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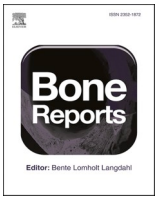

The practicality of using bone impact microindentation in a population-based study of women: A Geelong-Osteoporosis Study

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ABSTRACT

Impact microindentation (IMI) is a minimally invasive technique that allows the assessment of bone material strength index (BMSi) in vivo, by measuring the depth of a micron-sized, spherical tip into cortical bone that is then indexed to the depth of the tip into a reference material. In this study, we aimed to assess the practicality of its application in 99 women aged 42-84 yr from the Geelong Osteoporosis Study. Impact microindentation was performed in the mid-shaft of the right tibia using the OsteoProbe. Immediately following measurement, each participant was requested to rate on a Visual Analogue Scale [0−10] the level of discomfort anticipated and experienced, any initial reluctance towards the measurement and whether they were willing to repeat the measurement. Of 99 potential participants who attended this assessment phase, 55 underwent IMI measurement. Reasons for non-measurement in 44 women were existing skin conditions (n = 8, 18.2 %) and excessive soft tissue around mid-tibial region (n = 32, 72.2 %). An additional four (9.1 %) participants did not provide any reasons for declining. For 55 participants who had underwent IMI, the expectation for pain when briefed about the procedure was low (2.28 ± 2.39), as was pain experienced during the measurement (0.72 ± 1.58). Participants were not reluctant to undergo the measurement (0.83 ± 1.67), and all indicated a willingness to repeat the measurement. Results of this study showed that the IMI technique is well tolerated and accepted by women participating in the Geelong Osteoporosis Study, suggesting that the technique shows promise in a research or clinical setting.

1. Introduction

Fracture risk assessment constitutes a significant challenge in clinical practice. Current techniques for the evaluation of bone and determination of fracture risk include measurement of bone density using dual energy x-ray absorptiometry (DXA) (Stone et al., 2003), peripheral quantitative technology (pQCT) (Engelke et al., 2008) and the assessment of clinical risk factors using the FRAX algorithm (Watts, 2011). Although low DXA-derived areal bone mineral density (BMD) is associated with an increased fracture risk, there are many individuals who experience fractures despite having normal BMD (Pasco et al., 2006). This suggests that bone strength does not only depend on BMD, but also additional factors such as the architecture at the nano, micro and macro levels and its material composition (Seeman and Delmas, 2006). Thus far, tools for the evaluation of these other components of bone include bone histomorphometry using bone biopsy samples and nano-indentation techniques to evaluate the material properties of bone (Petar et al., 2015). However, there is a dearth of in vivo information on the influence of altered bone material properties to bone strength in humans as, until recently, there were no methods available to evaluate the biomechanical properties of bone in situ.

A relatively novel technique, impact microindentation (IMI), has shown promise in the direct assessment of the mechanical properties of cortical bone in humans, opening a new dimension in the assessment of

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bone strength (Bridges et al., 2012). The technique involves the use of a handheld device, the OsteoProbe, to impart a single impact load to the surface of the bone. When the probe is driven into the bone surface, the resistance of bone tissue to a mechanical challenge, in reference to a calibration material, poly methyl methacrylate, is measured as Bone Material Strength index (BMSi) (Randall et al., 2013). A greater indentation depth reflects less resistance to propagation of microcracks, thus, a lower BMSi. There is evidence that IMI can differentiate between control groups and those at increased risk for fracture, independent of BMD (Pérez-Sáez et al., 2017; Farr et al., 2014; Malgo et al., 2017; Nogues et al., 2017; Mellibovsky et al., 2015). Notwithstanding, an improved understanding of the limitations of the OsteoProbe is critical towards the successful utilisation of the device in the advancement of fracture risk assessment in clinical practice. Although a minimally invasive technique with micrometre-level indentations on the tibia following administration of local anaesthetic, one reasonable concern is the tolerability of the technique in a research setting. The contraindications for performing the procedure also pose a valid concern within the research community. It is crucial to know if participants would be willing to undergo the procedure because if it is not well accepted, then it cannot be successful in providing information for regular assessments of bone health or be routinely used in a clinical environment. This is important because it would otherwise be used irregularly, perhaps only for specific patients and provide much less benefit on a population level, since very few people would have the measurement completed.

We have previously reported the feasibility of using IMI in men enrolled in the Geelong Osteoporosis Study (Rufus-Membere et al., n.d.). In this study, we assessed its practicality in women from this cohort.

2. Methods

2.1. Study population

This was a cross-sectional study including women from the Geelong Osteoporosis Study, a population-based cohort study situated in a geographically well-defined region in south-eastern Australia, known as the Barwon Statistical Division (Pasco et al., 2012). The female arm of the Geelong Osteoporosis Study commenced in 1993 with recruitment of 1494 women aged 20 to 92 years. An additional sample of women aged 20–29 years was recruited 2006–2008. Participants are reassessed every few years, and data for this cross-sectional analysis were generated from the first 99 women assessed in the current follow-up phase (ages 42–84 years), in 2022 and 2023. All participants returning as part of the GOS 25-year follow-up phase were considered for inclusion in the study. Participants were only excluded if they had an excessive of soft tissue around the mid-tibial region, swelling/oedema, or an existing local skin condition in both right and left legs, or a needle phobia.

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

2.2. Impact microindentation (IMI)

IMI was measured using the OsteoProbe (Active Life Scientific, Inc., Santa Barbara, CA, USA). The procedure was performed by three trained operators (PR-M, KBA and KLH-K) using recommendations published for using the device (Diez-Perez et al., 2016). Prior to the measurement, participants were briefed about the procedure. They were informed that the measurement is a relatively novel technique that assesses the resistance of bone to fractures by inducing microfractures on a small area of the tibia. Additionally, they were told the technique is minimally invasive and would not affect their ability to walk. They were then provided with the opportunity to opt in or out of the procedure. Participants who chose to take part were further assessed by palpation of both their right and left legs to determine their eligibility to have the measurement performed. Using BMI only was not always accurate in differentiating those who could or could not have the measurement performed, due to uneven fat distribution in the human body.

The measurement site was located at the measured mid distance between the distal apex of the patella and the medial malleolus, with the participant in the supine position (Fig. 1A). Following disinfection of the area and local anaesthesia of the skin and periosteum with Lidocaine 2 %, the probe was inserted in the skin until the bone surface was reached. While maintaining probe contact with the bone surface, as well as orienting the probe perpendicular to the tibia surface, the outer housing of the device was slid towards the participant's leg to initiate an indentation. In this study, 7–10 indentations were performed on each participant, of which the first measurement was systematically disregarded. Seven measurements were then performed on a polymethylmethacrylate (PMMA) calibration phantom (Fig. 1B). BMSi was computed by the software system as 100 times the harmonic mean of the indentation distance increase from impact into the PMMA block divided by the average indentation distance from impact into bone (Randall et al., 2013).

Immediately following measurement, each participant was requested to rate their experience on a Visual Analogue Scale (VAS) [0–10], where 0 represents ‘no pain’ or ‘not reluctant’ and 10 represents ‘maximum level of pain’ or ‘extremely reluctant’, in relation to the level of discomfort anticipated, the level of discomfort experienced and their initial reluctance towards the measurement. Each participant was further asked whether they were willing to repeat the measurement. The validity of the VAS has been reported (Chapman et al., 1985; Gallagher et al., 2002).

2.3. Other measures

Height was measured using a Harpenden stadiometer to the nearest 0.1 cm and weight measured using a Bioimpedance Analysis machine to the nearest 0.1 kg. Body mass index (BMI) (kg/m^2) was calculated.

2.4. Statistical analyses

All variables were assessed for normality using a Ryan-Joiner test; age was non-parametric while BMSi, weight, height and BMI were normally distributed. Participants were divided into two groups: those who did and those who did not have IMI performed. The homogeneity of variance in normally distributed confounding variables (height, weight, BMI) was tested between the groups, with only BMI identified as not meeting this assumption (multiple comparisons $p = 0.045$; Levene's test $p = 0.051$). Thus, inter-group differences between participants included and excluded from the analyses were identified using two sample *t*-tests for weight and height, the Welch-corrected t-test for BMI, and the Mann Whitney test for age.

Associations between BMSi and age, weight, height, and body mass index (BMI) were identified using Spearman's correlation. Statistical analyses were performed using Minitab V.17 (State College, Pennsylvania, USA).

3. Results

Of the first 99 potential participants (aged 42 to 84 years) who attended this follow-up phase, 55 underwent IMI measurement. Characteristics of participants who did and did not have IMI performed are shown in Table 1. Further, a Mann-Whitney test revealed no difference in age between participants (median = 67, $n = 55$) and non-participants (median 66, $n = 44$), $p = 0.602$.

Reasons for non-measurement in 44 women were existing skin conditions ($n = 8$), excessive soft tissue around the mid-tibial region ($n = 32$) and four participants did not provide a reason for declining.

For 55 participants who had IMI performed, the expectation for pain when briefed about the procedure was low (2.28 ± 2.39), as was pain experienced during the measurement (0.72 ± 1.58). Participants were not reluctant to undergo the measurement (0.83 ± 1.67), and all

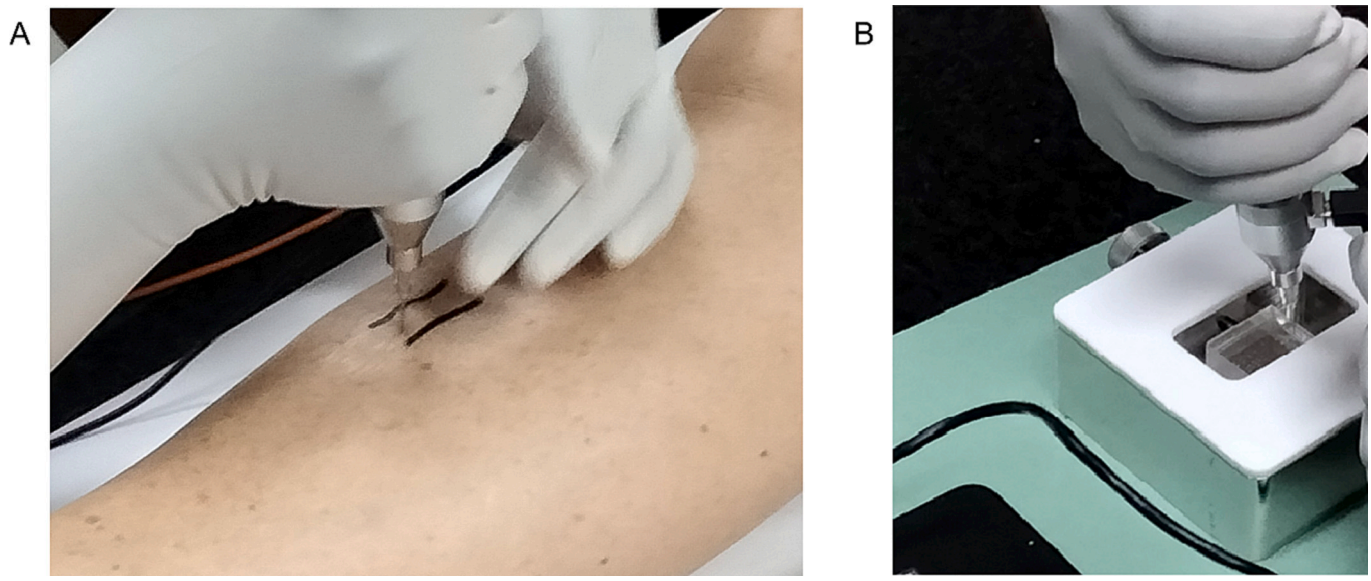

Fig. 1. [A] Positioning of the OsteoProbe on the midshaft of the tibia after the application of a local anaesthetic [B] measurement performed on the polymethylmethacrylate [PMMA] reference phantom.

Table 1
Characteristics of the study participants who did and did not have the IMI measurement performed.

	Yes (n = 55)	No (n = 44)	*P*-value
Height (cm)	161.5 ± 7.5	162.2 ± 6.1	0.527
Weight (kg)	71.2 ± 13.8	85.4 ± 16.9	<0.001
BMI (kg/m^2)	27.2 ± 4.3	32.4 ± 5.8	<0.001

Data shown as mean (±SD).

indicated a willingness to repeat the measurement.

BMSi ranged from 59.4 to 91.7 (mean BMSi ± SD: 75.9 ± 7.4). No associations were observed between BMSi and age ($r = -0.164$, $p = 0.232$), height ($r = -0.038$, $p = 0.784$), weight ($r = -0.182$, $p = 0.184$) or BMI ($r = -0.160$, $p = 0.243$) (Fig. 2A-D).

4. Discussion

We report here that IMI was well tolerated in a population-based sample of women; the expectation for pain was low, as was actual pain experienced. Participants were not reluctant to undergo the measurement, and all indicated willingness to repeat the measurement.

This is promising, particularly as more evidence is emerging on the usefulness of the technique for the overall improvement of assessment of bone fragility. Its effectiveness will depend substantially on how well it is accepted and tolerated by the general population. A valid concern was that the invasiveness of the technique, although minimal, would affect the desire of individuals to undergo the measurement. As compared to our previous report (Rufus-Membere et al., n.d.), the expectation for pain, actual pain experienced, and level of reluctance in this group were slightly higher, noting that the previous report included a much larger participant group. Taken together, these reports should help quell such concerns that the minimally invasive procedure might limit participant and patient involvement in research and/or clinical settings.

Notably, only four participants in this group chose not to partake in the measurement, other exclusions were made based on ineligibility.

Another factor that may influence the tolerability of the technique is reporting of adverse events. To date, studies using the OsteoProbe in over 2000 individuals, have only reported minor complications including a mild allergic reaction to the local anaesthetic (Rozental et al., 2018), and a mild skin infection (Diez-Perez et al., 2016), both of which readily responded to treatment. However, there is a dearth of studies published with a specific focus on the safety and acceptability of the measurement. One study by Schoeb et al. (Manuela et al., 2023) examining the long-term safety and acceptability of IMI technique in patients being investigated from fragility fractures reported the technique was well accepted by all study participants and only three cases of minor adverse events: a small bruise at the indentation site in one patient, and very small hematoma in another two patients. An Investigational Device Exemption (IDE) clinical trial on the safety of the procedure was completed in 2020, with only one reported adverse event (classified by an independent Clinical Events Committee as “mild”), a report of joint pain with a reported pain of 1 out of 10 on the Numeric Rating Scale pain scale (US Library of Medicine, n.d.).

We observed no associations between BMSi and age, height, weight, or BMI in this sample of women. Rudang et al (Rudäng et al., 2016) reported an association between BMSi and weight, but no association with height. In our previous studies in men, BMSi was positively correlated with height (Rufus-Membere et al., 2020), and negatively with BMI (Rufus-Membere et al., 2020; Sundh et al., 2018). However, our present study included a smaller number of participants and we have previously shown that the discrepancy in literature can be partly explained by sample size, age ranges and sampling frames of participants studied (Rufus-Membere et al., 2020).

In this study, BMSi ranged from 59.4 to 91.7, aligning with values reported in a multi-centre international study that indicated that the healthy reference interval for women (aged 25-98y) ranges from 59.8 to 95.2 (Rufus-Membere et al., 2023).

IMI has enabled the clinical measurements of bone material properties which other techniques have not been able to quantify in vivo. Nonetheless, in some studies, its ability to discriminate fracture risk is still uncertain (Rozental et al., 2018; Rudäng et al., 2016; Popp et al., 2019; Raju et al., 2023; Johansson et al., 2018).

IMI is not a measure of bone mass, and reports on the associations between the two are not concordant, suggesting that its optimal clinical value will be achieved in combination with DXA BMD, particularly in circumstances where BMD does not fully explain fracture propensity (Pasco et al., 2006).

To our knowledge, this is the first study to explore the practicality of utilising the technique in women randomly sampled from the general population. Although there are well-known contraindications for performing the procedure (Diez-Perez et al., 2016), studies have not always

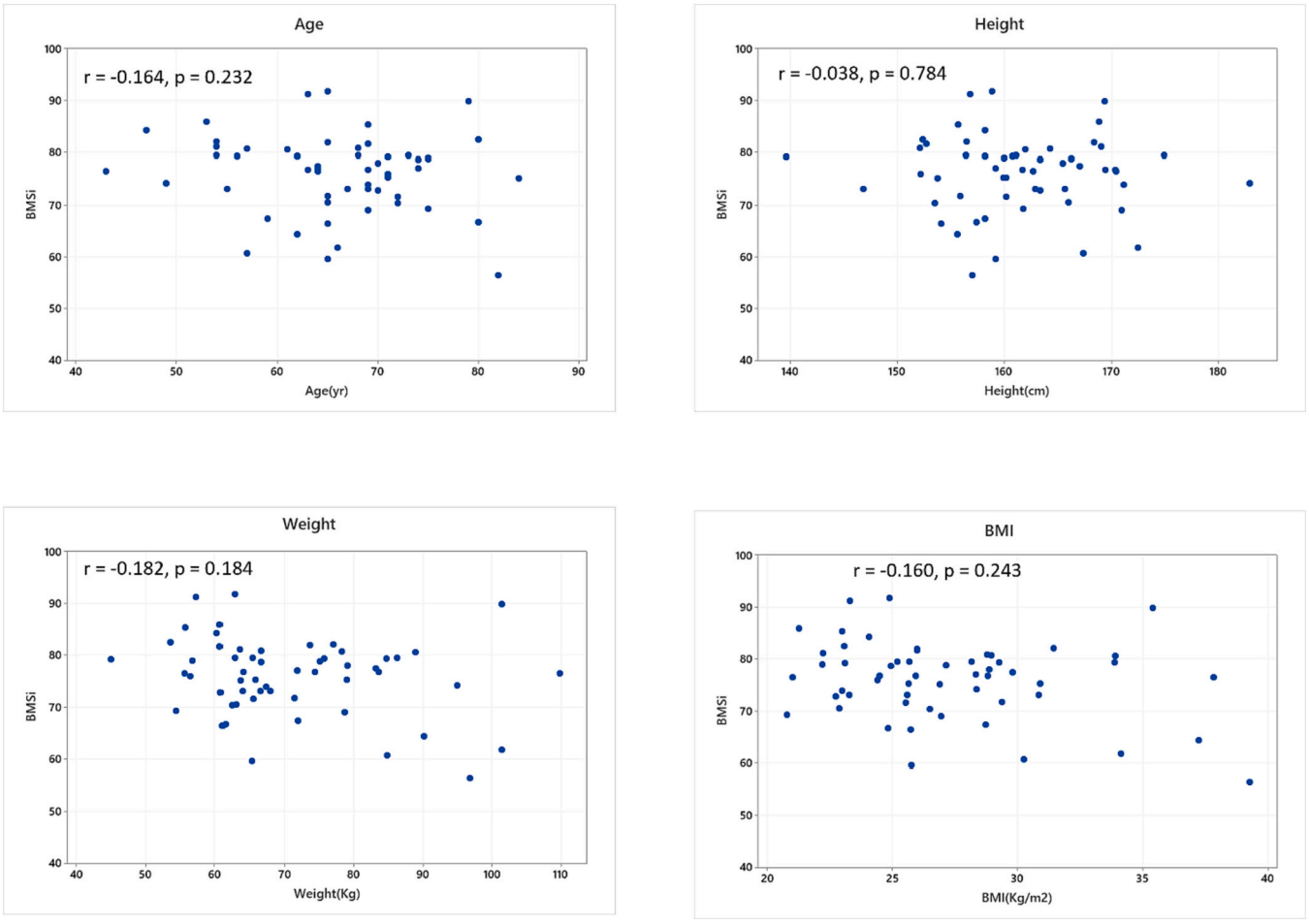

Fig. 2. A-D. Scatterplots showing associations between bone material strength index (BMSi) and (A) age; (B) height; (C) weight and (D) body mass index (BMI).

reported on numbers or reasons for exclusion. This is the only study to document reasons (contraindications as well as participant-centred considerations) that IMI may or may not be successfully performed in women. This is important in understanding crucial improvements needed prior to its introduction in clinical practice, particularly as these women are at risk for osteoporosis and fragility fracture (Henry et al., 2000).

However, exclusions for IMI testing and consequently a small sample size limited our ability to explore associations and any differences in tolerance across age groups, as excessive accumulation of soft tissue at the measurement site was the most common reason for non-participation. This raises the point that perhaps the technique has a practical limitation in very obese women that precludes reliable results and is likely the explanation for Sundh et al.'s report (Sundh et al., 2016) showing an inverse association between subcutaneous fat and BMSi. The thicker the layer of subcutaneous fat, the higher the probability of inducing a measurement error due to a purely mechanical reason. Our previous study in men reported on the reasons for non-participation (Rufus-Membere et al., n.d.), and although this current study includes a smaller sample of women, it is likely that this issue is more common in women. Tackling this challenge is critical to the utilisation of IMI in other research settings and in the clinic. Further, the authors acknowledge that as the participants in this study are already part of the long-running Geelong Osteoporosis Study, they are much more likely to consent to a related measure. However, each participant was provided the opportunity to decline involvement.

In summary, the present study demonstrates that IMI is well tolerated and accepted in a population-based sample of women and may have potential as a complementary tool to current bone measurement techniques in the assessment of fracture risk. Notwithstanding, improvement in the limitation associated with excessive soft tissue at the tibial site is critical towards the effective utilisation of the device in the advancement of fracture risk assessment in clinical practice, particularly as the risk of fracture is higher in those with high BMI (Giuseppe et al., 2021).

CRediT authorship contribution statement

Pamela Rufus-Membere: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kara B. Anderson:** Writing – review & editing, Methodology, Investigation. **Kara L. Holloway-Kew:** Writing – review & editing, Methodology, Investigation, Data curation. **Jacob W. Harland:** Writing – review & editing, Methodology, Investigation. **Adolfo Diez-Perez:** Writing – review & editing, Validation, Methodology. **Mark A. Kotowicz:** Writing – review & editing, Investigation, Funding acquisition. **Julie A. Pasco:** Writing – review & editing, Supervision, Methodology, Funding acquisition.

Declaration of competing interest

AD-P owns shares of Active Life Scientific, Inc., the manufacturer of the RPI device. MAK and JAP are recipients of grants from the National Health and Medical Research Council (NHMRC) Australia, and KLH-K, MAK and JAP are recipients of grants from Amgen-GSK OA-ANZBMS and Amgen Australia. PR-M, KA and JH have no conflicts to declare.

Data availability

Data will be made available on request.

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