FRAX (Australia) scores in women with impaired fasting glucose and diabetes

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ABSTRACT

Background: Diabetes is associated with higher fracture risk despite higher bone mineral density (BMD), with FRAX® underestimating risk. This study aimed to investigate FRAX score with and without BMD for women with normoglycaemia, impaired fasting glucose (IFG) and diabetes.

Methods: Among 566 women, aged 40–90 years, enrolled in the Geelong Osteoporosis Study, IFG was defined as fasting plasma glucose (FPG) ≥ 5.5 mmol/L and diabetes as FPG ≥ 7.0 mmol/L, use of antihyperglycaemic medication and/or self-report. FRAX (Australia) 10-year probabilities of major osteoporotic (MOF) and hip fracture were calculated, with and without BMD, producing four FRAX scores per participant. Kruskal-Wallis test for non-parametric data was used to examine differences between the three glycaemia groups. Fractures over 10 years were ascertained using radiological reports. The number of fractures predicted by FRAX was compared with the number of fractures observed using Chi-square tests.

Results: For MOF FRAX calculated without BMD, women with diabetes ($n = 67$) tended to have a higher median score 7.1 (IQR 2.7–12.0) than normoglycaemia ($n = 252$) (4.3 (IQR 1.9–9.9) and IFG ($n = 247$) (5.1 (IQR 2.2–9.6)). For hip FRAX without BMD, diabetes tended to have a higher score (2.5 (IQR 06–4.3)) than normoglycaemia (1.2 (IQR 0.3–4.1)) and IFG (1.3 (IQR 0.3–4.1)). In the normoglycaemia and IFG groups, MOFs were underestimated; 15 predicted vs 28 observed, $p = 0.038$; and 16 predicted vs 31 observed, $p = 0.021$, respectively. Fractures were accurately estimated in all other groups.

When including BMD, the association with diabetes was non-significant for both MOF FRAX (normoglycaemia 3.7 (IQR 1.9–8.0), IFG 4.3 (IQR 2.2–8.1) and diabetes 5.3 (IQR 2.7–9.4)) and hip FRAX scores (normoglycaemia 0.6 (IQR 0.2–2.5), IFG 0.8 (IQR 0.2–2.7) and diabetes 1.0 (IQR 0.3–3.0)). For normoglycaemia and IFG, MOFs were underestimated (normoglycaemia: 13 predicted vs 28 observed and IFG: 13 vs 31). For diabetes, both MOFs and hip fractures tended to be underestimated by FRAX with BMD (MOF: 4 predicted vs 11 observed, $p = 0.055$, hip: 1 predicted vs 6 observed, $p = 0.052$). Hip fractures were accurately estimated in the normoglycaemia and IFG groups.

Conclusions: Compared with women who had normoglycaemia or IFG, women with diabetes tended to have a higher FRAX score for both MOF and hip fractures when BMD was not included. When BMD was included, there was no difference. Fractures in diabetes tended to be underestimated by FRAX with BMD. This suggests that FRAX calculations including BMD may not be accurate for estimating fractures in those with diabetes.

1. Introduction

Almost a decade ago the University of Sheffield developed the fracture risk assessment tool (FRAX® (http://www.shef.ac.uk/FRAX)), which is a computer-based algorithm intended for primary care that gives the 10-year probability of hip fracture and major osteoporotic (clinical spine, wrist, hip or proximal humerus) fracture (Kanis et al., 2008). FRAX can be calculated with or without bone mineral density

(BMD) (Bauer, 2011; Source, 2016), and body mass index (BMI) is used to predict BMD when BMD is not entered into the algorithm (Bolland et al., 2011). The other clinical risk factors considered in the FRAX score are: age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis or secondary osteoporosis, and alcohol consumption of ≥ 3 units/day. When BMD is not entered into calculation of FRAX scores, the clinical risk factors assume higher weighting in the final result.

Diabetes is an epidemic disease that affects 347 million people worldwide (Danaei et al., 2011) and over 1.5 million people in Australia (Diabetes Australia, 2013). Furthermore, impaired fasting glucose (IFG), a precursor of diabetes, affects 33.8% of Australian women (de Abreu et al., 2015). Fractures and hyperglycaemia are associated with extensive public health costs (Watts et al., 2013; Zhang et al., 2010) and increased mortality (Danaei et al., 2006; Giangregorio et al., 2012). Patients with type 2 diabetes (T2D) have higher risk of fractures (Bonds et al., 2006; Forsen et al., 1999; Giangregorio et al., 2012; Janghorbani et al., 2006, 2007; Schwartz et al., 2001; Strotmeyer et al., 2005) despite higher or normal BMD compared with individuals with normoglycaemia (Bonds et al., 2006; Christensen and Svendsen, 1999; de Abreu et al., 2019; de Liefde et al., 2005; Hanley et al., 2003; Lunt et al., 2001; Nilsson et al., 2017; Oei et al., 2013; Okuno et al., 1991; Schwartz et al., 2001; Shanbhogue et al., 2016; Sosa et al., 1996; van Daele et al., 1995). Based on the observation that people with diabetes have higher fracture risk even with higher BMD (Bonds et al., 2006; de Abreu et al., 2019; de Liefde et al., 2005; Hanley et al., 2003; Oei et al., 2013; Schwartz et al., 2001), it is challenging to predict fracture risk in T2D. It has been reported that BMD does not provide an accurate estimation of bone fragility (Ferrari et al., 2018; Giangregorio et al., 2012; Leslie et al., 2018; Schacter and Leslie, 2017). Fracture risk assessment calculations have been shown to underestimate fracture risk in T2D, and this is particularly true when BMD is included (Ferrari et al., 2018; Giangregorio et al., 2012; Leslie et al., 2018; Schacter and Leslie, 2017). Therefore, it is difficult to predict and prevent fracture in T2D. On the other hand, individuals with IFG do not have different BMD or fracture risk compared to normoglycaemia (Strotmeyer et al., 2005). Thus, our study aimed to investigate FRAX scores with and without BMD for women with normoglycaemia, IFG and diabetes.

2. Materials and methods

2.1. Participants and settings

This study includes data from the Geelong Osteoporosis Study (GOS) which involves residents from the Barwon Statistical Division (BSD). This region is located in south-eastern Australia including a large, stable population of approximately 280,000 with a large range of socio-economic and cultural settings. The BSD is also representative of the Australian population, making it ideal for epidemiological studies. A detailed description of the study has been published elsewhere (Pasco et al., 2012). At baseline, 1993–1997, an age-stratified sample of women aged ≥ 20 years were selected at random from Commonwealth Electoral Rolls with a participation of 77%. The study was approved by the Barwon Health Human Research Ethics Committee, and written, informed consent was obtained from all participants. Only women aged 40–90 years (*n* = 1052) were included in this study because FRAX is not calibrated for use outside this range. A further 486 women were excluded because of the indeterminate glycaemia status or insufficient information to calculate a FRAX score. Thus, 566 women were eligible for baseline analysis. The women who were excluded from this analysis were younger, were more likely to have sustained a previous fracture and were less likely to have secondary osteoporosis. The excluded women who had sufficient data to determine glycaemic status (*n* = 207) were more likely to have normoglycaemia and less likely to have diabetes compared to the women included in this analysis. No differences in the other variables (e.g. weight, height, smoking, alcohol

consumption) were observed. The Australian version of FRAX (FRAX (Aus)) was used to calculate 10-year probabilities of major osteoporotic (MOF) and hip fracture, with and without BMD, resulting in four FRAX scores per participant: 1) MOF (clinical spine, wrist, hip or proximal humerus) with BMD; 2) MOF without BMD; 3) hip fracture with BMD and 4) hip fracture without BMD. Kruskal-Wallis test for non-parametric data was used to examine differences between the three glycaemia groups.

2.2. FRAX risk factors and glycaemia status

Femoral neck measurements were performed by dual energy x-ray absorptiometry (DXA, DPX-L, Madison, WI, USA) and used to calculate BMD (g/cm^2). Weight and height were measured to the nearest ± 0.1 kg and ± 0.1 cm, respectively, and BMI was calculated as weight/height^2 (kg/m^2). Information on fractures that occurred before recruitment was obtained by self-report. Radiological reports from the medical imaging centres in the BSD region were used to identify post-recruitment fractures. A parental history of hip fracture was obtained through self-reported questionnaire. Current smoking (yes/no) was defined at the time of assessment; ex-smokers were considered as non-smokers. Alcohol consumption was recorded as yes/no; either consuming ≥ 3 standard drinks of alcohol daily or < 3 drinks. According to the FRAX (Aus) guidelines, a single standard alcohol drink is equivalent to: a glass of beer (285 mL), a single measure of spirits (30 mL), or a medium-sized glass of wine (120 mL).

The use of oral glucocorticoids and presence of secondary osteoporosis (insulin dependent diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, premature menopause (before age 45 years), malabsorption or chronic liver disease) information were all collected by self-report. We could not determine chronic malnutrition for the participants in this study, therefore we considered malnourished as BMI ≤ 18.5 (underweight category).

Venous blood samples were collected at baseline after an overnight fast. Fasting plasma glucose (FPG) was measured using an adaptation of the hexokinase-glucose-6-phosphate dehydrogenase method (Kunst et al., 1984). Blood samples were collected in sodium fluoride tubes by the major pathology centre in the region and glucose measurement was completed soon after blood collection. There was no long term storage of blood samples before measurements. Glycaemia status was defined according to the 2003 ADA (American Diabetes Association) diagnostic criteria (Genuth et al., 2003), based on a single glucose measurement. Diabetes was classified if FPG ≥ 7.0 mmol/L (126 mg/dL), self-reporting diabetes, or use of antihyperglycaemic agents (antihyperglycaemic medication use referred to medications taken regularly and currently at baseline). IFG was considered present if FPG level was between 5.5 and 6.9 mmol/L (100–125 mg/dL). Approximately half of women classified as having diabetes were categorised using multiple criteria including FPG and self-report (14.9%), self-report and medication use (20.9%), and all three criteria (self-report and medication and glucose; 14.9%). Glucose only and self-report alone were used to categorise 22.4% and 26.9% of women with diabetes, respectively.

2.3. Fracture ascertainment

Major osteoporotic fractures (hip, clinical spine, forearm and wrist) occurring over the 10 years following baseline were ascertained through examination of radiological reports. High trauma and pathological fractures were excluded. The predicted number of fractures by each FRAX score was determined by multiplying the absolute risk by the proportion of years followed up (participants were censored at date of death). The difference between the total predicted and observed number of fractures was assessed with a chi-squared test.

Table 1

Descriptive characteristics of women at baseline stratified by glycaemic status (normoglycaemia, impaired fasting glucose (IFG), and diabetes). Data are shown as median (interquartile range) or n (%).

Variables	Normoglycaemia $N = 252$	IFG $N = 247$	Diabetes $N = 67$	p value
Age (yr)	64.0 (56.0–72.0)	68.0 (59.0–72.0)	71.0 (62.0–72.0)	**0.003**
Weight (kg)	66.8 (57.3–72.8)	69.8 (60.5–78.3)	72.0 (59.6–81.5)	**0.003**
Height (cm)	159.5 (155–163.7)	159.2 (155.0–163.1)	156.6 (153.0–161.1)	**0.003**
BMI (kg/m^2)	26.2 (23.1–28.7)	27.5 (24.1–30.7)	29.3 (25.5–32.9)	**< 0.001**
Previous fracture	55 (21.8)	31 (12.6)	15 (22.4)	**0.015**
Parent fracture	21 (8.3)	17 (6.8)	4 (6.0)	0.735
Current smoke	23 (9.1)	25 (10.1)	10 (14.9)	0.379
Glucocorticoids	8 (3.2)	5 (2.0)	3 (4.5)	0.508
Rheumatoid arthritis	27 (10.7)	38 (15.4)	15 (22.4)	**0.039**
Sec Osteo[b]	45 (17.9)	43 (17.4)	15 (22.4)	0.633
Alcohol	0 (0.8)	6 (2.4)	0 (0.0)	[a]
BMDf0 (g/cm^2)	0.842 (0.745–0.924)	0.858 (0.752–0.949)	0.865 (0.751–0.983)	0.386

BMDf0 = femoral neck bone mineral density.

Bold text indicates significant differences between groups.

[a] Too few participants to perform statistics analysis

[b] Secondary osteoporosis (Sec Osteo) = (insulin dependent diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, premature menopause (before age 45 years), malabsorption or chronic liver disease).

3. Results

3.1. Cross-sectional baseline data

Among 566 women, there were 252 (44.5%) with normoglycaemia, 247 (43.6%) with IFG and 67 (11.8%) with diabetes. The descriptive statistics for these women are presented in Table 1.

Women with diabetes were older, shorter and heavier than those with IFG and those with normoglycaemia. The presence of rheumatoid arthritis was higher in the diabetes group compared to the other two groups. Presence of prior fracture was lower in IFG compared to the diabetes and normoglycaemia groups. Other variables were similar between the three groups.

3.2. FRAX scores without BMD

Median FRAX scores for the three glycaemia groups are shown in Table 2. For MOF FRAX calculated without BMD, women with diabetes had a trend towards a higher median score (interquartile range (IQR)) (7.1, IQR 2.7–12.0) compared to normoglycaemia (4.3, IQR 1.9–9.9) and IFG (5.1, IQR 2.2–9.6) ($p = 0.053$). A similar pattern was observed for hip FRAX without BMD; diabetes had a higher score (2.5, IQR 0.6–4.3) than normoglycaemia (1.2, IQR 0.3–4.1) and IFG (1.3, IQR 0.3–4.1) ($p = 0.075$).

3.3. FRAX scores with BMD

When BMD was added to FRAX, there were no differences detected between the glycaemia groups. For MOF-FRAX with BMD, median

Table 2

FRAX score with and without bone mineral density (BMD) according to glycaemia status (normoglycaemia, impaired fasting glucose (IFG), and diabetes).

	Normoglycaemia $N = 252$	IFG $N = 247$	Diabetes $N = 67$	p value
MOF FRAX				
Without BMD	4.3 (1.9–9.9)	5.1 (2.2–9.6)	7.1 (2.7–12.0)	0.053
With BMD	3.7 (1.9–8.0)	4.3 (2.2–8.1)	5.3 (2.7–9.4)	0.119
Hip FRAX				
Without BMD	1.2 (0.3–4.1)	1.3 (0.3–4.1)	2.5 (0.6–4.3)	0.075
With BMD	0.6 (0.2–2.5)	0.8 (0.2–2.7)	1.0 (0.3–3.0)	0.410

MOF = major osteoporotic fracture.

scores were 3.7 (IQR 1.9–8.0), 4.3 (IQR 2.2–8.1) and 5.3 (IQR 2.7–9.4) for normoglycaemia, IFG and diabetes, respectively ($p = 0.119$). Hip FRAX scores for women with normoglycaemia, IFG and diabetes were, 0.6 (IQR 0.2–2.5), 0.8 (IQR 0.2–2.7) and 1.0 (IQR 0.3–3.0), respectively ($p = 0.410$).

3.4. Predicted and observed number of fractures

Table 3 shows the number of fractures predicted by FRAX, compared to the number of fractures actually observed. MOFs were underestimated for women with normoglycaemia and IFG by FRAX without BMD, 15 predicted vs 28 observed, $p = 0.038$ and 16 predicted vs 31 observed, $p = 0.021$ respectively. FRAX with BMD increased the underestimation of MOFs for both normoglycaemia and IFG, 13 predicted vs 28 observed, $p = 0.015$ and 13 predicted vs 31 observed, $p = 0.004$, respectively. There was a trend for MOF and hip fractures to be underestimated for women with diabetes using FRAX with BMD, MOF: 4 predicted vs 11 observed, $p = 0.055$, hip: 1 predicted vs 6 observed, $p = 0.052$.

4. Discussion

This study shows that FRAX without BMD tended to be different

Table 3

Number of fractures predicted by FRAX with and without bone mineral density and observed number of fractures, stratified by glycaemia status.

	Predicted	Observed	P value
Normoglycaemia			
MOF without BMD	15	28	**0.038**
MOF BMD	13	28	**0.015**
HIP without BMD	6	6	1.000
HIP BMD	4	6	0.523
Impaired fasting glucose			
MOF without BMD	16	31	**0.021**
MOF BMD	13	31	**0.004**
HIP without BMD	7	7	1.000
HIP BMD	5	7	0.559
Diabetes			
MOF without BMD	5	11	0.110
MOF BMD	4	11	0.055
HIP without BMD	2	6	0.145
HIP BMD	1	6	0.052

MOF = major osteoporotic fracture.

BMD = bone mineral density.

Bold text indicates significant differences between groups.

between the glycaemia groups, while the addition of BMD attenuated the observed inter-group differences in FRAX scores. FRAX with BMD underestimated fractures in the normoglycaemia and IFG groups. There was a trend for fractures to be underestimated by FRAX with BMD in the diabetes group. Putative reasons for increased fracture risk in T2D have been published in several reviews (Ferrari et al., 2018; Jiao et al., 2015; Russo et al., 2016; Shanbhogue et al., 2016; Wei and Karsenty, 2015; Yamaguchi and Sugimoto, 2011) and include direct effect of hyperglycaemia on bone that may cause hypercalciuria, accumulation of advanced glycation end products (AGEs) in the collagen fibres which may be responsible for bone structure impairment, decrease of insulin like growth factors-I and plasma insulin, low level of osteocalcin (Wei and Karsenty, 2015), lower bone turnover (Holloway-Kew et al., 2019) and an impaired vasculature (Ackermann and Hart, 2013). Moreover, patients with diabetes may develop peripheral neuropathy (Schwartz et al., 2002) and cognitive dysfunction (Munshi et al., 2006), which can impact balance and consequently result in an increased risk of falls and falls-related-fractures.

The impact of IFG on fracture risk is still unclear. There are few studies investigating this group. One study, showed no differences in fracture risk for participants with IFG (RR 1.34; 95% CI (0.67–2.67)) compared to those with normal blood glucose level (Strotmeyer et al., 2005). There are studies that have previously reported fracture risk for in women with diabetes. For example, a study by Bonds et al. (2006) followed 93,676 postmenopausal women from the Women's Health Initiative Observational Cohort for 7 years and showed that the risk of hip, foot, spine and any fracture was 20% higher in women with T2D (RR 1.20, 95% CI (1.11–1.30)) compared to women without diabetes. A study by Oei et al. (2013) including 4135 participants aged ≥55 years from the Rotterdam Study, which were followed for 12.2 years, showed that poor glycaemic control in T2D is associated with higher fracture risk compared to those with adequate blood glucose level (HR 1.47, 95% CI (1.12–1.92)) or those without diabetes (HR 1.62, 95% CI (1.09–2.40)). This increase in fracture risk was observed despite normal or higher femoral neck BMD in those with poor glycaemic control compared to adequate blood glucose level (0.89 vs 0.88, $p = 0.26$) or those without diabetes (0.89 vs 0.86, $p < 0.05$). In another study by de Liefde et al. (2005), 4878 women from also the Rotterdam study were followed for average period of 6.8 years and it was shown that participants with T2D had increased nonvertebral fracture risk (HR 1.28, 95% CI (0.92–1.77)), despite higher femoral neck and lumbar spine BMD. Strotmeyer et al. (2005) have also reported that the presence of diabetes is associated with higher fracture risk (RR 1.64; 95% CI 1.07–2.51) compared to the absence of diabetes, even after adjustment for hip BMD. In addition, in a study by Majumdar et al. (2016) including 48,938 women ($n = 8840$ with T2D, aged ≥40 years) followed over seven years, showed that duration longer than 10 years of diabetes was associated with a 30% higher risk of MOF. It was also shown that diabetes increased hip fracture risk, regardless of duration of disease; HR 1.54 (95% CI 1.19–1.99) for <5 years and HR 1.94 (95% CI 1.54–2.44) for >10 years. Additionally, FRAX significantly underestimated fracture risk for MOF and hip fracture, similar to what we report in our study.

Our findings are consistent with some other recent studies reporting that FRAX underestimates fracture risk in patients with T2D (Giangregorio et al., 2012; Schwartz et al., 2011). Analysing three prospective observational studies, which included data from 9449 women ($n = 770$ with T2D), Schwartz et al. (2011) reported that FRAX with BMD under-predicted fracture risk in patients with diabetes. Another study with 36,730 women ($n = 3054$ with T2D) reported that diabetes was a predictor for MOF and hip fracture risk. However, FRAX with BMD underestimated MOF and hip fracture risk in subjects with diabetes (Giangregorio et al., 2012).

Whether T2D should be included as a FRAX variable has been debated. Type 1 diabetes (T1D) decreases bone density and it is considered as a cause of secondary osteoporosis in the FRAX model. T2D increases fracture risk but it is independent of BMD, and FRAX does not capture this increased fracture risk. However, there are several reasons why incorporating T2D into FRAX is not feasible (Leslie et al., 2012). One is that medication use in diabetes can modify fracture risk (Meier et al., 2016), which would also need to be taken into account. Thiazolidinediones have been shown to directly increase fracture risk whereas other antihyperglycemic agents may increase fracture risk through hypoglycaemia mechanisms. Additionally, there are not sufficient international studies that can provide data for incorporation of T2D into FRAX. It has been shown that the impact of diabetes as risk factor for fracture is not consistent for different countries, thus, further data will be needed. A further complication is that T2D also increases the competing risk of mortality. One other problem with incorporating T2D into FRAX is that T2D is not independent of other variables in the model, particularly age and body composition (Giangregorio et al., 2012; Vestergaard, 2007). Our data indicate an imbalance in age, adiposity and exposure to oral glucocorticoids according to glycaemic status and these could all impact on the FRAX probabilities. More research will be needed to determine how T2D interacts with other FRAX variables in different populations.

Some suggestions for improving FRAX fracture risk predictions for individuals with T2D have been made by Schacter and Leslie (2017) and Leslie et al. (2018), such as using the rheumatoid arthritis input as a proxy for T2D, adding lumbar spine TBS or altering hip BMD T-score (lower by 0.5 units), and increasing the age input for FRAX by 10 years for patients with diabetes. Leslie et al. (2018) compared these four suggested methods using data from the Manitoba cohort study, which included 44,543 patients, aged ≥40 years, of which 4136 had diabetes. They found that all of the methods were better than making no attempt to adjust the FRAX scores, however no single one was superior. These adjustments can somewhat counteract underestimation of fracture risk in T2D by FRAX.

In addition to this, Ferrari et al. (2018) have proposed an algorithm to determine fracture risk in people with T2D, which includes assessing clinical risk factors, performing DXA measurements, ascertaining prevalent and incident fractures and calculating FRAX scores. In this algorithm, it is suggested that the FRAX scores are adjusted for diabetes using methods described by Leslie et al. (2018). Based on our work we also suggest giving consideration to using FRAX scores without BMD to improve assessment of fracture risk in people with T2D.

Our study has some strengths and limitations. A major strength is that the participants were randomly selected and thus are representative of the general population. Our study also included a wide age range. We also used a robust method for ascertaining diabetes, which combined a FPG measurement, self-report, and medication use. However, we acknowledge that there are some limitations to our study. We were unable to distinguish between type 1 diabetes, type 2 diabetes and secondary diabetes that might have differing effects on fracture risk. Additionally, the duration of diabetes was not known, thus there may not have been sufficient time prior to baseline ascertainment of diabetes status for effects upon bone to manifest. This could explain the lack of difference for prior fractures observed between glycaemia groups; indeed we have observed a higher rate of incident fractures in the GOS cohort after a median follow-up of 13.7 years (de Abreu et al., 2019). We also had a small sample size and a small number of fractures, particularly in the diabetes group, which would have limited the power of some analyses. Our study involved women only and the majority was white (99%), and our results may not be generalisable to other populations. The women who participated at baseline but who were excluded from the study due to insufficient information to classify diabetes status differed from those who were included in the study. Finally, we did rely on some self-reported data such as medication use, smoking, alcohol consumption, but it is important to note that most of our analyses were based on objective measures.

5. Conclusion

We conclude that women with diabetes tended to have a higher FRAX score for both MOF and hip fractures when BMD was not included. However, when BMD was included, the differences were attenuated. The results of this study concur with previous observations that fracture risk is higher in individuals with diabetes, despite a higher or normal BMD. Fractures in diabetes tended to be underestimated by FRAX with BMD. This suggests that FRAX calculations including BMD may not be accurate for estimating fractures in those with diabetes.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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