Title: The evolution of progressive, post-operative weight bearing following autologous chondrocyte implantation in the tibiofemoral joint.

Running Title: Evolution of weight bearing following ACL.

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ABSTRACT

Autologous Chondrocyte Implantation (ACI) has demonstrated good clinical success in the repair of articular cartilage defects in the knee. Post-operative rehabilitation following ACI is considered critical in returning the patient to an optimal level of function by attempting to create the appropriate mechanical environment for cartilage re-growth, and involves a progressive program that emphasizes full motion, controlled exercises and progressive partial weight bearing (PWB). While evidence-based research is clearly lacking in all components of ACI rehabilitation, one important element in this treatment algorithm which has been subjected to some early scientific study is the gradual progression of the patient back to full weight bearing (WB) gait following surgery. With the continual advancement of ACI surgical techniques, along with clinical experience, improved knowledge of histology and of the maturation process of chondrocytes, proposed post-operative WB protocols have evolved to better reflect the nature of the specific ACI surgery. The purpose of this manuscript is to present the varied PWB programs that have been practiced alongside the evolving ACI surgical technique, the experimental basis for such protocols, the issues pertinent to the accurate prescription of WB and future directions for developing such methods in order to best return the patient to an optimal level of function after ACI.

INTRODUCTION

Articular cartilage defects of the knee are prevalent,^{1, 2} and are a common cause of pain and functional disability. Despite the remarkable load bearing properties of articular cartilage tissue, it is well known that following injury the cells are unable to regenerate.³ A number of cartilage repair techniques have been employed to address these focal defects, some of the more common methods including debridement/chondroplasty, microfracture and marrow stimulation, and osteochondral autografts and allografts.⁴⁻¹² These procedures may alleviate symptoms such as pain temporarily; however, while outcomes following microfracture have generally been good,¹³⁻¹⁵ it is not indicated for larger chondral lesions¹⁶ and a fibrocartilage repair tissue is produced, which is biomechanically inferior to hyaline cartilage.¹⁷ Furthermore, while osteochondral autografting may directly transplant hyaline cartilage plugs into the lesion and has shown good outcomes,^{18, 19} it is also recommended for smaller lesions with particular reference to donor site morbidity.²⁰ While allografts may be used for larger lesions, these do carry a risk of immunologic rejection and disease transmission.^{16, 21} Nevertheless, these procedures are routinely employed though appropriate patient selection is critical for their most optimal use.⁴

Due to the aforementioned problems of existing current repair and replacement techniques, development of new methods has centered on cell regeneration therapies, such as Autologous Chondrocyte Implantation (ACI), making the long-term regeneration of hyaline-like articular cartilage possible. While encouraging outcomes have also been observed for ACI,²²⁻²⁴ most surgeons and therapists agree that post-operative rehabilitation is crucial in achieving an optimal

repair tissue and return of the patient back to full function.²⁵ While there are several important components of this rehabilitation program, and good quality evidence is clearly lacking to support these notions, one important element in this treatment algorithm is the gradual progression of the patient back to full weight bearing (WB) gait following surgery. With the evolving nature of the ACI surgical technique, along with clinical experience and a growing knowledge of tissue histology and maturation post-operatively, proposed post-operative WB protocols have evolved to better reflect the nature of the specific ACI surgery. The purpose of this manuscript is to present the varied WB protocols that have been practiced alongside the evolving ACI surgical technique, the experimental basis for such protocols, the issues pertinent to the accurate prescription of WB and future directions for developing such methods in order to best return the patient to an optimal level of function after ACI.

AUTOLOGOUS CHONDROCYTE IMPLANTATION (ACI)

First Generation ACI

ACI is a tissue regeneration technique first described in 1987,²⁶ though has evolved significantly since this time. The general ACI procedure involves isolating and culturing a patient's own cartilage cells (chondrocytes) *in vitro* and re-implanting them into the chondral defect. Initially, an arthroscopic biopsy of healthy articular cartilage is harvested from a non WB aspect of the knee and, using this cartilage tissue, chondrocytes are isolated and cultured resulting in an exponential increase in viable autologous chondrocytes.²⁷ Then, in a second-stage procedure through an open arthrotomy, the chondral defect is prepared by debriding the walls back to healthy cartilage and cleaned down to, but without penetrating, the subchondral bone.²⁸ In the

first generation ACI surgical technique, a periosteal flap was harvested from the proximal medial tibia²⁸ and sutured around the defect border. This acted as a cover for the defect and a water-tight seal, while also providing a semi-permeable membrane to supply nutrition to chondrocytes via synovial fluid.²⁸ It was also thought to enhance chondrocyte growth via the interaction of growth factors between cartilage cells and bone.²⁸ The integrity of the periosteal flap was assessed via injection of a saline solution to check for leakage, before the suture line was further sealed with fibrin glue, with the chondrocytes suspended in fluid and injected under the periosteal flap. Early clinical success of periosteal-covered ACI as a repair procedure for focal articular cartilage defects has been reported.²²⁻²⁴ However, despite the encouraging outcomes, complications associated with the use of the periosteal cover have limited its success. These include incomplete incorporation of the periosteal graft to the host cartilage, graft hypertrophy and delamination of the periosteal patch.²⁸

Second Generation ACI

Second-generation ACI employed a biodegradable three-dimensional scaffold to contain the implanted chondrocytes, in place of the periosteal graft. Therefore, this removed the need to harvest a periosteal graft and reduced the morbidity associated with the periosteal harvest site. It also removed some of the aforementioned complications associated with the use of periosteum.²⁸ While comparable outcomes to its predecessor (periosteal ACI) have been reported,²⁹ further issues related to the micro-trauma associated with suturing the collagen (or periosteal) cover, as well as possible cell leakage through the membrane,³⁰ still remained.

Third Generation ACI

Matrix-induced ACI (MACI) is the third generation of ACI, and differs from previous ACI techniques in that it does not use a patch to contain the implanted cells. Instead, the cultured cells are seeded directly onto the same biodegradable three-dimensional scaffold used in second-generation ACI and implanted into the defect, secured in place to the subchondral bone bed with fibrin glue. This glue acts not only to fix the seeded membrane in place, but also as a transport medium for chondrocyte migration throughout the defect, encouraging repair tissue proliferation and remodeling.^{30, 31} Therefore, MACI requires a smaller incision for defect exposure³² and is technically less complex when compared to first and second generation ACI. Furthermore, MACI becomes a faster surgical procedure to perform and the associated reduced anesthetic and tourniquet time makes undertaking concurrent procedures such as anterior cruciate ligament (ACL) reconstruction more favorable.³³ MACI too has demonstrated early success as a viable surgical option for repairing articular cartilage defects in the knee.³⁴⁻³⁷

Arthroscopic MACI

While chondrocyte implantation techniques have, until recently, required an open arthrotomy, MACI now lends itself to an arthroscopic implantation technique.³⁸⁻⁴⁴ This may decrease the associated co-morbidity of arthrotomy, reducing such complications as adhesions, decreased post-operative range of movement, excessive pain and impressive scarring.⁴⁵ Furthermore, this may also allow for accelerated post-operative WB rehabilitation and an earlier return to full physical function.⁴⁵ Certainly, the progression from open to arthroscopic surgery has proven successful in other knee procedures such as ACL reconstruction and meniscal repair.⁴⁶

ACI POST-OPERATIVE REHABILITATION

Four primary factors that influence graft and patient outcome following ACI surgery have been proposed: 1) successful cell culturing; 2) efficiency of surgical procedure; 3) patient cooperation in all aspects of the pre and post-operative program, and; 4) timely progression of WB and post-operative rehabilitation.⁴⁷ While surgical and cell culturing methods have evolved significantly since the inception of the general ACI procedure, post-operative rehabilitation is currently based on a combination of expert opinion, animal studies, basic science and clinical biomechanics,⁴⁸ though little high quality research involving randomized controlled trials (RCTs) or an actual ACI population. Nonetheless, most surgeons and therapists agree that post-operative rehabilitation is crucial in achieving optimal patient outcomes (ICRS – International Cartilage Repair Society Survey, Rehabilitation after Cartilage Repair, 2006).

The goal of post-operative rehabilitation following ACI is to return the patient to an optimal level of function by attempting to create the appropriate mechanical environment for cartilage re-growth. This involves a progressive program that emphasizes full motion, controlled exercises and progressive PWB.²⁷ PWB refers to only a portion of the patient's individual body weight being applied through the base of the foot of the operated limb during ambulation and, therefore, through the tibiofemoral knee articular surface. Full WB refers to the indication and ability of the patient to bear their full body weight through the affected limb, as would be the case during unaided normal ambulation. Essentially, it is recommended that ACI patients undergo a progressive return to full WB (through various levels of PWB)⁴⁸ in order to facilitate the process of repair tissue remodelling and maturation, with a focus on protecting and progressively stimulating the implanted cells.⁴⁹ Therefore, an important element in this treatment algorithm is

the gradual progression of the patient back to full WB gait.

Basic science research does lend support to the stimulation of chondrocytes after ACI. Cyclic compressive loading has been shown to enhance chondrogenesis,⁵⁰ as well as matrix synthesis and gene expression in cartilage tissue,⁵¹⁻⁵³ dependent on the duration and frequency of dynamic compression.⁵⁴ While shear loading across the knee articular surface has also been shown to result in increased matrix production and improved biomechanical structure,⁵⁵⁻⁵⁷ it may also contribute to early cell damage and/or graft delamination.⁵⁸ Furthermore, static compression^{53, 59-62} and immobilization⁶³ during the post-operative period appear detrimental to the development and repair of cartilage and, therefore, a progressive and well-controlled increase in dynamic (compressive) loading is employed to stimulate the cells. This appears to be best provided through a progressive PWB rehabilitation program.

The quality of the repair tissue after ACI is thought to be, at least in part, dependent on the magnitude and duration of the mechanical loading stimulus that the repair tissue receives in the initial post-operative period.^{64, 65} While the ideal cell stimulus required throughout the post-operative time line is not yet known, it is important to note that while an increasing dynamic stimulus to chondrocytes with time appears imperative for quality tissue repair, caution must be employed early in this post-operative process in order to avoid potentially detrimental movements or loads that may contribute to the characteristic complications and failures associated with ACI.⁶⁶⁻⁶⁸ Clinically, if the therapist is too aggressive in their rehabilitation approach there is risk of graft failure, while an over-conservative approach may not provide optimal chondrocyte stimulus. Therefore, it is the goal of this progressive, PWB rehabilitation

program to manipulate the mechanical environment by modifying the patient's knee loading profile. Subsequently, this may produce a specific and graduated WB program that will provide an optimal loading stimulus, without overloading and jeopardizing the integrity of the graft and early repair process. Certainly, the early post-operative period is important to the outcome of the procedure, whereby over-stimulation may lead to overload, early degeneration and failure of the graft, whereas lack of stimulus may not encourage optimal chondrocyte differentiation and development.⁴⁹

Evolution of Post-operative Partial Weight Bearing (PWB) following ACI

While progressive mechanical stimulation of the primitive repair following ACI is crucial, allowing cells to differentiate into a hyaline-like repair tissue resembling that required during load bearing activity, the nature of the surgery will also act to dictate the intensity of load and movement that the graft can tolerate without potential harm. For this reason, along with ongoing clinical experience with these cell regenerative therapies, we have also seen an evolution in proposed post-operative WB protocols as the ACI surgical technique has evolved. For example, the complexity and fragile nature of the graft at implantation following first generation ACI that will effectively sit at, or above, the walls of the adjacent native cartilage at the time of implantation, demands a more conservative post-operative WB progression. This may reflect the reported complications with this first generation such as higher rates of graft delamination,²⁸ particularly with the contact it makes with the opposing articular surface during movement and load bearing. However, with MACI the membrane is glued to the subchondral bone, affording it some protection from the adjacent healthy cartilage walls in a well contained defect in the earlier post-operative stages.

With the inception of the first generation ACI procedure, the proposed WB protocol consisted of a conservative 6-week period of toe-touch ambulation, followed by a stepwise increase over the next six post-operative weeks, achieving full WB by 11-12 weeks post-operatively²⁸ (Figure 1A). As per the aforementioned surgical issues with this technique, the cautious and conservative rationale for the delayed return to full WB was required. While studies often do not outline the course of rehabilitation in detail, those that have mentioned the WB protocol undertaken following first generation ACI generally only specify the length of the early period of protected WB and the time to return to full WB. Again, these typically favor long periods of either non or toe-touch WB (6-8 weeks),⁶⁹⁻⁷⁷ with full WB not attained until at least 10-12 weeks post-operatively.^{69, 70, 73-75}

With the advancement from first to second generation ACI, as well as further clinical experience, a more graduated return to full WB was proposed,^{78, 79} removing the initial 6-week period of toe-touch ambulation; progressing from 20% of the patient's body weight being applied through the affected leg within two weeks of the operation to full WB at 11-12 weeks post-operatively (Figure 1B). Again, given the similarity of both methods with respect to the suturing required of the defect cover, along with the cover sitting somewhat proud of the adjacent native cartilage walls, documented post-operative WB regimens have specified non or toe-touch phases of six weeks or more,^{78, 80-83} with full WB attained after 11-12 weeks.^{78, 82}

While somewhat conservative early-stage WB protocols have been reported following MACI,^{84, 85} encouraging clinical outcomes from more 'aggressive' and accelerated WB rehabilitation

protocols have been reported.⁸⁶⁻⁸⁸ It has been demonstrated that the time to full WB can be safely reduced from 12 to 8 weeks post-surgery (Figure 1C) following MACI in the tibiofemoral joint, without detriment to the patient or integrity of the graft, with improved clinical outcomes at three months,⁸⁹ maintained to two years^{90, 91} and five years post-surgery.⁸⁶ Furthermore, the return of gait normality was accelerated,⁹² minimizing the effects any ongoing, abnormal gait and knee joint loading patterns following the return to full WB may have on short- and long-term graft success. Recently published pilot outcomes of a randomized controlled trial (RCT) have since demonstrated no detriment to graft or clinical outcomes with an accelerated WB protocol focused on achieving full WB after six weeks, compared with 10 weeks, following MACI (Figure 1D).⁸⁸ This is also supported by another RCT that has demonstrated at least comparability to 12 months in patients undertaking a 6-week return to full WB following open and arthroscopically performed MACI, versus an 8-week approach.⁸⁷ Certainly, the potential benefits afforded by arthroscopic implantation methods such as reduced adhesions, swelling and pain, and improved early post-operative range of movement,⁴⁵ may better allow these accelerated regimens, with other arthroscopic-based MACI techniques also reporting a return to full WB at 6-8 weeks.^{41, 43, 93}

Individual Patient Characteristics and Influence on WB Progression

A large amount of individual variation exists between patients undergoing ACI; including age, gender, body mass index (BMI), physical function, other co-morbidities, defect size and location, and the amount of prior knee surgeries and pre-operative duration of pain and symptoms. In addition to the aforementioned evolution of the surgical technique, these individual patient differences must be acknowledged in the prescription of a specific post-operative WB

progression after ACI. Age restrictions are generally indicated for ACI,^{32, 94} with age demonstrating a significant negative correlation with clinical outcome.⁹⁵⁻⁹⁷ As one ages, there is an associated reduction in tissue regenerative capacity and, therefore, the gradient of post-operative WB may require a more conservative approach. Of particular importance to ACI on the tibiofemoral joint, any reduction in body weight results in a four-fold reduction in loads experienced at the knee during normal ambulation.⁹⁸ This is further highlighted by the significant negative correlation of increasing BMI with poorer clinical outcome.^{91, 99} BMI should be <30 ,⁹⁴ and the progression of post-operative WB in patients with excess body weight may also require a more conservative approach.

A shorter duration of pre-operative symptoms and a lower number of prior knee surgeries have been associated with improved post-operative outcome following ACI,^{91, 100-102} and articular cartilage repair patients have been likened to those suffering from osteoarthritis, whereby pain and symptoms may have persisted over a prolonged period of time.¹⁰³ Furthermore, long-standing lesions may experience advanced degeneration of the surrounding bone and cartilage, providing a possible adverse intra-articular environment.¹⁰⁴ Patients with long-standing pain and/or those that have undergone previous surgical knee procedures may require a more conservative post-operative WB approach.

Chondral defect size has exhibited a significant negative correlation with clinical outcome following tibiofemoral ACI^{86, 91, 105} and, while contradictory results have been reported,^{68, 97, 106} a more conservative approach to post-operative WB may be required for larger and less contained WB grafts, as may a small and well contained graft permit a more aggressive return to full WB.

The influence of graft location on the tibiofemoral joint remains less clear, though movement of the medial and lateral compartment does differ due to altered femoral condyle geometry. The medial femoral condyle remains in the central portion of the tibial plateau as the knee flexes from full extension; however, the lateral femoral condyle translates posteriorly with increasing flexion.¹⁰⁷ Therefore, throughout WB ambulation in combination with knee flexion and extension, a lateral femoral or tibial graft may be subjected to an increased degree of shear loading, suggesting more caution may be required with respect to WB progression with laterally located grafts to reduce adverse loading at the graft site. Furthermore, the posterior aspect the femoral condyles generally makes contact with the tibial plateau between 90 to 120 degrees of knee flexion¹⁰⁸ and, therefore, posterior femoral ACI grafts may permit a more aggressive WB progression given the knee does not flex to that degree during the stance phase of gait during walking.

Finally, it must also be acknowledged that ACI is often undertaken in combination with a range of concomitant surgeries, given contraindications for undertaking ACI include co-existent knee joint malalignment, ligamentous instability and/or meniscal deficiency.^{109, 110} While in our mind, undertaking an ACL reconstruction or meniscectomy in combination with ACI may not necessarily require a deviation in the specified post-operative WB progression, a high tibial osteotomy employed to address a malaligned tibiofemoral joint may indeed require a prolonged period of reduced WB post-operatively.¹¹¹ In summary, the population undergoing ACI is quite varied, and it is the responsibility of the treating clinician to effectively adapt post-operative WB rehabilitation protocols to suit a wide array of patients, surgical variations and unexpected complications.

Teaching WB Restrictions

While the exact WB protocol and how we need to incorporate individual variation remains to be determined, the basic science research (in combination with the obvious need to protect the graft in the early stages for risk of damage or delamination) supports the requirement of a progressive PWB protocol after ACI. However, there is also a requirement of the therapist to implement this protocol in way that can be learnt and retained by the patient at any given time. Several methods exist for teaching progressive PWB program to patients, including verbal instruction,¹¹² pressure applied to the hand of a licensed physical therapist,¹¹³ the use of standard bathroom scales,^{48, 113-120} “limb load monitors”¹²¹ or pressure insoles,^{122, 123} and force monitoring platforms.¹¹³ While the bathroom scale method remains the most practical and widely used modality for teaching WB restrictions,^{48, 115} mixed results surround its use with both good^{117, 120} and poor^{113, 114, 124} replication ability reported. Certainly, research has demonstrated improved WB accuracy with higher frequency of practice¹¹⁵ and, therefore, irrespective of the chosen method for educating patients on desired WB levels, training should be an important component of each and every post-operative rehabilitation session up until the return to full WB gait.

Other issues arise with respect to training and patient replication of these WB regimes. Firstly, the ability of the patient to accurately reproduce certain levels of WB within a clinic setting does not improve their level of compliance throughout their daily activities. Compliance to rehabilitation in general remains a problem and, unfortunately, the only method of improving compliance outside of supervised clinical rehabilitation is through quality patient education on the increased risks of an adverse event in the presence of non-compliant actions, including WB

performance. Secondly, we generally assume that the external loads experienced at the base of the foot of the operated limb translate to the tibiofemoral knee articular surface, and this may not necessarily be the case. PWB training using bathroom scales, which involves unidirectional loading in a stationary position, fails to reproduce the situation experienced during dynamic gait¹¹³ whereby body and limb accelerations are introduced. Furthermore, factors such as pain¹¹⁴ and reduced muscle power¹²⁵ affect PWB ability, as may an altered mental state and fragility after the operative procedure. Nevertheless, these methods are currently employed and ongoing development of efficient and inexpensive biofeedback devices may improve WB accuracy and compliance into the future for ACI patients.

RESEARCH LIMITATIONS AND FUTURE DIRECTIONS

While the progressive return to full WB following ACI is an important component of the patient's rehabilitation after ACI,²⁷ evidence-based clinical research exploring optimal WB protocols is in its infancy. It is important to note that with the evolution of the general ACI technique, current WB programs for tibiofemoral ACI have progressed accordingly, albeit with scarce quality clinical research. While basic science research has been undertaken to support the anabolic effect of dynamic⁵⁰⁻⁵⁴ and shear loading⁵⁵⁻⁵⁷ in promoting cell differentiation and proliferation, as opposed to static loading^{53, 59-62} and immobilization,⁶³ further research is required to better determine the optimal duration and magnitude of cell loading, and how this translates to what is prescribed clinically. The volume and magnitude of compressive and/or shear force that becomes injurious to repair tissue following ACI throughout the early progressive WB period is unknown, and to assess this *in vivo* may prove unethical. Further

research into the time and gradient at which patients can return to full WB is required, and the few clinical RCTs that do exist have been undertaken with relatively low patient numbers and with strict patient inclusion criteria.⁸⁶⁻⁸⁸

While improving our knowledge into the best loading stimuli for ACI grafts throughout the early post-operative time line is important, we also need to work toward improved strategies for implementing these regimes. We know that several methods exist for teaching WB restrictions as described previously, and the ability of these to assist WB retention specifically following ACI requires investigation. Accurate and inexpensive methods of promoting improved WB training and replication ability should be explored to improve the accurate prescription of desired WB levels. Furthermore, the effect of WB inaccuracy (and in particular overloading) on graft development and/or damage, especially in the early crucial stages after ACI, requires further investigation.

CONCLUSIONS

With the continual advancement of ACI surgical techniques, along with clinical experience, improved knowledge of histology and of the maturation process of chondrocytes, further acceleration of these post-operative WB protocols may arise and will be incorporated into an evidence-based approach for treating ACI patients. This may further reduce time and expenses associated with the rehabilitative process, and enable the patient to return to normal activities earlier. However, any accelerated WB rehabilitation approach must be thoroughly investigated to ensure it is not detrimental to both short, and long-term graft and patient outcomes. As a final

note, it should be remembered that large variation exists between ACI patients that must be taken into account whilst undertaking the early rehabilitative process and considering the return to competitive activity. Therefore, these progressive PWB programs should be based on the patient's individual status and needs, the location and size of the defect, and any additional surgical procedures that may have been performed.¹²⁶

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FIGURE LEGENDS

Figure 1. The evolution of post-operative partial weight bearing (PWB) since the inception of the general autologous chondrocyte implantation (ACI) procedure, demonstrating: A) the progressive weight bearing (WB) gradient proposed for periosteal-covered ACI by Minas and Peterson (1999) involving a 6-week period of non WB with only toe-touch ambulation, with a stepwise increase in load over the next six post-operative weeks achieving full WB by 11-12 weeks post-operatively; B) the WB gradient proposed for collagen-covered ACI by Robertson et al. (2004) initiating WB from 20% of the patient's body weight within two weeks of the operation, with a more graduated increase to full WB also at 11-12 weeks post-surgery; C) the accelerated WB protocol proposed for matrix-induced ACI by Ebert et al. (2008) achieving full WB at eight weeks post-surgery and; D) the accelerated WB protocol proposed for matrix-induced ACI by Wondrasch et al. (2009) achieving full WB at six weeks post-surgery.