorded (max 60 sec)
- relevant to functional tasks as walking, standing bladder holding & sexual function

EXPERIMENT 1: VALIDITY TEST

n=28 post-prostatectomy patients

PFM function assessed using:

- RRT and SET tests
- DRE (0-5 scale muscle strength), traditional method
- Anal perinometry (Peritron A) to record rectal sphincter squeezing pressure/PFM strength (cmH20)[7]

EXPERIMENT 2: RELIABILITY TEST

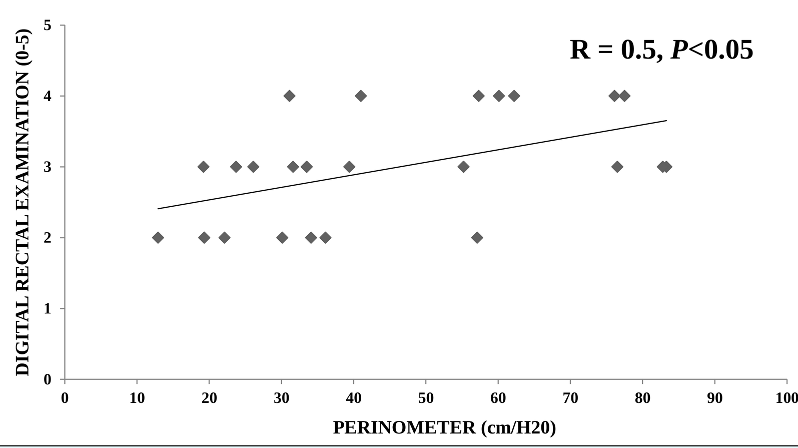
n=80 post-prostatectomy patients

PFM assessed:

- using the RRT and SET
- 2 different testers to assess reproducibility

results: validity

FIGURE 1. Relationship between pelvic floor muscle (PFM) strength measured *subjectively* (DRE + Brink test) versus *objectively* using perinometer (cmH_2O)

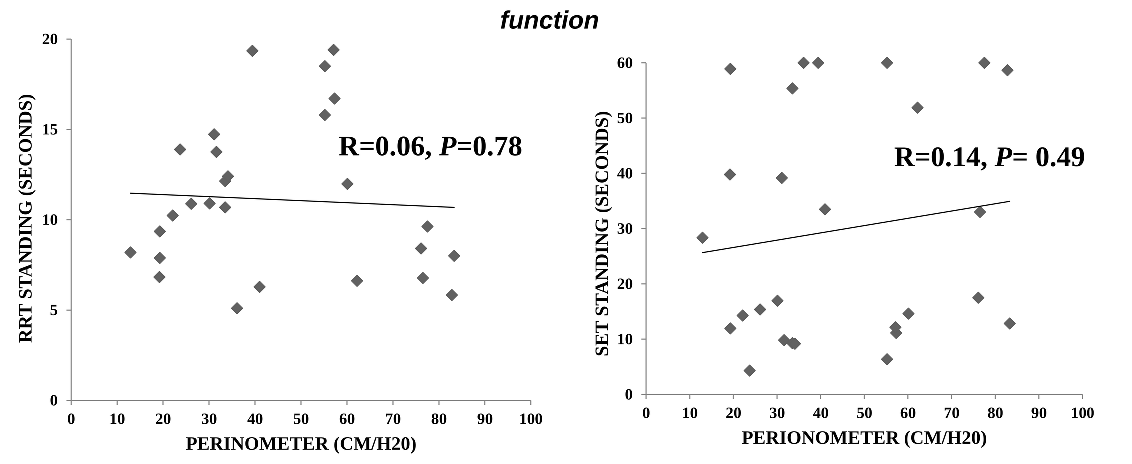


The DRE is subjective and modestly correlated with objective perinometer measurement of PFM strength

results: reliability

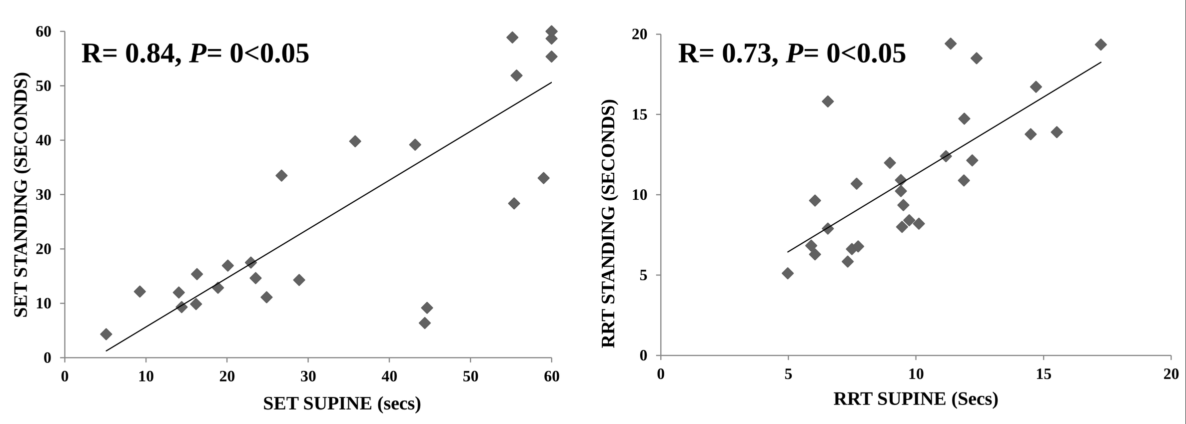
FIGURE 2. Relationship between novel measures of Pelvic Floor Muscle (PFM) function and objective assessment of PFM strength

RRT = Rapid Response Test. Time taken to perform 10 rapid PFM raises. *Tests fast twitch function*
SET = Sustained Endurance Test. Time for sustained contraction (to 60s). *Tests slow twitch function*



Our surrogate measures of reflex (RRT) and endurance (SET) capacity of the pelvic floor muscles are not related to simple strength measures

FIGURE 3. Relationship between novel tests of pelvic floor muscle function, performed *standing versus supine*

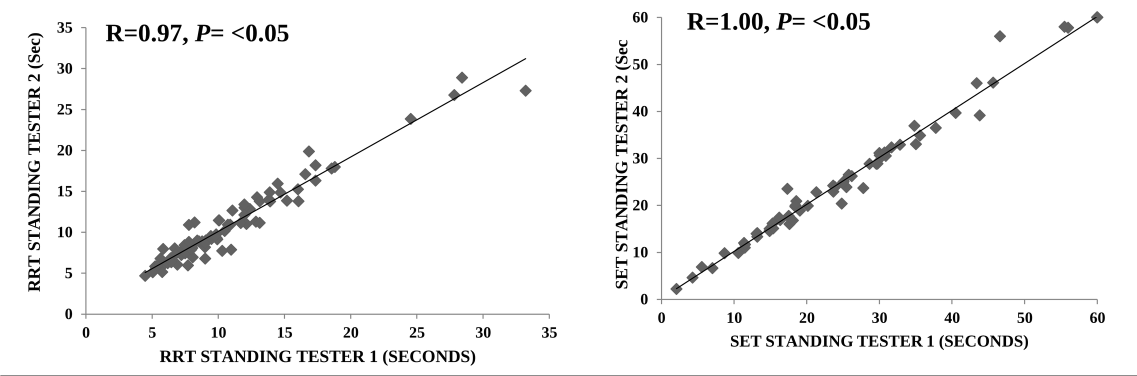


High correlations existed between standing and supine measures of our novel measures fast and slow twitch function

results

FIGURE 4 Inter-operator reliability of novel and physiologically valid measures of pelvic floor muscle function

RRT = Rapid Response Test. Time (sec) taken to perform 10 rapid PFM raises. *Tests fast twitch function*
SET = Sustained Endurance Test. Time (sec) of sustained contraction (60s max). *Tests slow twitch function*



The tests are reproducible and not influenced by operator or by the posture of the subject

discussion

EXPERIMENT 1: VALIDITY TEST

The DRE is subjective and invalid for assessment of pelvic floor function

Our novel measures of the reflex (RRT) and endurance (SET) capacities of the pelvic floor are not related to simple strength measures

High correlations existed between standing and supine measures of SET and RRT

- Standing tests are recommended as the clinical presentation of incontinence occurs upright under stress and loading

EXPERIMENT 2: RELIABITY TEST

Validity :Inter-tester for the DRE is *R*=0.7[4], *CV= 22%*[4]
Inter-tester reliability for the RRT *R=0.97*, *P*=<0.05, *CV*=5 %
Inter-tester reliability for the SET *R=1.0*, =<0.05, *CV*=12%

The tests are VALID, RELIABLE, REPRODUCIBLE and not influenced by the operator or subject posture

conclusion:

- Here we introduce novel, non-invasive tests of pelvic floor muscle function which are valid and reliable
- The tests may be translated across populations and are ecologically relevant to clinical experience

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TAKE HOME MESSAGE

Pelvic floor muscle tests need updating. The "floor" is part of the "core". Its relevance to continence, pain & sexual health warrants discussion among all members of the collaborative health team. Functional signs & symptoms require functional tests to guide treatment plans.

15th Asia-Pacific Prostate Cancer Conference 2014
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THE ROLE OF PHYSIOTHERAPY IN PEYRONIES DISEASE: DOES THERAPEUTIC ULTRASOUND IMPROVE PENILE CURVATURE IN MEN?

Presented at the WCPT Congress 2017, Cape Town.

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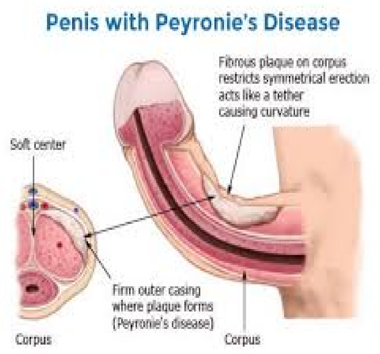
background:

- Peyronies Disease (PD) is a debilitating condition characterised by penile pain, curvature and deformity, palpable plaque formation and erectile dysfunction (1).
- Aetiology may be variable but is generally linked to trauma affecting the penis, causing local inflammation, inelastic scar tissue development and fibrosis of the tunica albuginea leading to calcified plaques, altered penile appearance and sexual dysfunction (1).

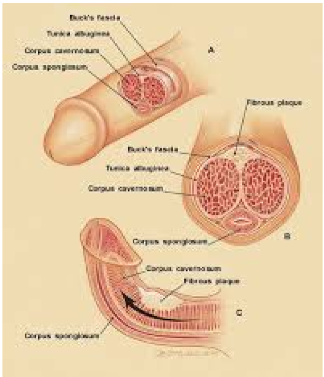


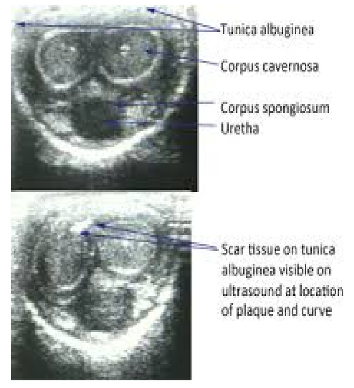
- PD occurs:
- in 1- 9% of the normal population
- In 19 % of men following treatment for prostate cancer (PCa)

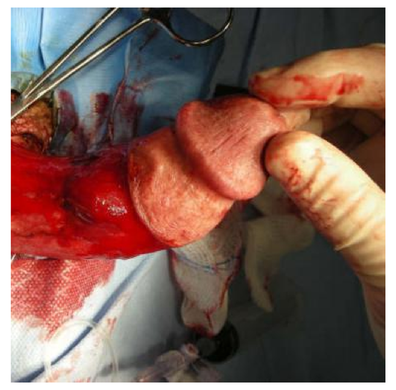
PD can greatly impact on male self esteem (3) leading to relationship issues (54%), psychological distress (81%) the development of depression (48%),relationship breakdown (3) and an associated increased risk of suicide (4). In PCa populations there is enhanced risk of these issues (2).

purpose:

PD is a common condition that has had limited options for treatment. Currently, despite extensive investigation over many years effective non-invasive options remain elusive. Only one previous study has investigated the use of therapeutic ultrasound in PD. Surgical correction is the gold standard but typically results in further penile shortening and scar tissue. Men with PCa are at increased risk of PD.







participants:

Three men with PD were involved on a pilot study:

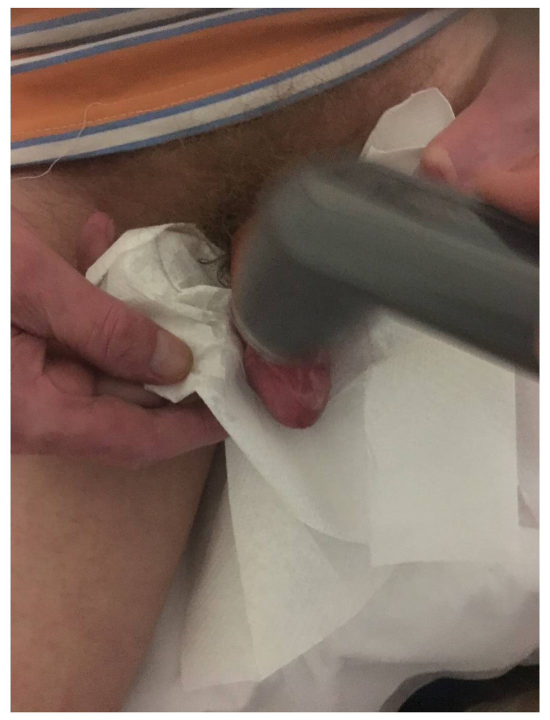
Subject A; 45 yr developed PD following Robotic Assisted Radical Prostatectomy for PCa 13 months earlier (*see results pre & post)

Subject B; 55 yr developed PD after being kicked in the groin by a kangaroo 2 years earlier

Subject C: 65 yr developed PD 5 months after radiation therapy for recurrence of PCa 2 years after radical prostatectomy

methods:

- All participants provided written consent and underwent Penile Duplex Doppler Ultrasound (PDDU) to confirm the diagnosis of PD and to measure the degree of fibrosis and the +/- presence of plaque formation by an expert radiologist blinded to the subsequent Physiotherapy intervention.
- Participants then completed the Peyronies Disease Questionnaire (PDQ) and International Index of Erectile Dysfunction scoresheet IIEF5/(SHIM)
- Participants attended for 12 sessions of clinical Therapeutic Ultrasound (TUS).
- Upon completion, a second PDDU was performed and the PDQ and IIEF5 repeated.



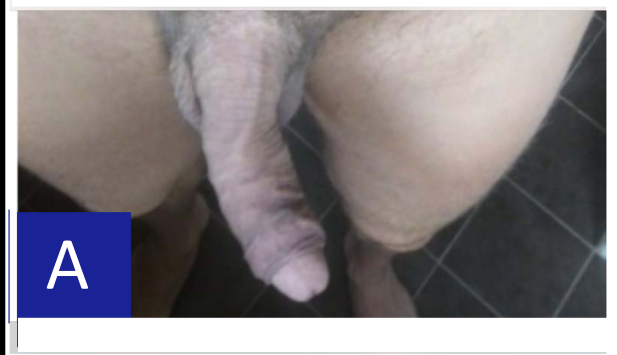
Therapeutic Ultrasound

- 3 sessions /week x 4 weeks =12 X doses
- 3MHz ultrasound probe x 10 min / Rx
- 1.5-2.5 w/cm^2 applied directly to the penis
- Condom over probe
- TUS directed to region of fibrosis as confirmed by PDDU

results:

*Pre TUS X12

*Post TUS x12



- Subject A: reduction in penile curvature from 85^{0} to 15^{0}, improved IIEF5 from severe to mild, improved PDQ score, improved penile length, resumed intimacy, 100% resolution of PD on PDDU
- Subject B: reduction in penile curvature from 35^{0} to 5^{0}, improved IIEF5 from severe to mild, improved PDQ score, reduced fibrosis on PDDU, resumed intimacy after 2 year hiatus
- Subject C: improved IIEF5 from moderate to mild, improved PDQ score, reduced curvature & fibrosis
- As a result , a randomised controlled trial is now under way with a cohort of 40 men with PD in Western Australia.

results: randomised control trial now under way n=40

- HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA
- Ultrasound therapy for Peyronie's Disease: A novel, non-invasive treatment approach.

Men with suspected PD referred to Physio trial by Urologist or GP
PD confirmed with PDDU n=40
Complete IIEF5 and PDQ, pre & post TUS photo
Randomisation

Group 1
n=20
Intervention
4 weeks

Group 2a
n=20
Delayed entry
4 weeks

Repeat DPPU
Repeat IIEF5 (SHIM)
Repeat PDQ

Group 2b
N=20
Intervention
4 weeks

Repeat DPPU
Repeat IIEF5 (SHIM)
Repeat PDQ

Statistical Analysis
Results
Paper Submission to Journal

New Physiotherapy treatment
Education & Exposure
Reduction in PD and improved Men's Health

discussion:

- TUS has not been used for PD in a Physiotherapy setting before. The widespread and effective use of TUS in soft tissue injury management generally, provided impetus to explore its use for an increasing clinical population seen in a Men´s Health practice.
- All three cases demonstrated improvement in subjective IIEF5 and PDQ outcomes, plus objective measures by PDDU and reduced angle deformities.
- These positive results prompted the design and approval of further research which is now under way in Western Australia, with n=40 men with confirmed PD.

conclusion:

- Men´s Health is a new frontier in Physiotherapy.
- Physiotherapists already have the necessary skills to provide therapeutic ultrasound to soft tissue injuries.
- Given the expected rise in obesity, erectile dysfunction and prostate cancer, the global presentation of PD is likely to increase and all Physiotherapists can offer this non-invasive treatment option with training.

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acknowledgements:

I would like to acknowledge my supervisors, Profs Daniel Green & Tim Ackland for their support of this research. I would also like to thank esteemed Urologist Prof John Mulhall for his leadership in treating men with Prostate Cancer, Australian Psychologist Patrick Lumbroso for his passion and dedication in treating men with erectile dysfunction, but mostly to my patients who teach me everything. PROST!

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New protocols for a faster return to continence and quality of life following radical prostatectomy

Joanne Milios[1], Timothy Ackland[1], Daniel Green[1],
1. University of Western Australia, Australia,

PROST! Men's Health Exercise 4 Prostate Cancer Inc

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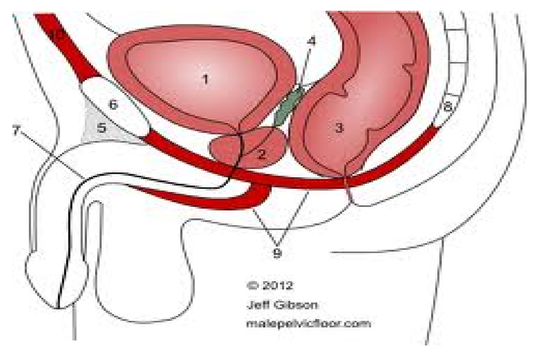
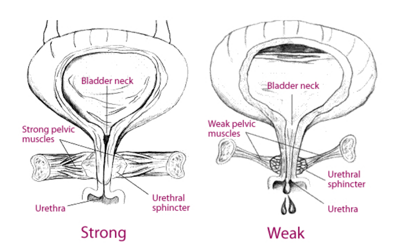
Introduction:

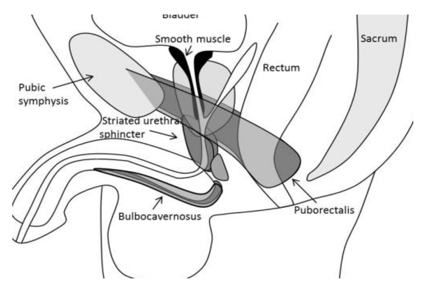


Post-Prostatectomy Incontinence (PPI) is a major quality of life (QoL) issue following Radical Prostatectomy (RP), affecting 69-98% of patients [1]. Pelvic floor muscle (PFM) training for PPI is considered a first line approach to rehabilitation but specific protocols for recommendation remain elusive [2]. Efficacy may have been compromised by insufficient PFM training methods for men, including incorrect anatomical focus, training position, exercise dosage and the lack of fast twitch muscle fibre recruitment [3-4].

Aims:

Commencing 4-6 weeks pre-operatively, and utilising both fast and slow twitch fibre training performed in standing, new protocols were developed to address clinical presentations with aims to reduce PPI severity, duration and QoL[5] Comparisons to 'usual care' PFMT pre and post- rehabilitation were assessed utilising both subjective and objective outcome measures.





FAST TWITCH MUSCLE FIBRES IN COUGHING, SNEEZING, BENDING, LIFTING,ORGASM, CLIMACTURIA
30% PFM

SLOW TWITCH MUSCLE FIBRES IN WALKING, ENDURANCE TASKS OR 'holding on' in BLADDER CONTROL & SEXUAL FUNCTION, ED, PE,
70% PFM

Methods:

A randomised controlled trial of 97 men undergoing radical prostatectomy (RP) were allocated to either a control group (n=47) performing 'usual care' of 3sets/day PFMT, or an intervention group (n=50), performing 6 sets/day in standing, commencing 5 weeks prior to RP and continuing for 12 weeks following catheter removal. Participants were assessed pre-operatively and at 2, 6 and 12 weeks post-RP using 24 hour pad weights, IPSS, EPIC-CP and recently validated real time ultrasound (RTUS) measurements of PFM function [6-9].

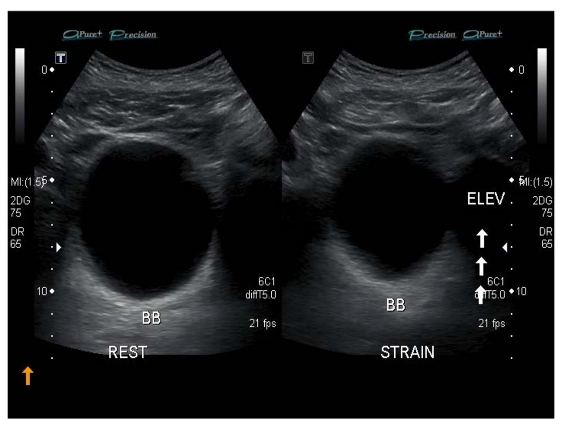
Methods:

97 PARTCIPANTS
ALL 5 WEEKS Pre- RP PFM TRAINING
12 weeks post-RP PFM TRAINING

CONTROL:
3 sets/ PFM day
1 each in supine, sit, stand
Each set =
10s lift, 10s rest
SLOW TWITCH
n=30 PFMs/day
47 men

INTERVENTION:
6 sets PFM/ day
ALL STANDING
Each set =
10 FAST(1sec)
10 SLOW (10sec)
FAST & SLOW TWITCH
n=120 PFMs/day
50 men

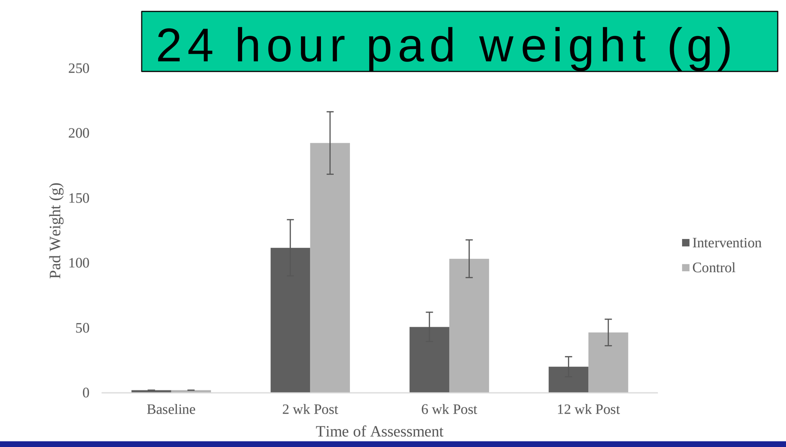
ASSESSED PRE-OP & POST-OP
2 WEEKS, 6 WEEKS, 12 WEEKS
24 hour pad weight, PFM function tests
IPPS and EPIC-CP questionnaires,



Results:

1

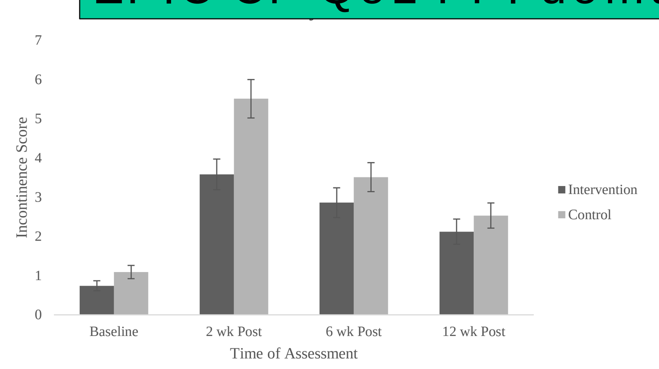
24 hour pad weight (g)



- CONTROL group experienced significantly (p<0.05) more leakage at all time points vs INTERVENTION group in 24 hour pad weights.
- A 2 weeks post-RP CONTROL leaked 200g/24 hours, INTERVENTION 100g
- INTERVENTION group had a FASTER rate of recovery (i.e. nil pads) vs CONTROL group.

2

EPIC-CP QoL PPI domain

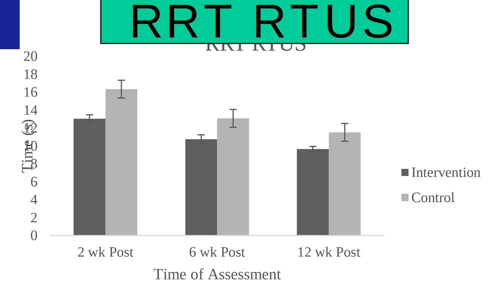


- Pre-surgery EPIC-CP QoL scores were similar between groups, however the INTERVENTION group scored significantly (p<0.05) better QoL scores at 2 weeks post-RP due to 50% less leakage from outset vs CONTROL group

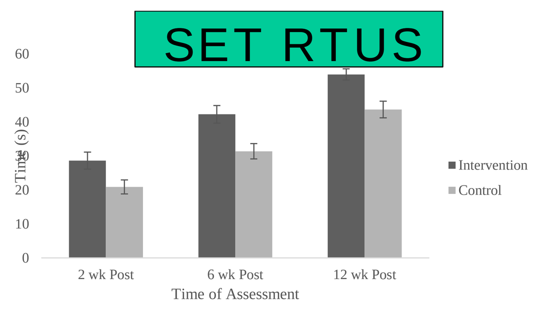
Results: Pelvic Floor Muscle Tests via RTUS

3

RRT RTUS



SET RTUS



- RRT – Rapid Response Test- measures speed of 10 PFM contractions (fast twitch fibers) & urethral sphincter closure time [6-9].
- Control group had HIGHER RRT scores at all time points i.e.= slower , more PPI

- SET –Sustained Endurance Test- measures PFM holding time (slow twitch fibers) and PFM fatigue up to 60s [6-9].
- Control group had LOWER SET scores at all time points= weaker, more PPI

Conclusions:

Utilising a HIGH intensity pelvic floor muscle exercise intervention protocol commencing 6 weeks PRIOR to RP and performed in standing postures, PPI can be REDUCED in TIME and SEVERITY with LESS leakage from the outset, IMPROVED QoL outcomes & FASTER integration of PENILE REHABILITATION. Patients, their medical team & caregivers all benefit.

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Acknowledgements:

I would like to acknowledge my supervisors, Profs Daniel Green & Tim Ackland, for their support & guidance. I would also like to thank esteemed Urologist Prof Patrick Walsh for his leadership and Australian Psychologist Patrick Lumbroso (RIP) for his passion and dedication to improving the quality of life in men & their partners dealing with Prostate Cancer. Finally, a big thank you to my patients who both inspire and teach me everything. PROST!

Therapeutic Ultrasound for Peyronie's Disease in Prostate Cancer: A novel, non-invasive approach to treatment.

Joanne Milios[1], Timothy Ackland[1], Daniel Green[1], Alar Kaard[2], Chris Bevan[2] , Stephen Adams[3]
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2. SKG Hollywood Radiology, Western Australia
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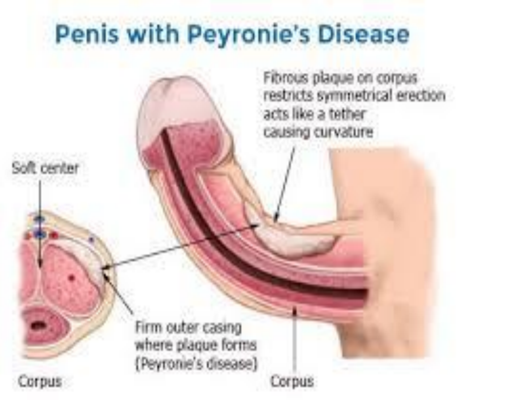
Introduction:

Peyronie's Disease (PD) is a debilitating condition characterised by penile pain, curvature and deformity, palpable plaque formation and erectile dysfunction [1]. Aetiology may be variable but is generally linked to trauma affecting the penis, causing local inflammation, inelastic scar tissue development and fibrosis of the tunica albuginea leading to calcified plaques, altered penile appearance and sexual dysfunction [1,2].

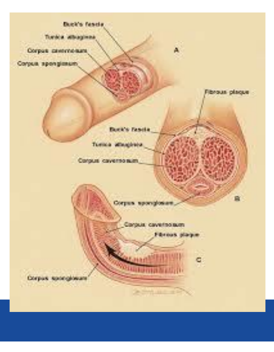


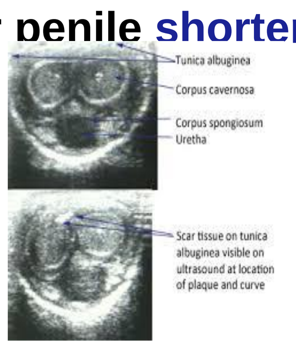
- PD occurs:
- in 3-9% of the normal population
- In 16 % of men following treatment for prostate cancer (PCa)

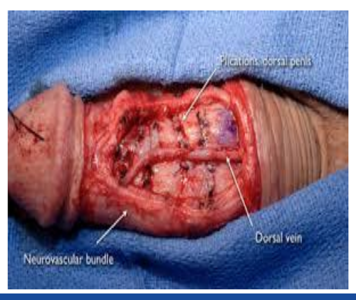
PD can greatly impact on male self esteem, [3] leading to relationship issues (54%), psychological distress (81%), depression (48%), relationship breakdown [3] and an associated increased risk of suicide [3]. In prostate cancer populations there is enhanced risk . [4]

Aim:

Following radical prostatectomy (RP), 16% of men acquire Peyronie's disease (PD) causing pain and curvature of the penis [5]. Lesser known, but seen clinically, PD may also develop after external beam radiation therapy (EBRT) for Prostate Cancer (PCa). Therapeutic Ultrasound (TUS) is a non-invasive treatment for soft tissue injuries, however research for its in PD is limited [6] . Surgical correction is the gold standard however, this may result in further penile shortening and scar tissue [7].

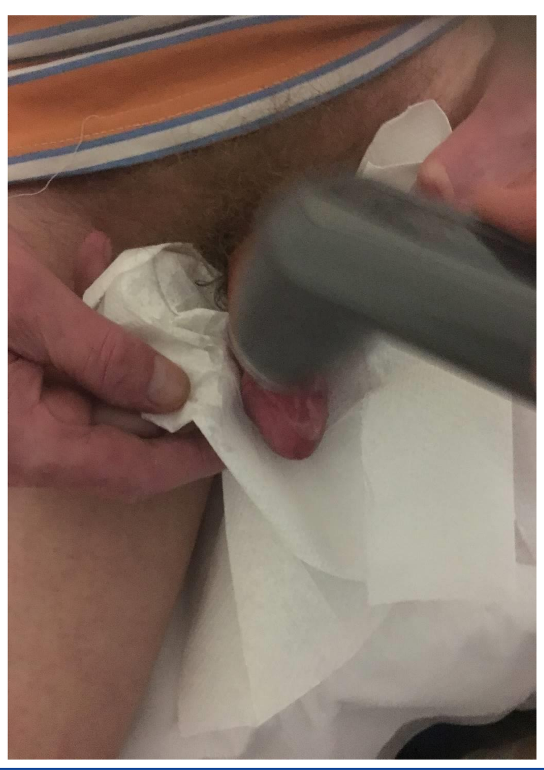






Methods:

Ten men (8 = RP, 2 = EBRT) with a history of PD following treatment for PCa were participants in this study assessing the effect of TUS. Each participant underwent Penile Duplex Doppler Ultrasound (PDDU) pre- and post-intervention to confirm PD, tunica fibrosis and plaque formation as well as completing the Peyronie's disease Questionnaire (PDQ) and IIEF-5. Twelve TUS sessions were provided over 4-6 weeks utilising 1.5-2.5 W/cm^2, 3 MHz x 10mins/session.



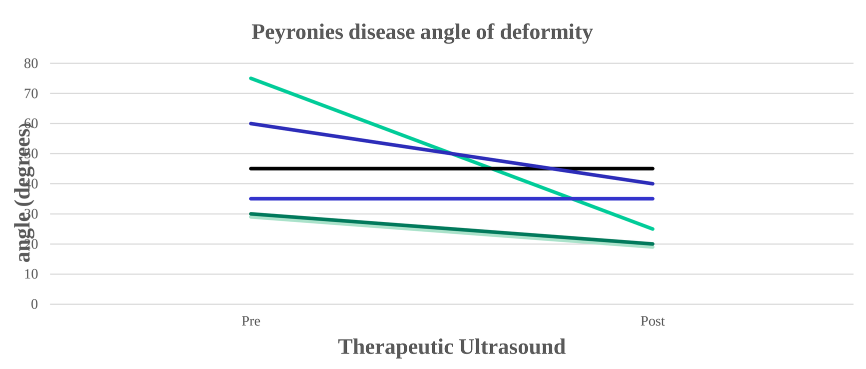
Therapeutic Ultrasound

- 3 sessions /week x 4 weeks =12 doses
- 3MHz ultrasound probe x10 mins / Rx
- 1.5-2.5w/cm2 applied directly to the penis
- Condom over probe
- TUS directed to region of fibrosis as confirmed by PDDU

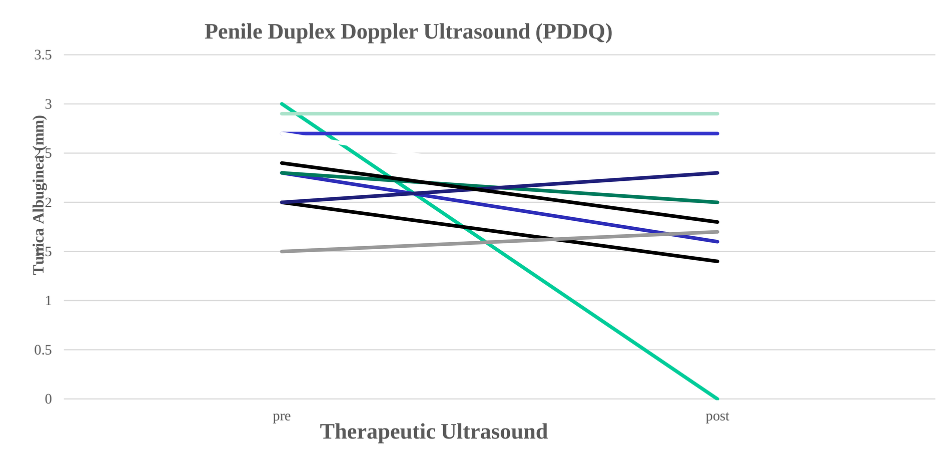
Results:

In 6 of 8 RP participants, partial or complete resolution of PD was observed on PDDU with the remainder stable due to presence of calcified plaques. PDQ and angle of deformity improved in most participants. One participant with post- EBRT PD demonstrated reduction of fibrosis on PDDU, improved IIEF-5 and PDQ score, the other showed mixed results, due to ongoing EBRT effect of EBRT.

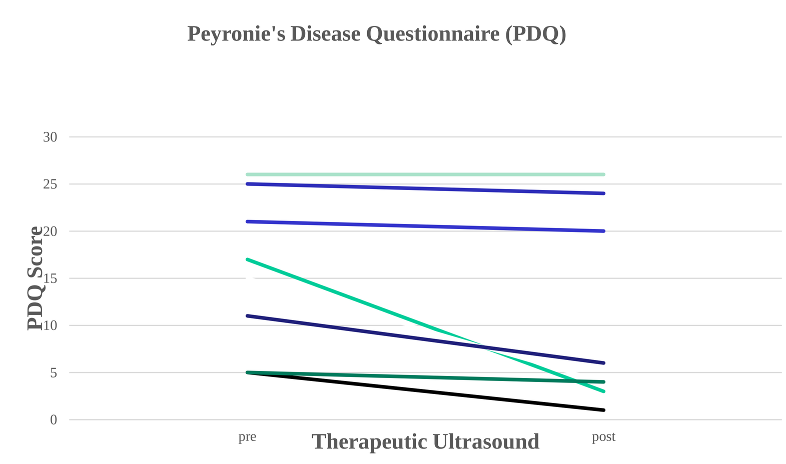
A) Pre TUS X12 B) Post TUS x12



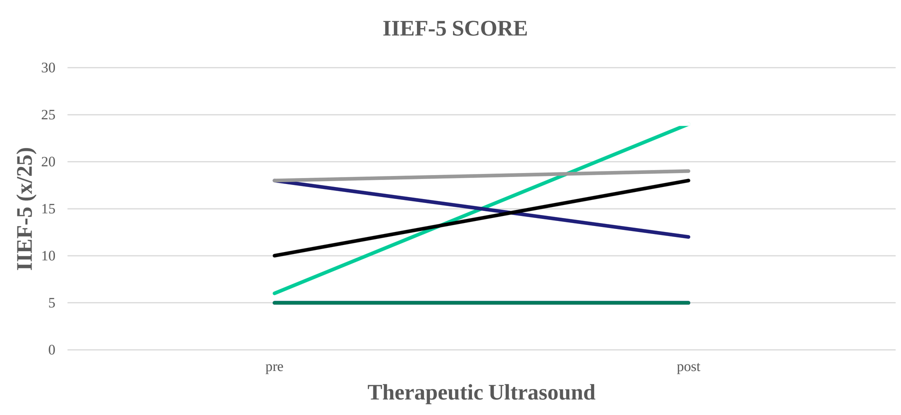
1 Angle of deformity improved in 5 of 7
No improvement in 2 of 7 due to calcification
1 had pain only, 2 others penile indentations



2 Reduction in tunica albuginea fibrosis (mm) occurred in 6 of 9 on PDDQ scan = biological change, confirmed pre vs post PDDU scans.



3 Pain and distress due to Peyronie's disease measured by PDQ scores reduced in 7 of 8



4 Perception of erectile function improved in 3 of 8 and remained stable in 4 of 8, with 1 EBRT worsening, possibly due to ongoing EBRT effects

Results: RCT now under way

- HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA Ultrasound therapy for Peyronie's Disease: A novel, non-invasive treatment approach.

Men with suspected PD referred to Physio trial by Urologist or GP
PD confirmed with PDDU n=40
Complete IIEF5 and PDQ, pre & post TUS photo
Randomization

Group 1
n=20
Intervention
4 weeks

Group 2
n=20
Delayed entry
4 weeks

Repeat DPPU
Repeat IIEF5 (SHIM)
Repeat PDQ

Repeat DPPU
Repeat IIEF5 (SHIM)
Repeat PDQ

Group 2
N=20
Intervention
4 weeks

Statistical Analysis
Results
Paper Submission to Journal

New Physiotherapy treatment
Education & Exposure
Reduction in PD and improved Men's Health

Conclusions:

Peyronie's disease is an acquired connective tissue disorder[1] causing physical and psychological burden in 50% of men affected. (3) In this series of cases, TUS offered an apparently effective first line, non-invasive approach to treatment for PD as confirmed on PDDU and subjective reporting. Future randomized controlled trials should formally assess the efficacy of TUS for Peyronie's disease and this is now under way.

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PROST!

A bend in the men's health learning curve

MEN'S HEALTH To coincide with Movember and dedicated to psychologist Patrick Lumbroso, Jo Milios, APAM, discusses the diagnosis and treatment of Peyronie's disease, a health issue indicative of men's reticence to seek professional help when their health is suffering.

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It's not every day that a fit, good-looking young man knocks on my door with tears in his eyes and begs for five minutes of my time. In my experience, when a man asks for help he really means it; it's not a case of me fobbing him off and saying 'Sure, Dave, come back next week' or 'Is it okay if I call you back tomorrow?' Nope. No way. Full-stop. This is actually a point of desperation and a critical moment in a man's life, and a moment that needs to be seized and immediately prioritised. Because all around the world, men live an average of five years less than their female counterparts and traditional male attitudes towards health may well be a big part of the problem. Few men sit comfortably with chinks in the armour and, culturally, men are far less likely to seek help when things start to go awry. Rather, a man is far more likely to wait until blood his pouring from his rectum before seeing the GP for a problem that hasn't gone away for a few months.

Back to Dave…I'll never forget the photograph on his mobile phone thrust in my hand—the shock made me recoil with morbid curiosity. 'I took this picture of my… you know, penis…this morning,' he said. It wasn't pretty. In fact, it was very severely bent, twisted approximately 85 degrees to the left and in an upward curve. 'Sex with my wife is now impossible', Dave stammered, before asking timidly, 'Is the cancer back?'

Immediately, I knew that Dave had a condition known as Peyronie's disease (PD), and that it was most likely subsequent to his robotic-assisted radical prostatectomy 12 months earlier. What I didn't know was why, how and what could be done about it. And so my learning curve began—a fork in my PhD road that not even my two male university supervisors were keen to pursue, because this is not what men want to know, let alone talk about. Yet, if you look up the scientific papers, this kind of information is easy to find:

Peyronie's disease is a symptomatic disorder characterised by a variety of penile symptoms, including penile pain, curvature, shortening, narrowing, indentation, hinge deformity, palpable plaque and erectile dysfunction (Chung et al 2016). Patients with Peyronie's disease develop penile deformity due to the formation of a plaque in the tunica albuginea (TA) of the corpora cavernosa (Nelson & Mulhall 2012) which is believed to occur as a result of aberrant wound healing in physically susceptible individuals (Chung et al 2016, Nelson & Mulhall 2012). Formation of fibrous inelastic plaques within the TA potentially leads to compromised sexual function, with the reduced ability for sexual penetration and with it, psychological and psychosocial distress (Nelson & Mulhall 2012).

For the everyday patient, it is a soul-destroying, catastrophic and self-esteem blasting sequalae that can occur from injury, after surgery, or as a result of atherosclerotic change, cardiovascular disease or a genetic predisposition. Caucasian men with A-positive blood type, aged 51 years on average, and a positive family history of Dupuytren's contracture will best fit the identikit. But why, Dave, this fit, 45-year-old man who had recovered from prostate cancer with early urinary continence recovery from four weeks' post-op and full erectile function recovery at eight months' post-op?

Fast-forward several weeks of internet research and consulting my university's online library, I soon had my answers. As I discovered, men require 24-hour penile blood flow to maintain 'physiological erections', or penile tumescence, with six to eight nocturnal erections typical for the average bloke per night to maintain his 'housekeeping erections', with most usually occurring during REM sleep. For Dave, the initial eight months following surgery—in which the cavernosal nerves that previously surrounded his prostate were damaged and stretched during the 'nerve sparing' procedure, reduced blood flow—which led to the onset of scar tissue formation.

According to Sydney-based psychologist Patrick Lumbroso, this 'equates to approximately 2000 lost housekeeping erections per year, regardless of sexual activity'. Figuratively, a tap being turned off from full bore to zero overnight…with current research even further compounding Dave's dilemma.

Incidence-wise, up to nine per cent of men (Chung et al 2016) and 16–19 per cent (Teloken & Mulhall 2013) of men following radical prostatectomy—far more than the one to three per cent generally reported—experience PD in their lifetime, with 22 per cent (Smith 1969) confirmed on autopsy. With as many as 81 per cent of men with PD reporting emotional difficulties, 48 per cent clinically meaningful depression and 54 per cent relationship difficulties, the impact on individuals and their relationships can be dire (Lumbroso & Woo 2013). The challenges of PD include alterations in sexual relationships, restrictions in intimacy, socialisation and stigmatisation, along with complete deferment of relationships (Chung et al 2016), which, in younger patients, may lead to avoidance of fathering and parenthood options.

So what I did next for Dave was the only thing could do. A fortuitous conversation with US physical therapist Sandy Hilton, one promising research paper from 1983, six months of ethics applications and amendments, two frowning supervisors, a series of penile duplex doppler ultrasound (PDDU) scans from Dave, showing 'complete resolution' with photographic evidence to confirm, and a happy wife all came together. Two years, 40 participants, one World Congress of Physical Therapy poster presentation and one randomised controlled trial (RCT) later, I'm happy to report that there is indeed a role for physiotherapy in the treatment of Peyronie's disease. It's simple, non-invasive and any physiotherapist has the skill to do it. It involves therapeutic ultrasound directly to the affected area applied over 4–6 weeks, with pre- and post-treatment PDDU scans to confirm progress. A subsequent second project of the RCT involved the use of a specially designed vacuum pump, and the combination proved even more helpful in most cases than the ultrasound alone. Today, I'm in the midst of collating the results, but hope to share more in 2018.

Use Movember to improve your own awareness and education about the impact of men's health issues like PD and depression—potential treatment options need further development but just reading this article is a colossal start.

For a fully-referenced version, email inmotion@physiotherapy.asn.au.

Jo Milios is principal physiotherapist at Perth's Complete Physiotherapy and has a special interest in men's health, yoga and Pilates. She is currently undertaking a PhD at the University of Western Australia's Department of Human Services (Sport Science, Exercise and Health). In 2012 Jo established PROST! Exercise 4 Prostate Cancer, a not-for-profit community education and exercise program for men.

Patrick Lumbroso passed away from brain cancer on 11 September 2017. Patrick was a friend, teacher, mentor and passionate professional, forever dedicated to assisting men in their sexual health burdens. His website can be found at lifeafterprostatecancer.com.au.

For more men's health information, visit menshealthphysiotherapy.com.au and andrologyaustralia.org.au.

GP Fact sheets:

Title: Men's Pelvic Floor Health: Pelvic Floor Muscle Dysfunction in Men **(written by Jo Milios)**

What is Men's Pelvic Floor Health?

Male Pelvic Floor Health is related to bladder and bowel continence, posture, core strength and the sexual functions of erection and ejaculation in men. Pelvic Floor Dysfunction can be treated with a range of physiotherapy options, such as pelvic floor exercises and should be seen as the first line approach to treatment when more serious diagnoses have been ruled out.

The pelvic floor muscles act like a hammock at the base of the body, positioned between the pubic bone and coccyx to support organs, control continence and assist in sexual function. Any problems such as involuntary leakage, pain or a change in any of these functions may indicate a range of disorders treatable by a Physiotherapist. Determining if a muscle is weak (hypotonic) or tight (hypertonic) is one of the first goals of assessment and helps determine a baseline for treatment.

Anatomically, there are three layers of pelvic floor muscles (PFM) including the superficial layer (pouch) consisting of the bulbocavernosus, External Anal Sphincter (EAS), superficial transverse perineal and the ischiocavernosus muscles. The second layer, the Urogenital Diaphragm, is made up of the Perineal Membrane, External Urethral Sphincter (SUS) and the deep transverse perineal muscles, whilst the third layer, the Pelvic Diaphragm, is the deepest layer of muscles consisting of the Levator Ani (pubococcygeus, illiococcygeus, puborectalis) and coccygeus muscles. In addition, a large network of fascia, ligaments and connective tissue bind the muscles of the pelvic floor to the hips, spine, sacrum and coccyx to help maintain tone and stability of the pelvis.

As the pelvic floor is innervated by Pudendal Nerve S2-4, referred pain via pathways from the thoraco-lumbar spinal nerves, sacroiliac joints, hip and coccyx can also impact on pelvic floor presentation and Physiotherapists are skilled in the assessment and treatment of each of these areas.

What causes it?

Pelvic Floor Dysfunction in men usually occurs as a consequence of a range of physical factors:

- Benign Prostatic Hyperplasia (BPH) is possibly the most common contributor to changes in urinary flow and PFM function, as enlargement with the normal consequence of aging leads to reduced urine stream and decreased bladder capacity. This can lead to less efficient bladder emptying and an impact on normal PFM function to control urinary continence.
- Bio-mechanical imbalances of the musculo-skeletal system such as poor core strength, osteoarthritis of the hip, sacroiliac joint immobility or wedge compression of lumbar vertebrae can cause weakness, contraction or shortening of PFMs which may impact on bowel/bladder health and erectile function.
- In surgery such as radical prostatectomy, where removal of the prostate and disruption of the internal urethral sphincter at the bladder neck affect urinary continence, the PFM must quickly adapt from an automatic to a manual system of control, and this causes fatigue and stress urinary incontinence during the period of rehabilitation. The increased workload on the PFM necessitates increased strengthening.
- Direct or indirect trauma such as sports injuries, motor vehicle accidents, falls, surgeries of the bowel, bladder and pelvis and over-use syndromes such as osteitis pubis, can cause PFMs to be stretched, weakened or torn and extensive PFM re-education may be necessary.
- Anxiety and stress may also contribute to PFM dysfunction in conditions such as Chronic Pelvic Pain Syndrome/ Prostatitis, whereby hypertonic muscles that are constantly in a contracted state, can cause perineal ,penile, bladder, urethral, rectal and/or testicular pain for which no other cause can be found.
- Lifestyle factors such as increased weight/obesity, a chronic cough such as in smokers, chronic constipation associated with poor diet and fluid intake, a lack of exercise and a sedentary lifestyle- all of which can weaken the PFMs and contribute to dysfunction.

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What are the implications of Male Pelvic Floor Dysfunction?

More than 4.8 million Australians experience bladder or bowel problems and 40% of men report erectile problems. As the PFMs are integral to bladder, bowel and sexual health, each of these are worthwhile discussing individually, although in some conditions such as Chronic Pelvic Pain (CPP) all three may co-exist with varying levels of dysfunction.

Bladder Health: **B**ladder dysfunction in men this usually presents as over-activity, urgency, frequency (or a mix of both), urinary incontinence, incomplete bladder emptying, urinary tract infections, dysuria, post-void dribble, climacturia or urinary retention. This may lead to a reduction in quality of life, ill-health, social isolation, depression and anxiety in some and a cost factor for individuals for continence aids such as pads and mattress protectors or corrective surgeries.

Bowel Health: Issues of the bowel include constipation, diarrhea, soiling, fecal incontinence, anal pain, prolapse, anal fissures, hemorrhoids and rectoceles. The PFMs can be strained with frequent defecation or constipation leading to a range of conditions that can worsen over time, potentially leading to surgery. The cost to individuals is similar to that outlined for bladder health, however the impact of bowel dysfunction may cause even more significant distress with the potential for social isolation and avoidance of normal activities such as work, exercise and outings.

Sexual Health: PFM Dysfunction in men can cause a range of erectile issues including premature (PE) or delayed ejaculation (DE), erectile dysfunction (ED), post-ejaculatory pain, retrograde ejaculation, anorgasmia and in some cases infertility, due to the lack of ejaculate fluid. PFMs that are weak or tight can negatively impact on the penile tumescence, possibly leading to the inability to have sexual intercourse (SI) or SI that is unsatisfactory. All of these conditions may greatly impact on male self-esteem, relationships and the mental health of the individual.

Symptoms: PFM Dysfunction can cause a range of symptoms affecting the bowel, bladder and sexual function
Bladder symptoms- weak or tight PFMs may contribute to:

Frequency -the need to empty the bladder frequently (normal /day is 4-65 bladder empties, 1/ night), inability to hold longer than 2 hours between voids
Urgency- constant bladder irritation and a feeling of needing to urinate often.
Stress Incontinence- involuntary leakage of urine especially during activity, cough, sneeze, laughter or passing wind
Incomplete Emptying- feeling the need to strain to pass urine or awareness that the bladder is not empty after voiding
Post-void dribble- the loss of urine at the end of bladder void, or unexpected dribble after emptying.

Bowel symptoms- weak or tight PFMs may contribute to:

Frequency- more than 3 bowel motions/day or less than 1 bowel motion every 3 days
Urgency- constant pressure in the rectum or a feeling of need to defecate often
Fecal Incontinence- any involuntary loss of feces including soiling or whole bowel motions
Incomplete Emptying- feeling the need to strain excessively or awareness that bowel is still full

Sexual Health- weak or tight muscles may contribute to:
Erectile dysfunction including reduced quality, endurance or rigidity of erections
Reduced, delayed or absent ejaculation and emission
Pain or reduced sensation in penis, testes, perineum during orgasm or after sexual activity

What treatments are there for Pelvic Floor Muscle Health?

Physiotherapists are trained in the diagnosis and treatment of PFM Dysfunction and will provide a thorough subjective and objective assessment before designing a rehabilitation plan. PFM exercises are designed appropriate to a patient's individual presentation and include down training for relaxation of tight muscles or strength training for weak muscles. External and internal massage of trigger points, muscle stretches, spinal and SIJ mobilsation, biomechanical correction and home-based activities such as bladder diaries may be part of treatment. More functional execise prescription such as Pilates or Yoga may also be prescribed for relaxation, core stability, whole body training and postural improvement.

Managing Pelvic Floor Muscle Dysfunction in Men

PFM health in males can be best managed by men having an awareness of this region of their bodies and to know when to seek help for changes or problems occurring here .Usually, PFM training and various physiotherapy approaches combine to improve or cure pelvic conditions, however working in tandem with GPs, Urologists, Sexual Health Physicians and Psychologists may also be necessary to completely address the needs of men with PFM dysfunction. Once health PFM improves, performing 3 sets of PFM exercises/day will usually maintain function.

Appendix 2 : Thesis Publications and Presentations

2012 Presentation : Thesis Proposal University of Western Australia

2014 Presentation : AOFS Conference: Asia-Oceania Federation of Sexology: 'The role of pelvic floor muscles in prostate cancer & Chronic Pelvic Pain :Valid & reproducible PFM tests for men in distress.'

2014 Poster Presentation: Asia- Pacific Prostate Cancer Conference (APCC) Title: 'Stop giving your patients the finger: A focus on real time ultrasound tests'.

2014: Publication: 'The Nuts and Bolts of Radical Prostatectomy.' Bridge Magazine Continence Foundation of Australia. Spring 2014

2014: Presentation: Western Australian Sexology Association 'Chronic Pelvic Pain in Men'

2015: Presentation: Continence Foundation of Australia (CFA) Queensland State Conference. 'The nuts and bolts of men's health: A focus on urinary incontinence and erectile dysfunction in physiotherapy'.

2015: Presentation: World Confederation for Physical Therapy (WCPT) Singapore. 'Introducing novel, non-invasive pelvic floor muscle function tests for men: A focus on radical prostatectomy and men in distress.'

2015-18 : Presentations: 'Mastering the Martians: Men's Health Physiotherapy Workshops x5 Sydney, Brisbane, Melbourne, hosted by Australian Physiotherapy Association

2013-18 Presentations : Prostate Cancer Foundation of Australia 'The Nuts and Bolts of Men's Health'. Regional Western Australia, Perth and Sydney, Australia

2016: Presentation: Australian Physiotherapy Association, Western Australia 'The Nuts and Bolts of Men's Health: A physiotherapy perspective.'

2016-18 Presentation 'The Nuts and Bolts of Men's Health Physiotherapy'. One and two day courses in UK, Ireland, Portugal, New Zealand, South Africa and Japan for relevant, national physiotherapy associations.

2016-19 Guest lecturer: Curtin University Post-graduate course in Sexology ' Men's sexual and reproductive health'

2016: Publication: (Journal article) Sport Health Journal 'Men's Health on the horizon: The 5-year lifespan inequality'. Vol 34 No 3 15-18

2017: Platform presentation WCPT South Africa : Focussed Symposium 'Men's Health: A new frontier in physiotherapy' co-chaired with Prof Paul Hodges.

2017 : Platform Presentation WCPT South Arica 'Pelvic floor muscle function tests: Comparing transabdominal to transperineal real time ultrasound approaches.'

2017: Poster Presentation WCPT South Africa ‘Is there a role for therapeutic ultrasound in Peyronie’s disease: 3 case studies?’

2017 : Publication Australian Physiotherapy Association (APA)’s In Motion Magazine ‘A bend in the road of men’s health physiotherapy: A focus on Peyronie’s Disease’

2018 : Publication: Pelvic floor muscle assessment in men’s health: Comparing traditional and novel approaches in radical prostatectomy patients. ANZ Cont J

2018: Publication : Application of novel pelvic floor muscle function tests in men following radical prostatectomy: Relationship to urinary incontinence. ANZ Cont J

2018 Presentation: APCC Asia Pacific Prostate Cancer Conference : “ New protocols for a faster return to continence and quality of life following radical prostatectomy”.

2018 Presentation : APCC “Therapeutic ultrasound for Peyronie’s disease in prostate cancer: A non-invasive approach to treatment”.

2018: Presentation: Australian New Zealand Urological Society (ANZUS) State Meeting, Western Australia. ‘New protocols for a faster return to continence, erectile dysfunction and quality of life following radical prostatectomy: A physiotherapy approach utilising pelvic floor muscle training.’

2018 : Guest lecturer: Charles Sturt University Physiotherapy Course Men’s Health in Physiotherapy’ lecture series

2017-2019 Invitation to participate in Australian Physiotherapy Association’s working party on post-graduate pelvic health courses for physiotherapists, Men’s Health section. Delivered.

2018-19: Invitation to develop a peer reviewed webinar for the American Physical Therapy Association’s Women’s Health Section: ‘The Nuts & Bolts of Men’s Health’. For delivery 2019

2018-19 Working group member/Co-author International Continence Society (ICS) Report on Terminology for Sexual Health in Men with LUTS and PFM Dysfunction.

2019: Presentation Geneva ‘New protocols for a faster return to continence, erectile function and quality of life in radical prostatectomy patients.’ May 2019. To deliver

2020: Invitation to provide a men’s health physiotherapy course at Combined Specialist Meeting(CSM) conference in Denver Colarado for Women’s Health Section, American Physiotherapy Association. To deliver.

Community:

2012 : Established not for profit organisation ‘ PROST! Exercise 4 Prostate Cancer.inc’. An organisation dedicated to providing exercise, education and peer support for any man diagnosed with prostate cancer’. 6 weekly exercise sessions at Subiaco Football Club & UWA.

2013-19 Men’s health representative in Media Stable, Australian media company providing information and education for the public, including numerous articles and radio interviews.

2013- 2019 Community talks on prostate cancer and men’s health for PCFA, Regional Men’s Health Network, Men’s Sheds Australia, local government Men’s Health awareness days, Rotary Western Australia, ProState Active Cycle Ride, The Yoga Vine and the mining industry.

2013-18 Physiotherapist for ProState Active Bicycle Ride, 2-day event for raising awareness of Prostate Cancer in the community. Providing support and injury management to cyclists.

2016- Australian Physiotherapy Association 24- hour Q&A Live Twitter Chat for Physical Therapists globally. Men’s Health Week event to promote men’s health in physiotherapy.

2015-18 Interviews on Prof Stacy Loeb’s Men’s Health radio program on Siriusx FM radio, New York, USA with a focus on prostate cancer rehabilitation and men’s health.

2018-19 Working party member and instigator of public health program to provide sanitary bins for men in public toilet facilities in conjunction with CFA, PCFA, Andrology Australia, Men’s Sheds Australia and Rotary.