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Impact microindentation in men with impaired fasting glucose and type 2 diabetes

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ABSTRACT

Background: Individuals with type 2 diabetes (T2DM) are at increased fracture risk, with bone mineral density (BMD) measurements underestimating risk. Impact microindentation (IMI), a technique that measures bone microindentation distances, expressed as bone material strength index (BMSi), may improve fracture risk estimation in individuals with T2DM. This study describes the relationship between BMSi and glycaemia status in men and makes a comparison with bone measures from dual energy X-ray absorptiometry (DXA).

Material and methods: Participants were 340 men aged 33–96 yr from the Geelong Osteoporosis Study. Impaired fasting glucose (IFG) was defined using fasting plasma glucose (FPG) between 5.5 and 6.9 mmol/L. Diabetes was defined as FPG ≥ 7.0 mmol/L, use of antihyperglycemic medication and/or self-report. Two participants with type 1 diabetes were excluded. BMSi was measured using an OsteoProbe. Femoral neck (FNBMD) and lumbar spine (LSBMD) were measured using DXA (Lunar Prodigy) and trabecular bone score (TBS) was calculated (TBS iNsight Version 2.2).

Using linear regression techniques, the relationship between glycaemia status and BMSi was evaluated, adjusting for other potential confounders (including lifestyle factors, clinical measurements and FNBMD). Glycaemia status was also considered as a binary variable (T2DM vs normoglycaemia and IFG).

Results: There were 234 (68.8%) men with normoglycaemia, 59 (17.4%) with IFG and 47 (13.8%) with diabetes. When considering glycaemia status as a binary variable, men with T2DM had lower mean BMSi compared to those without T2DM (normoglycaemia and IFG combined) (79.8; 95%CI 77.0–82.6 vs 83.0; 82.2–83.8 $p = 0.043$) and this difference in BMSi was independent of FNBMD. No differences were observed for either FNBMD or LSBMD; however, TBS was lower (1.177; 1.121–1.233 vs 1.256; 1.240–1.272, $p = 0.015$, independent of FNBMD).

For glycaemia status considered in three groups, there were no differences in mean BMSi values between men with normoglycaemia, IFG and T2DM (82.9 (95%CI 82.0–83.8), 83.5 (81.8–85.2) and 79.8 (77.0–82.6), respectively; ANCOVA, $p = 0.104$).

Conclusions: Measures reflecting bone material properties and microarchitecture (BMSi and TBS) might be better than measures of bone mass (BMD) in identifying individuals with T2DM at risk of fracture.

1. Introduction

It has been reported in many studies that individuals with type 2 diabetes (T2DM) are at an increased risk of fracture [1–7]. This is despite individuals with T2DM having increased bone mineral density (BMD) compared to those without T2DM, which is counter-intuitive to the observed increase in fracture risk [1,6,8–11].

Other measures have been useful in detecting differences in bone that occur in patients with T2DM that might render the bone more susceptible to fracture. One such example is trabecular bone score

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(TBS), which provides an indication of trabecular microarchitecture [12]. Two recent studies have reported that TBS is lower in postmenopausal women with T2DM compared to those without T2DM [13,14]. Another study has reported that TBS values are also lower women in a wider age range (aged 30–90 years) with T2DM [15]. Lower TBS values have also been reported for men with T2DM. Two studies, one from Korea and another from Australia, showed lower TBS values in men, as well as women, with T2DM compared to those without T2DM [16,17]. However, one study including both older men and women has reported no differences in TBS between those with and without T2DM [18]. One possible reason for this differing observation could be that only individuals with T2DM < 5 years duration and not taking insulin were included in the study, and there may have been insufficient time for T2DM-related bone changes to develop. One other Korean study involving postmenopausal women with T2DM has reported that TBS is also useful for differentiating between those with and without vertebral fractures [19]. That study showed women with T2DM and vertebral fractures had a lower TBS than women with T2DM and no vertebral fractures.

Impact microindentation (IMI) measurement is another possible technique for assessing bone fragility in individuals with T2DM. These measurements are performed using the OsteoProbe [20], and involve indenting the bone surface of the tibial plateau, and measuring the depth the probe tip penetrates into the bone. The device measures the indentation distance from the starting position (resting on the surface of the bone at 10 N) to the maximum depth upon an impact load (~40 N). The indentation distance is standardised by comparison to a plastic reference material (poly methyl methacrylate) and expressed as bone material strength index, or BMSi.

To date, three studies have reported lower BMSi values for those with T2DM compared to controls [21–23]. All studies included women only and two had small sample sizes. Another study examined differences in BMSi values between participants with recently diagnosed T2DM (< 5 years), prediabetes and controls [18]. The authors reported that there were no differences in BMSi values for white individuals across the glycaemia groups, however, there were differences observed between black individuals with T2DM and normoglycaemia. Further studies with larger sample sizes are needed to confirm these observations. Another recent study also showed no differences in BMSi between men and women with and without T2DM [24]. Additionally, only one of the studies [18] examined whether BMSi values differed between individuals with moderately elevated fasting glucose levels; i.e. prediabetes or impaired fasting glucose (IFG). The reasons for the differing results observed in these previous studies could be related to the inclusion/exclusion criteria employed. One of the studies that showed no differences in BMSi [18] excluded participants with T2DM duration ≥5 years and those that used insulin. Additionally, the two studies that showed no differences in BMSi both included pooled data from men and women [18,24], while the other studies included postmenopausal women only. These studies detected no differences in BMSi values between men and women and thus analysed the two sexes together, but the impact of T2DM on BMSi values may differ between men and women. Several differences between men and women have been noted, in particular, men are considered to have a higher risk of developing T2DM and are diagnosed at a younger age and lower level of obesity [25]. In addition, it has been reported that the increased risk of T2DM-related cardiovascular complications is greater in women than men [26].

Therefore, the aim of this study was to determine the association between BMSi and glycaemia status in a sample of men. A secondary aim was to compare these results with those obtained from dual energy X-ray absorptiometry (DXA; BMD and TBS).

2. Methods

2.1. Participants

This study included male participants of the Geelong Osteoporosis Study (GOS), a population-based cohort study of participants residing in the Barwon Statistical Division, located in south-eastern Australia [27]. Participants were randomly selected from Australian electoral rolls and since voting is compulsory in Australia, the electoral roll captures almost all adults in the region. Baseline assessment occurred during 2001–2006 and included 1540 men, aged 20–92 years. The data for this study were drawn from the 15-year follow-up phase (2016–2019). Of 1540 men recruited at baseline, 424 had died prior to the 15-year follow-up, 217 were unable to be contacted, 24 had moved outside the region and nine were not able to provide informed consent. Of the remaining participants (n = 866), 241 declined to participate for the following reasons: time constraints (n = 45), illness (n = 33), old age (n = 48), language barriers (n = 1), distance (n = 2), personal reasons (n = 108) and repeated failure to keep appointment (n = 4). Thus, for the purpose of this study there were 625 eligible for inclusion.

The study was approved by the Human Research Ethics Committee at Barwon Health. All participants provided written informed consent.

2.2. Measurements

IMI measurements to determine BMSi were performed using the OsteoProbe RUO (Active Life Technologies, Santa Barbara, CA, USA). IMI measurements were made on the anterior surface of the mid-tibia. The measurement site was determined by measuring the midpoint from the medial border of the tibial plateau to the distal edge of the medial malleolus. Following disinfection and local anaesthesia, the probe tip was inserted through the skin to rest on the surface of the bone. The operator then pressed down on the outer housing of the device to initiate the measurement. The measurements were conducted following the recommended international guidelines [28]. The first indentation was systematically removed, as this is often affected by insufficient penetration through the periosteum. Then, at least 10 indentations were performed for each participant. The indentations were performed in a methodical way by trained operators; in two rows of five indentations. The probe tip was moved between each indentation, producing indentations with a separation of approximately 2 mm. When the data were being collected, there was no automated process to remove invalid measurements and thus we followed the previously reported guidelines [28]. Specifically, a measurement was considered invalid if it lay outside the “green zone” area flagged by the software, or if the operator reported that the “texture” of the indented bone was abnormal. The measurements were conducted by three trained operators, however most (90.9%) were performed by a single operator. The coefficient of variation (CV) for microindentation was 2% for repeated measures. Precision was calculated as the mean (expressed as %) of SD/mean for two sets of indentations for 10 participants. Participants experienced minimal discomfort during this procedure, as previously reported [29].

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. DXA scans were performed to determine femoral neck (FNBMD) and lumbar spine (LSBMD) BMD (GE-Prodigy, Prodigy; GE Lunar, Madison, WI, USA). TBS was determined using TBS iNsight software (Version 2.2) by retrospective analysis of lumbar spine DXA scans. DXA scans were completed on the same day as IMI measurements.

Blood samples were collected after an overnight fast and analysed for fasting plasma glucose (FPG). Participants were categorised as having IFG using the American Diabetes Association (ADA) criteria [30]: FPG between 5.5 and 6.9 mmol/L. Diabetes was classified if participants had any of the following: FPG ≥ 7.0 mmol/L, use of antihyperglycaemic medication and/or self-reported diabetes. Self-

Table 1
Descriptive characteristics of the men included in the study, stratified by glycaemia status. Data presented as mean ± SD, median (IQR) or n (%).[b]

	Normoglycaemia (N = 234)	Impaired fasting glucose (N = 59)	Type 2 diabetes (N = 47)	P value
Age (yr)	61.3 (51.6–70.9)	65.5 (60.2–73.6)	73.5 (64.1–80.3)	< 0.001
Weight (kg)	81.1 ± 11.6	83.9 ± 9.9	83.4 ± 10.2	0.150
Height (cm)	174.9 ± 6.9	173.7 ± 6.9	172.3 ± 6.3	0.042
Body mass index (BMI)	26.5 ± 3.1	27.8 ± 2.9	28.1 ± 3.2	< 0.001
Prior fracture	51 (21.8)	10 (17.0)	9 (19.2)	0.689
Smoking	21 (9.0)	3 (5.1)	2 (4.3)	[a]
High alcohol consumption	41 (17.5)	16 (27.1)	10 (21.3)	0.243
Low mobility	44 (18.8)	17 (28.8)	15 (31.9)	0.061
Bisphosphonate use				
Current	2 (0.9)	1 (1.7)	0 (0.0)	[a]
Past	3 (1.3)	0 (0.0)	0 (0.0)	[a]
Denosumab use				
Current	4 (1.7)	0 (0.0)	0 (0.0)	[a]
Past	0 (0.0)	0 (0.0)	0 (0.0)	[a]
Glucocorticoid use				
Current	5 (2.1)	0 (0.0)	1 (2.1)	[a]
Past	3 (1.3)	0 (0.0)	1 (2.1)	[a]
Diabetes medication use[c]	–	–	33 (70.2)	–
Metformin	–	–	30 (63.8)	–
Insulin	–	–	3 (6.4)	–
Sulfonylureas	–	–	13 (27.7)	–
Thiazolidinediones	–	–	1 (2.1)	–
Other diabetes medications[d]	–	–	7 (14.9)	–

[a] Too few to conduct statistical analysis.
[b] Shapiro-Wilks test used as a test of normality, to determine whether mean ± SD or median(IQR) was reported.
[c] Note that some participants may be taking more than one type of medication for diabetes.
[d] Includes medications such as SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 receptor antagonists.

reported information included age of onset (in years). Where a participant was classified as having diabetes, physician review of medical records was undertaken, to determine whether the participant had type 1 or type 2 diabetes.

2.3. Other data

Prior low trauma fractures in adulthood (≥20 years) were ascertained by self-report and confirmed by an examination of radiological reports across the region. Fractures were excluded if they were a result of high trauma such as a motor vehicle accident and/or if they occurred at one of the following skeletal sites: skull, face, fingers or toes. Self-reported questionnaires were used to determine current smoking status, high alcohol consumption, mobility and medication use. Alcohol consumption was determined using the Victorian Cancer Council Food Frequency Questionnaire [31]. High alcohol consumption corresponded to ≥3 units per day. Mobility ranged from very active to bedfast, and was dichotomised into “high” (very active or active) and “low” (sedentary, limited, inactive, chair or bedridden, bedfast). Medication use was self-reported and included current and past use of bisphosphonates and oral glucocorticoids, as well as current use of anti-hyperglycaemic agents. Data were collected and managed by the Research Electronic Data Capture (REDCap) tool, hosted by Barwon Health [32].

2.4. Statistical analysis

Normality of continuous variables (age, weight, height, BMI) was tested using the Shapiro-Wilk test. All were normal except for age; inter-group differences for weight, height and BMI were identified using parametric (ANOVA) tests, while differences in age were assessed using a non-parametric (Kruskal-Wallis) test. Categorical variables were compared using Chi squared tests.

Linear regression was used to examine associations between BMSi and glycaemia status. Associations between glycaemia status and FNBMD, LSBMD and TBS were similarly assessed. Potential confounding variables were tested in the models and retained if $p < 0.05$. Potential confounders included age, weight, height, prior fracture, smoking status, alcohol consumption, mobility, medication use, onset and duration of diabetes. FNBMD was also included in the models for BMSi and TBS, to investigate whether any differences observed were independent of FNBMD. BMD at this site was chosen because it is the routine site for clinical assessment, while the other routine site, LSBMD can be affected by the presence of spinal artefacts [33]. Interaction terms were checked in final models. Normality of residuals in each model were checked and the parametric assumptions about residuals were met. Results for normoglycaemia and IFG were similar, and thus an additional analysis was undertaken using a dichotomised variable for glycaemia status (T2DM vs no T2DM).

3. Results

Of 625 men who were eligible for inclusion, 471 provided sufficient information to determine glycaemia status. Of these, two had type 1 diabetes and were excluded from the analyses. Of the remaining 469 participants, 340 (72.5%) had the IMI measurement completed. Reasons for non-participation included excessive soft tissues around the mid-tibia (n = 82, two related to oedema), existing skin conditions (n = 19), needle phobia (n = 6), discomfort following first indentation (n = 5) and no reason given (n = 16). One elderly participant did not understand the measurement well enough to provide informed consent.

Of the participants who did not complete the IMI measurement, 87 (67.4%) had normoglycaemia, 22 (17.1%) had IFG and 20 (15.5%) had T2DM. For participants included in this study, there were 234 (68.8%) men with normoglycaemia, 59 (17.4%) with IFG and 47 (13.8%) with T2DM. The proportions of men with normoglycaemia, IFG and T2DM was not different between those who did and did not complete the IMI measurement (p = 0.898). There was no difference in mean height (mean ± SD: no IMI; 174.6 ± 7.3 vs IMI: 174.3 ± 6.9, p = 0.729) between those who did and did not complete the IMI measurement. For men with T2DM, there were no differences in number of diabetes medications used (median (IQR) no IMI: 1 (0–2) vs IMI: 1 (0–2),

$p = 0.656$) and duration of diabetes (median (IQR) no IMI: 11.1 (3.6–17.6) vs IMI: 11.3 (5.7–18.6), $p = 0.689$). However, there were differences in median age (median (IQR): no IMI; 69.2 yr (57.3–77.9) vs IMI; 64.5 yr (54.0–73.6), $p = 0.005$), mean weight (no IMI: 92.8 ± 17.3 vs IMI: 81.9 ± 11.1, $p < 0.001$) and mean BMI (no IMI: 30.4 ± 5.3 vs IMI: 26.9 ± 3.2, $p < 0.001$).

3.1. Descriptive characteristics

Table 1 shows the descriptive characteristics of the participants. Age and BMI increased across the three glycaemia groups. Men with T2DM had shorter stature than the other two groups. No other differences between the groups were observed. The median duration of T2DM was 11.3 yr (range 0.5–28.0 yr) and age of onset 62 yr (40–86 yr).

3.2. Glycaemia status in three groups (normoglycaemia, IFG and T2DM)

The ANCOVA analysis showed no differences in BMSi when comparing the three groups, after adjustment for age, weight and height ($p = 0.104$). The mean (95% CI) BMSi values for the normoglycaemia, IFG and T2DM groups were 82.9 (82.0–83.8), 83.5 (81.8–85.2) and 79.8 (77.0–82.6), respectively. Therefore, analyses continued considering glycaemia status as two groups (normoglycaemia and IFG vs T2DM).

3.3. Glycaemia status in two groups (T2DM and no T2DM)

The unadjusted and adjusted results considering glycaemia status as a binary variable are shown in Table 2. In unadjusted analyses, men with T2DM had lower mean BMSi (−2.9%) and TBS (−5.1%). They also had a higher mean LSBMD (+5.3%), however, no differences were observed for FNBMD.

Following adjustment for other variables, men with T2DM had lower mean BMSi (−4.0%) than the normoglycaemia group and this association was sustained after including FNBMD in the model. There were no differences observed between men with and without T2DM for either FNBMD or LSBMD. Men with T2DM had lower mean TBS (−6.8%) than those without T2DM, and this association was sustained after inclusion of FNBMD in the model.

4. Discussion

This study reports that T2DM was associated with a lower BMSi and TBS, however no differences were observed for FNBMD or LSBMD. No differences were detected for the bone measures between men with IFG and normoglycaemia.

Our results are consistent with previous reports in the literature for BMD; that individuals with T2DM have a higher, or normal BMD compared to those without T2DM, despite their increased risk of fracture [1,6,9–11,13,34]. Similar to our study, TBS values have been reported to be lower for those with T2DM compared to healthy controls [13,15,16,35,36]. We have also previously reported that compared to men and women with normoglycaemia, those with T2DM had a lower mean TBS, and no differences were observed for those with IFG [17]. Another study including Korean postmenopausal women with T2DM reported that TBS and TBS-adjusted FRAX scores were able to identify those with prior vertebral fractures, while BMD and unadjusted FRAX scores were not different between the groups [19]. Additionally, a study from Canada followed 29,407 women aged ≥50 yr, 2356 of whom had diabetes, over 4.7 years [37]. The results showed that TBS was effective at predicting fracture risk over the follow-up period in both those with and without diabetes, independent of BMD. Overall, previous studies have shown that TBS may be useful for capturing the increased risk of fracture in individuals with T2DM.

Five studies have previously reported BMSi values for participants with T2DM. The first was Farr et al. [22], which included 60 postmenopausal women, 30 with T2DM and 30 controls. The study reported that BMSi values were 9.2% lower in women with T2DM compared to controls after adjusting for other factors. The authors also reported that bone turnover markers were lower in those with T2DM, however, BMD and bone microarchitecture, as assessed using high-resolution peripheral quantitative computed tomography, were not different. The second study, by Furst et al. [21], included 16 postmenopausal women with T2DM and 19 matched controls. That study also reported that BMSi was lower in women with T2DM by 9.2%. The third study by Nilsson et al. [23] included 1053 women (99 with T2DM) aged 75–80 yr, of whom 477 (45.1%) had IMI measurements. The study reported that women with T2DM had lower mean BMSi values (−4.8%), and this was sustained after adjustment for other covariates. Additionally, BMD at the femoral neck, total hip and lumbar spine were higher in women with

Table 2
Predicted values for bone material strength index (BMSi), femoral neck bone mineral density (FNBMD), lumbar spine BMD (LSBMD) and trabecular bone score (TBS) in men, stratified by diabetes status. Data shown as mean (95%CI).

	N[a]	No diabetes ($n = 293$)	Type 2 diabetes (n = 47)	P value
Unadjusted models				
BMSi	340	82.9 (82.1–83.7)	80.6 (78.7–82.5)	0.029
FNBMD	336	0.958 (0.943–0.973)	0.947 (0.910–0.985)	0.607
LSBMD	330	1.303 (1.279–1.327)	1.376 (1.315–1.436)	0.029
TBS	330	1.252 (1.236–1.269)	1.191 (1.149–1.232)	0.007
Adjusted models				
BMSi[b]	340	83.0 (82.2–83.8)	79.8 (77.0–82.6)	0.043
BMSi (including FNBMD)[c]	340	83.1 (82.3–83.9)	79.6 (76.8–82.4)	0.027
FNBMD[d]	336	0.957 (0.944–0.970)	0.953 (0.919–0.988)	0.851
LSBMD[e]	330	1.305 (1.283–1.328)	1.363 (1.298–1.427)	0.114
TBS[f]	330	1.255 (1.239–1.271)	1.175 (1.118–1.232)	0.015
TBS (including FNBMD)[g]	330	1.256 (1.240–1.272)	1.177 (1.121–1.233)	0.015

Potential confounders tested in the adjusted models: age, weight, height, prior fracture, smoking status, alcohol consumption, mobility, medication use, onset and duration of diabetes. Confounders were retained if $p < 0.05$.

[a] Number of observations included in the model.
[b] Model adjusted for age, weight, height and diabetes medication use.
[c] Model adjusted for age, weight, height, diabetes medication use and FNBMD.
[d] Model adjusted for age and weight.
[e] Model adjusted for age, weight and prior fracture.
[f] Model adjusted for age, weight, smoking and diabetes medication use.
[g] Model adjusted for age, weight, smoking, diabetes medication use and FNBMD.

T2DM compared to controls, however this was attenuated after adjustment for other factors. In another study, Dawson-Hughes et al. [18] compared BMSi, BMD and TBS in black (n = 35) and white (n = 149) participants with recently diagnosed diabetes (≤5 years duration) and prediabetes with controls. The results showed no differences in BMSi between glycaemia groups in white participants, however in black participants, BMSi was lower for those with diabetes. Additionally, BMD was higher, or not different between glycaemia groups. TBS was also not different between glycaemia groups. These results suggest that there are differences in ethnic groups in terms of BMSi in recently diagnosed T2DM, which may be due to a variety of factors, including access to healthcare and delays in diagnosis as well as biological differences. However, the sample size for black participants in the study was small, highlighting the need for further studies. The most recent study by Samakkarnthai et al. [24] reported no differences between men and women with T2DM (n = 171) and age-matched controls (n = 108) recruited from the local population. The study also reported higher BMD at the femoral neck, total hip, lumbar spine, distal radius, ultradistal radius and total body for those with T2DM compared to controls, even after adjusting for age, sex and BMI. Our results are consistent with some findings from these previously published studies; BMSi and TBS were lower in those with T2DM, while no differences in FNBMD or LSBMD were detected. However, we report a smaller difference for T2DM compared to normoglycaemia of ~4.0%. The reasons for this could be due to differences in the population being studied, particularly that our sample includes men only, as well as geographical differences. Indeed, a previous study has reported differences in BMSi values between women from Spain and Norway [38].

We have previously reported on associations between BMSi and T2DM status in preliminary analyses [39]. These analyses reported no differences in BMSi between men with and without T2DM, however, that study had a smaller sample size, and did not consider duration, age of onset and antihyperglycaemic medication use, all of which are important in the progression of bone deterioration with T2DM.

The reasons that BMSi and TBS were different in men with T2DM, while no differences were observed for FNBMD or LSBMD are likely to be multifactorial. Individuals with T2DM have a higher BMI than those without diabetes, and it has been reported that greater BMI is associated with increased BMD [40]. This results in a mean BMD within the normal range, despite those with T2DM having an increased risk of fracture. Additionally, bone microarchitecture is affected in T2DM. Previous studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) have reported that individuals with T2DM have poorer values for cortical parameters, while trabecular bone values appear to be positively affected [22,41,42]. In particular, those with T2DM have lower cortical volumetric BMD, reduced cortical thickness and higher cortical porosity. These differences in cortical bone parameters may be captured to some extent by IMI measurements, which assess cortical bone of the tibia. Although TBS assesses primarily trabecular bone, it appears that some of the differences in bone parameters for individuals with T2DM are being captured by this measurement. It is also possible that there are differences in how bone is affected throughout the skeleton, as TBS assesses bone at the spine, while HR-pQCT assesses bone at the radius and tibia. Additionally, TBS is derived from a texture analysis of lumbar spine DXA images, while HR-pQCT directly measures the trabecular microarchitecture. Differences in bone turnover could also contribute to the observed results in this study. We have previously reported, along with other studies [43–47], that bone turnover markers are lower in those with T2DM. Lowered bone turnover can lead to accumulation of microdamage and consequently increase the risk of fracture [48]. An increased amount of microdamage on the surface of the bone at the tibia may affect the ability of bone to resist propagation of microcracks during the IMI measurement, leading to a lowered BMSi value. Finally, advanced glycation end-products (AGEs) have been suggested to play a role in the bone fragility observed in T2DM [49]. These compounds, which arise from non-enzymatic glycation of proteins including type 1 collagen, can interfere with the proper functioning of osteoclasts and osteoblasts [50]. The increase in bone fragility as a result of higher levels of AGEs in individuals with T2DM may be detected by IMI measurements, as the bone will be less able to resist microcrack propagation. Data from the studies by Furst et al. [21] and Samakkarnthai et al. [24] supports this, which show that BMSi values correlated with AGEs measured using skin autofluorescence. Lower bone turnover in T2DM may exacerbate the accumulation of AGEs, and may also affect the degree of mineralisation, leading to reduced bone resistance to damage, which may be reflected in lower BMSi values.

This study has several strengths. Participants were randomly selected and are representative of the broader white Australian population. While it was possible to adjust for multiple other variables in the models, there may still be unrecognised residual confounding. This study also utilised multiple different methods to classify individuals with diabetes including FPG level, self-report and/or medication use. We also excluded participants with type 1 diabetes. There are also limitations including that this study was cross-sectional and further research is needed to investigate whether BMSi predicts incident fractures in individuals with T2DM. Our sample included men only and thus may not be generalisable to other populations. Although we had data on duration of diabetes, it ranged from six months to 28 years and thus in some individuals there may not have been enough time for bone changes to develop. Therefore our results may be conservative for individuals with long-standing diabetes. Further limitations include that the number of participants with T2DM in this study was small, and we did not have HbA1c data, which would greatly enhance the interpretation of the results. Additionally, some of the data was self-reported and may have been affected by recall bias.

Additionally, we were unable to conduct IMI measurements for all participants. Although the proportions of participants with normoglycaemia, IFG and T2DM did not differ between the two groups who did and did not provide IMI measurement, we cannot exclude possible differential participation bias according to glycaemia status. Both of these possibilities could have affected differences observed between the glycaemia groups.

5. Conclusion

Men with T2DM had lower BMSi and TBS compared to those without T2DM (normoglycaemia and IFG combined), however there were no differences observed for FNBMD or LSBMD. Bone measures for men with IFG were not different to those with normoglycaemia. Measurements of BMSi and TBS may be better than BMD for detecting bone fragility in individuals with T2DM.

CRediT authorship contribution statement

Kara L. Holloway-Kew: Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Amelia Betson:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Pamela G. Rufus-Membere:** Data curation, Investigation, Methodology, Writing - review & editing. **James Gaston:** Formal analysis, Methodology, Writing - review & editing. **Adolfo Diez-Perez:** Methodology, Supervision, Writing - review & editing. **Mark A. Kotowicz:** Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. **Julie A. Pasco:** Conceptualisation, Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing.

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