Title

HbA1c is associated with frailty in a group of Aboriginal Australians

Short title

HbA1c and frailty

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Brief report

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Author contributions

Dina Lo Giudice, Leon Flicker, Kate Smith, Stephen Fenner, and David Atkinson conceived and designed the study. Zoë Hyde performed the statistical analyses and wrote the initial draft of the manuscript. Dina Lo Giudice, Leon Flicker, Stephen Fenner, Linda Skeaf, and Roslyn Malay collected the data. All authors reviewed and revised the manuscript for intellectual content, and

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Abstract

In this cross-sectional study of 141 Aboriginal Australians aged ≥45 years living in the remote Kimberley region of Western Australia, we explored whether glycated haemoglobin (HbA1c) levels were associated with frailty. Sixty-four participants (45.4%) had a HbA1c level ≥6.5% and 84 participants (59.6%) were frail. A significant trend was observed with regard to HbA1c levels and frailty, with those having HbA1c levels ≥6.5% having the greatest prevalence of frailty (70.3%). In binary logistic regression analyses, having a HbA1c level ≥6.5% was associated with being frail after adjustment for age, sex, and education. This association was attenuated after further adjustment for body mass index (BMI). Poorer glycaemic control is very common and a potential risk factor for frailty in remote-living Aboriginal Australians, and appears to be partly mediated by BMI, a known risk factor for diabetes mellitus. Obesity and diabetes mellitus are potentially important modifiable risk factors for frailty.

Key words

Frailty, diabetes, ageing, aboriginal, indigenous

Introduction

Unlike normal ageing in which a gradual loss of physiological reserve occurs, frailty is an abnormal state in which homeostasis is lost. Minor stressors can induce a worsening syndrome, increasing the risk of disability and mortality (1). The development of insulin resistance and diabetes has been hypothesised as a risk factor for frailty (2).

Aboriginal Australians experience health disparity compared with the general Australian population, and have high levels of chronic diseases such as diabetes (3). We recently observed a very high prevalence of frailty in Aboriginal people living in the remote Kimberley region of Western Australia, with 65% of those aged ≥45 years affected (4).

Given the potential role of diabetes in the aetiology of frailty, we investigated whether glycaemic control was associated with frailty in Aboriginal Australians. We hypothesised that elevated HbA1c levels would be associated with frailty.

Methods

Study population

This was a cross-sectional study of 289 Aboriginal Australians aged ≥45 years living in the remote Kimberley region of Western Australia between 2011 and 2013. Participants were recruited from 6 Aboriginal communities and one town representative of the region. Full details regarding the study are published elsewhere (5).

Study design

Research assistants administered a culturally specific questionnaire to each participant and a nominated family member/carer. HbA1c was measured using a DCA Vantage Analyser and participants were classified as either being normal (<5.7%), pre-diabetic (5.7-6.4%), or diabetic (≥6.5%) as per American Diabetes Association guidelines (6). HbA1c could not be measured for some individuals due to difficulty with the equipment in the climate conditions of the Kimberley and some participants electing not to participate in this aspect of the study.

From these data, we constructed a frailty index (FI) comprising 28 items using the approach described by Searle and colleagues (7). Participants were excluded from analyses if they did not have data for at least 20 items. The items and scoring schema for the index are provided as supplementary material (Supplementary Table 1). We considered participants with a FI score ≥0.2 frail (4).

Ethics

Approval was obtained from the councils of the communities involved; Kimberley Aged and Community Services; Kimberley Aboriginal Medical Services Council; Kimberley Aboriginal Health Planning Forum Research Subcommittee; Human Research Ethics Committee of the University of Western Australia; WA Aboriginal Health Ethics Committee; and the Department of Health WA Human Research Ethics Committee.

Statistical analyses

Analyses were performed using the Stata statistical package version 11.2 (StataCorp, College Station, Texas). Of 289 participants, we excluded 89 who did not have at least 20 items with which to construct a frailty index and 59 people with missing data for HbA1c, leaving 141 participants. People with missing data for HbA1c were more likely to be younger (58.4 vs. 62.2 years), male (55.9% vs. 31.9%), have some formal education (84.8% vs. 67.4%), and a lower BMI (25.3 vs. 28.5 kg/m^2). They were also slightly but not significantly less likely to report being diagnosed with

diabetes (46.6% vs. 51.1%). We used Pearson's Chi square test, Cuzick's non-parametric test for trend, and the Mann-Whitney U test and Kruskal-Wallis test to investigate associations between variables. We performed binary logistic regression to investigate associations with frailty, and used Hosmer and Lemeshow's goodness-of-fit test to ensure model fit. We considered p values <0.05 statistically significant.

Results

Characteristics of the sample are presented in Table 1. The mean age of participants was 62.2±11.1 years (range: 45.0-88.9 years). Chronic disease, particularly diabetes, was common. Participants who reported diabetes (51.1% of the sample) had a mean HbA1c of 7.9±2.1%, those who did not report diabetes had a mean HbA1c of 6.1±0.9%, while in the overall sample the mean HbA1c was 7.0±1.9% (range: 5.1-14.3%). Twenty-one participants (14.9%) had a HbA1c level <5.7%, while 56 (39.7%) had levels between 5.7-6.4%, and 64 (45.4%) had a HbA1c level greater than or equal to 6.5%. The mean BMI of participants was 28.5±7.1 kg/m^2 (range: 13.9-52.1 kg/m^2). Eighty-four participants (59.6%) met criteria for frailty.

There was a clear association between HbA1c levels and the proportion of participants with frailty, with a statistically significant trend for greater frailty by higher category of HbA1c (p=0.025). The proportion of people who were frail was relatively similar among those with a HbA1c level <5.7%, and those with HbA1c levels between 5.7 and 6.4% (frailty prevalence: 47.6% vs. 51.8%). However, the proportion of people meeting criteria for frailty was much higher among those with HbA1c levels ≥6.5% (frailty prevalence: 70.3%). When frailty was examined as a continuous variable, a similar trend was observed, as depicted in Figure 1.

An apparent threshold effect existed with regard to BMI. The proportion of participants meeting criteria for frailty was reasonably similar for those who were underweight (50.0%), of normal weight (59.3%), and overweight (53.7%). In those who were obese, however, the proportion of frail individuals reached 70.5%. When frailty was examined as a continuous measure, a U-shaped association appeared to be present. Those with both a low body mass index and those who were obese had a higher frailty index score than those of normal body weight.

A clear and statistically significant difference was observed in HbA1c levels by BMI. Mean HbA1c was above the threshold of 6.5% for all categories of BMI, except in those who were underweight (p=0.003). No statistically significant difference was observed in HbA1c levels between those who were of normal weight, overweight, or obese.

Having a HbA1c level ≥6.5% was associated with being frail (OR=2.31; 95% CI 1.15, 4.64). This association persisted after adjustment for age, sex, and education (OR=2.39; 95% CI 1.17, 4.89). Associations between age, sex, and educational attainment with frailty did not reach statistical significance (data not shown). After adjustment for BMI, the association between having a HbA1c level ≥6.5% and frailty was somewhat attenuated (OR=2.10; 95% CI 0.92, 4.80), indicating that

BMI was possibly a confounder in the association between HbA1c and frailty.

Discussion

In this cross-sectional study of remote-living Aboriginal Australians, individuals with higher HbA1c levels were more likely to be frail. This was attenuated by BMI, which is also a risk factor for diabetes. Both diabetes and high BMI were very common in this population, making them important potential risk factors. BMI might be a mediator in the relationship between glycaemic control and frailty, or a shared risk factor for both frailty and diabetes.

Interestingly, we observed a U-shaped association between BMI and frailty when frailty was examined as a continuous measure, but not as a categorical variable. This association between obesity and frailty is noteworthy and may reflect a "fat frail" phenotype in which both muscle wasting and excess fat co-exist, as described by Morley (8). In contrast, mean HbA1c levels were normal in underweight individuals, and elevated (≥6.5%) in those who were obese suggesting a potential role for diabetes in the aetiology of frailty.

The prevalence of both diabetes and frailty was very high. A high prevalence of frailty has also been described in Indigenous populations outside Australia. A recent study of 1,820 Canadian First Nations people reported that 47.3% of those aged ≥65 years were frail, and that diabetes was strongly associated with frailty (OR=3.53; 95% CI 2.64, 4.73) after adjustment for age and sex (9). Diabetes and/or impaired glycaemic control has previously been associated with frailty in other studies of non-Indigenous populations, and attenuated after adjustment for obesity or BMI (10, 11).

Ageing biomarkers are accelerated in people with type 2 diabetes (12), probably increasing the risk of developing frailty at a younger age. The normal age-related decline in muscle mass is also accelerated, potentially resulting in sarcopenia and likely compounded by myosteatosis. Peripheral neuropathy impairs balance and decreases motor innervation. Other complications of diabetes, such as peripheral vascular disease, are also associated with decreased muscle mass. Diabetes is also associated with decreases in anabolic hormones such as testosterone, and increases in inflammatory cytokines. Additional complications of diabetes, such as hypertension, renal failure and cognitive impairment likely further increase the risk of frailty and associated adverse outcomes such as falls. Finally, although bone mineral density may be normal or even increased in people with type 2 diabetes, bone structure may be abnormal, which appears to be associated with increased fracture risk (2, 8, 13-15).

Strengths of our study include a high response fraction, comprehensive assessment using culturally-specific instruments, active participation of Aboriginal research assistants, and measurement of

HbA1c. Limitations include a relatively small sample size and the possibly of response and recall bias. A further limitation of this study is the use of a frailty index comprising at most 28 items, which is less than the minimum of 30 suggested by Searle and colleagues (7).

In summary, this study suggests that poorer glycaemic control is a potential pathway to frailty in remote-living Aboriginal Australians, and to at least some extent influenced by BMI. Obesity and diabetes are very common in this population and appear to be modifiable risk factors for frailty. Health promotion measures addressing nutrition, physical activity, and other behavioural risk factors could potentially decrease the incidence of frailty in this population.

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Conflict of interest statement

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Tables

Table 1 Sociodemographic and clinical characteristics of the sample

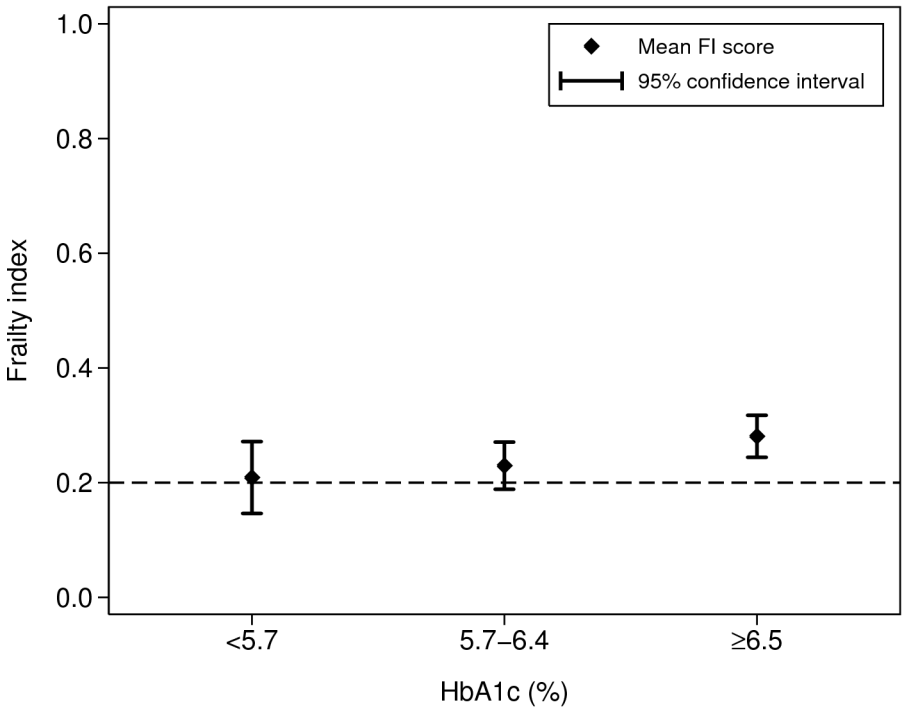
Characteristic	n (%) or Mean±SD
Age (years)	
45-49	21 (14.9)
50-59	49 (34.8)
60-69	31 (22.0)
70-79	26 (18.4)
80+	14 (9.9)
Sex	
Male	45 (31.9)
Female	96 (68.1)
Some formal schooling	95 (67.4)
Drink alcohol	33 (23.4)
Smoke tobacco	32 (22.7)
Chew tobacco[2]	60 (42.6)
Poor vision	62 (44.0)
Poor hearing[2]	30 (21.3)
Prior stroke[3]	20 (14.2)
Diabetes[6]	72 (51.1)
Hypertension[21]	64 (45.4)
Heart problem[8]	39 (27.7)
Kidney problem[9]	45 (31.9)
Urinary incontinence[1]	43 (30.5)
Poor mobility[2]	65 (46.1)
Pain[1]	76 (53.9)
Recent fall[1]	33 (23.4)
Head injury with loss of consciousness[3]	34 (24.1)
BMI (kg/m^2)[17]	
Underweight (≤19.9)	12 (8.5)
Normal (20.0-24.9)	27 (19.2)
Overweight (25.0-29.9)	41 (29.1)
Obese (≥30.0)	44 (31.2)
HbA1c (%)	
<5.7	21 (14.9)
5.7-6.4	56 (39.7)
≥6.5	64 (45.4)
KICA-Dep[5]	4.8±5.1
KICA-Cog[17]	36.0±3.9
Frail (FI score ≥0.2)	84 (59.6)

Note: Percentages calculated without excluding missing data (i.e., denominator is entire sample). Column percentages are shown. Numerals in superscript denote number of people with missing data for that variable. Higher KICA-Dep scores indicate greater depressive symptoms; higher KICA-Cog scores indicate better cognition. BMI = body mass index; HbA1c = glycated

haemoglobin; SD = standard deviation.

Figure legends

Figure 1 Frailty index score by HbA1c level



Note: Dashed line denotes cut-off for frailty. FI = frailty index.