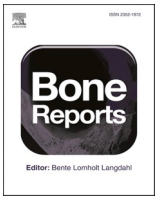
Bone Reports 19 (2023) 101727

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr



For older individuals there is greater variance in low mean Bone Material Strength Index values obtained with the OsteoProbe

Kara B. Anderson [a,*], Pamela Rufus-Membere [a], Jacob W. Harland [a], Julie A. Pasco [a,b,c,d], Adolfo Diez-Perez [e], Mark A. Kotowicz [a,b,c], Kara L. Holloway-Kew [a]

[a] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Geelong, Australia
[b] Barwon Health, Geelong, Australia
[c] Department of Medicine, The University of Melbourne – Western Health, St Albans, Australia
[d] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
[e] Barcelona-Department of Internal Medicine, Hospital del Mar-IMIM, Autonomous University of Barcelona and CIBERFES, Instituto Carlos III, Spain

ARTICLE INFO

Keywords:
Impact microindentation
Bone Material Strength Index
Men
Women

ABSTRACT

Purpose: Bone Material Strength Index (BMSi) quantifies the resistance of bone to a specified force in vivo at the mid tibia using impact microindentation (IMI). Anecdotal evidence suggests that within-participant variance in BMSi may be associated with the individual's mean BMSi. This study aimed to investigate associations between mean and variance of IMI measures in a population-based study.

Methods: Participants were men ($n = 420$) and women ($n = 55$) from the Geelong Osteoporosis Study who underwent BMSi measurement using the OsteoProbe at recent follow-up phases (men 2016–2022; women 2022–2023). Median age was 63.7 yr (IQR 53.0–71.8). BMSi standard deviation was skewed and therefore natural log transformed (referred to as ln-SD). Linear regression models were developed with ln-SD as the dependent variable and mean BMSi as the independent variable adjusting for sex, age, height and weight.

Results: In unadjusted models, greater BMSi was associated with lower ln-SD ($\beta = -1.58$, $p = 0.042$). This association was sustained after adjustment ($p = 0.013$), and an interaction between BMSi and age was observed ($p = 0.004$). In those aged 63.7 yr and over (median age), mean BMSi was inversely associated with ln-SD ($\beta = -3.22$, $p = 0.002$). Sex was not identified as an effect modifier. In younger participants, no BMSi*ln-SD association was observed.

Conclusion: In older men and women, there was greater variance in low BMSi values. This suggests that standard deviation of the BMSi measure may provide additional information in the assessment of bone health and is worthy of further investigation.

Mini abstract: In older men and women, greater variance is observed when BMSi values are low, reflecting potential variation in the bone surface.

1. Introduction

Current techniques for assessing bone health focus on the amount and distribution of bone in a given area. A new technique, known as impact microindentation (IMI), captures a different component of bone health, resistance to indentation (Bridges et al., 2012). The OsteoProbe is a handheld device that measures the indentation distance of bone and compares it to the indentation distance of a reference material, whereby the ratio of these two distances is expressed as a unitless value: Bone Material Strength Index (BMSi) (Randall et al., 2013). Data suggest that BMSi measured using the OsteoProbe may be useful in assessments of fracture risk, both independently and in conjunction with other measures of bone (Rufus-Membere et al., 2019). Case-control studies of participants with and without fracture report varying results (Malgo et al., 2017a; Duarte Sosa et al., 2015; Rudäng et al., 2016), yet prospective fracture risk has yet to be clearly elucidated.

During IMI measurements using the OsteoProbe, which has a spherical micron-sized tip, approximately eight to ten indentations are

* Corresponding author at: Epi-Centre for Healthy Ageing (ECHA), IMPACT Institute, School of Medicine, Deakin University, Health Education and Research Building, Level 3 (Barwon Health), PO Box 281, Geelong, VIC 3220, Australia.
E-mail address: k.anderson@deakin.edu.au (K.B. Anderson).

https://doi.org/10.1016/j.bonr.2023.101727
Received 9 November 2023; Accepted 13 November 2023
Available online 14 November 2023

made, moving approximately 2 mm across the bone surface between each indentation (Diez-Perez et al., 2016). The average value of all valid indentations is calculated and compared to indentations on the reference block to provide the final BMSi score. Throughout this paper, this is referred to as the mean BMSi, relating to an individual participant. The standard deviation of valid indentations is also reported by the software.

Anecdotal evidence from experienced OsteoProbe operators suggests that within-participant variance in BMSi may be associated with the mean individual level BMSi. That is, when a participant is measured using the OsteoProbe and returns a low mean BMSi, the variability in individual indentation values appears to be higher.

This study aimed to investigate associations between mean and variance of BMSi in a population-based study to further explore this anecdotal evidence.

2. Methods

2.1. Participants

Participants for this analysis were drawn from the Geelong Osteoporosis Study (Pasco et al., 2012), a cohort study located in south-eastern Australia. Participants were initially recruited using random sampling from the Australian electoral roll, which provides a near comprehensive sampling frame for Australian citizens. IMI was measured at the most recent follow-up phase for men (2016–2022, $n = 420$) and in the first wave of assessments for the current follow up phase for women (2022–2023, $n = 55$).

2.1.1. Impact Microindentation (IMI)

IMI measurements to determine BMSi were undertaken using a previously recommended procedure (Diez-Perez et al., 2016) for the OsteoProbe (Active Life Technologies, Santa Barbara, CA, USA). Measurements were performed on the midpoint of the tibia after application of local anaesthetic. The first for each participant was systematically discarded due to an established artefact of insufficient penetration through the periosteum. At least eight subsequent measurements were performed with the tip being moved approximately 2 mm each time and removing measurements that appeared outside the established "green zone" area indicated by the software, or when abnormal "texture" was observed by the operator. The authors have reported previously that participants experience minimal discomfort during the procedure (Rufus-Membere et al., 2018).

Over the duration of data collection, there were four trained operators performing IMI measurements, however most (85.3 %) were undertaken by one operator (PR-M). The same instrument was used across the duration of the study. Average intra-rater agreement across the four operators was calculated as 2.4 %; using a purpose-made calibration material, each operator independently completed three sets of 10 indentations which were used to calculate coefficients of variation by operator, and then averaged across all operators. The calculations were undertaken by an independent researcher blinded to operator identity.

2.1.2. Potential confounders

Weight was measured to the nearest 0.1 kg using electronic scales and height measured to the nearest 0.01 cm using a Harpenden stadiometer. Body mass index (BMI) was calculated as weight(kg)/height $(m)^2$. Diabetes was classified as either self-reported diabetes, current use of an antihyperglycaemic medication, or a fasting plasma glucose greater than or equal to 7.0 mmol/L. Prior low trauma fractures other than digits or skull were self-reported and verified where possible via radiological reports.

2.2. Statistics

Participant characteristics are described using means and SD or median and interquartile range (IQR) as appropriate based on the normality of data. The distribution of SD of individual participant BMSi variables was skewed, and therefore natural log transformed (ln-SD). Multivariable linear regression modelling was performed considering ln-SD as the independent variable and mean BMSi as the dependent variable, adjusting for sex, age, BMI, diabetes, and prior fracture. To explore interactions with age, a dichotomous age variable was created with the median age of the sample used as a cut-point. Additionally, the ratio of BMSi-SD/mean BMSi was calculated and plotted against age. Analyses were completed using Stata (Version 17. StataCorp. 2017. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

3. Results

Table 1 shows the participant characteristics. Women were older, weighed less and were shorter than male counterparts, however there was no sex-difference in BMI. Predictably, mean BMSi was higher in men, but there was no difference in BMSi-SD between groups.

In unadjusted models, greater mean BMSi was associated with lower ln-SD ($\beta = -1.58$, $p = 0.042$). This association was sustained after adjustment for age, sex and BMI ($p = 0.013$). However, an interaction was observed in this model between ln-SD and age ($p = 0.004$), whereby this association was driven by those of older age. Sex and BMI were not identified as effect modifiers in this model. Further adjustment for diabetes and prior fracture was performed, these were not significant in multivariable regression modelling and were therefore stepwise removed.

A sensitivity analysis excluding those with diabetes produced similar results. Unadjusted models showed that greater mean BMSi was associated with lower ln-SD ($\beta = -1.68$, $p = 0.035$). When adjusted for age, sex and BMI, results persisted ($p = 0.004$) with an interaction observed with age ($p = 0.001$).

To clarify the effect of age on the association between ln-SD and mean BMSi, age-stratified models (adjusted for sex and BMI) revealed that for older participants (age > 63.7 years), BMSi was inversely associated with ln-SD ($\beta = -3.22$, $p = 0.002$). In younger participants, no association was observed ($\beta = 0.61$, $p = 0.548$). Fig. 1 provides a visual depiction of this relationship.

To further elucidate the relationship between BMSi-SD, mean BMSi and age, Fig. 2 plots the ratio of BMSi-SD/mean BMSi against age. It can be observed that among those aged over approximately 75 years, the number of participants with a low ratio (indicating that the SD of the measurement as a percentage of the measurement mean is small) decreases. However, the number of participants aged over 75 years was too small for subgroup analyses to explore this relationship further.

4. Discussion

This study indicated a relationship between the variance of BMSi individual scores within a participant and the overall mean BMSi of that individual, and suggests this relationship may be more important in

Table 1
Participant characteristics by sex. Data presented as mean ± SD, n(%) or median (IQR), as appropriate, with p value presented for difference between groups.

	Men (n = 420)	Women (n = 55)	p value
Age (y)	62.7 (52.0–71.8)	67.4 (62.0–71.2)	0.005
Weight (kg)	81.9 ± 11.4	71.0 ± 13.9	<0.001
Height (cm)	174.6 ± 6.9	161.5 ± 7.5	<0.001
Body Mass Index (kg/m^2)	26.9 ± 3.3	27.2 ± 4.4	0.549
Bone Material Strength Index (BMSi)	82.6 ± 6.9	75.7 ± 7.4	<0.001
BMSi-SD	5.4 (4.2–7.2)	5.8 (4.0–7.9)	0.312
Diabetes (y/n)	47 (13.8)	3 (6.4)	0.156
Prior fracture (y/n)	79 (18.9)	15 (27.3)	0.146

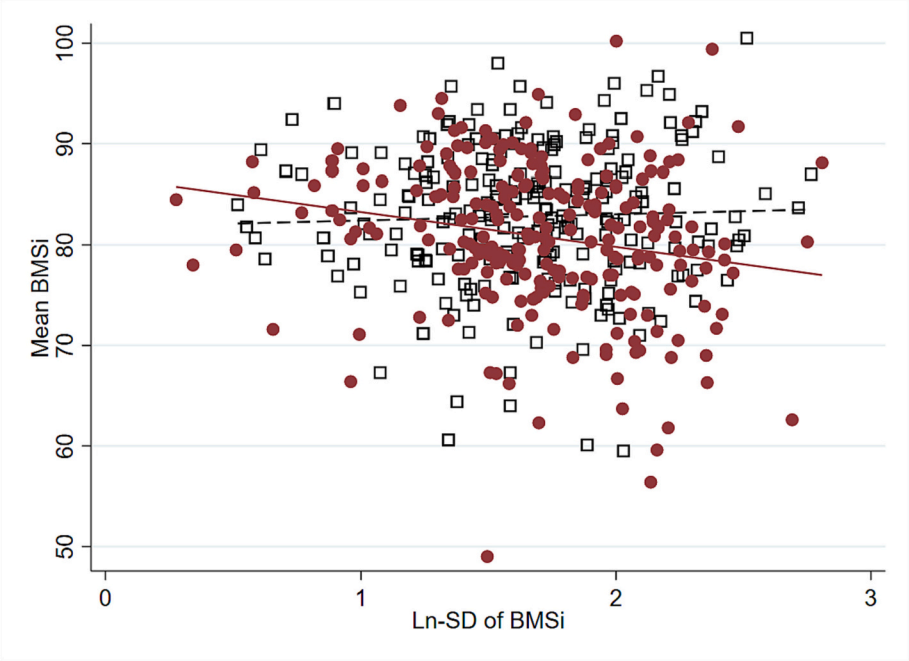


Fig. 1. Mean Bone Material Strength index vs ln-SD, stratified by age (cut-off 63.7 yr). Data for participants in the older age category are marked in red, with the line indicating linear fit. The black square and dashed line indicate the data and linear fit of participants in the younger age category.

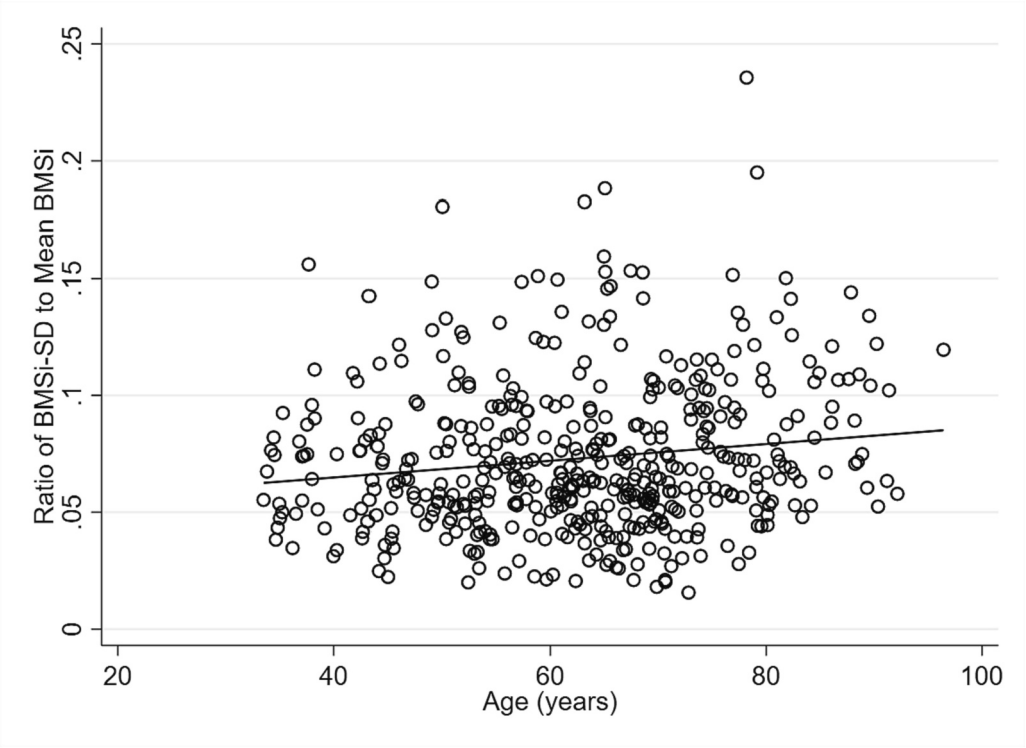


Fig. 2. The ratio of the standard deviation of BMSi over within-participant mean BMSi (BMSi-SD/mean BMSi), plotted versus age in years.

older age. This supports the anecdotal evidence as experienced by our team when assessing participants.

Of relevance to these results, a multi-centre study of BMSi globally reported no association between BMSi and age (Rufus-Membere et al., 2023), however within the Geelong Osteoporosis Study cohort, BMSi was negatively correlated with age in men ($r = -0.152$, $p = 0.002$) (Rufus-Membere et al., 2020). This may be related to the large number of exclusion criteria which were applied in the multi-centre study, for example excluding participants with primary or secondary osteoporosis, or taking any number of drugs related to bone metabolism. In contrast, the Geelong Osteoporosis Study cohort does not apply exclusions on the basis of disease or drug states.

We posit the association between BMSi-SD and mean BMSi may be due to variation in cortical bone toughness which is exacerbated in those

with deteriorating bone health (Wang and Puram, 2004). For example, reduced bone turnover in older age, and in particular the slowing of bone formation, could result in increased cortical porosity (Nirody et al., 2015). Other changes in bone with ageing including reduced collagen cross-linking may also contribute to variation in resistance to indentation across the bone surface (Wang and Puram, 2004).

Research from Rokidi et al. (Rokidi et al., 2020) suggest that BMSi measures distinct mechanical properties of cortical bone, in particular within the first 5 μm from the subperiosteal edge, including mineral content, nanoporosity (an indicator of water content) and bone matrix quality. Variations in these components with ageing may play a role in the observed findings.

A prior study in a small sample of individuals with and without Paget's disease reported that the SD of individual indentations performed on a single participant was higher in those with Paget's disease than those without, despite similar mean BMSi scores (Malgo et al., 2017b). In the current study, although participants were not selected on the basis of disease, those with higher variance across the measure were older and had lower mean BMSi, suggesting poorer bone health. The standard deviation of the measurement on bone may thus be a useful clinical indicator and worthy of further investigation.

Some strengths and limitations of our study should be considered, including that the sample was randomly selected from the general population, and not selected on the basis of disease. Further, most measurements were made by a single operator. Women were under sampled in this analysis, and with the inclusion of a larger group of women, sex related differences may have been observed.

5. Conclusion

Here we report that for older men and women, a lower mean BMSi score is associated with a greater variation in that set of repeated BMSi measurements within that individual. This information suggests that standard deviation of the BMSi measure may provide additional information in the assessment of bone health and is worthy of further investigation.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Barwon Health Human Research Ethics Committee (projects 92/01 and 00/56). Each participant provided informed consent to participate in the study.

CRediT authorship contribution statement

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

Declaration of competing interest

Kara Anderson, Pamela Rufus-Membere, Jacob Harland, Julie Pasco, Mark Kotowicz and Kara Holloway-Kew have no competing interests to declare. Adolfo Diez-Perez owns shares of Active Life Scientific, Inc., the manufacturer of the reference point indentation device.

Data availability

Data will be made available on request.

Acknowledgements

This study was funded by Amgen Inc. and the National Health and Medical Research Council (Australia). KBA is supported by an Australian Government Research Training Program Scholarship, PR-M by a Deakin University Postgraduate Industry Research Scholarship; JH by a Deakin University Postgraduate Research Scholarship. KLH-K is supported by an Alfred Deakin Postdoctoral Research Fellowship.

References

Bridges, D., Randall, C., Hansma, P.K., 2012. A new device for performing reference point indentation without a reference probe. Rev. Sci. Instrum. 83 https://doi.org/10.1063/1.3693085.

Diez-Perez, A., Bouxsein, M., Eriksen, E., et al., 2016. Technical note: recommendations for a standard procedure to assess cortical bone at the tissue-level in vivo using impact microindentation. Bone Rep. 5, 181–185. https://doi.org/10.1016/j.bonr.2016.07.004.

Duarte Sosa, D., Vilaplana, L., Güerri, R., et al., 2015. Are the high hip fracture rates among Norwegian women explained by impaired bone material properties? J. Bone Miner. Res. 30, 1784–1789. https://doi.org/10.1002/jbmr.2537.

Malgo, F., Hamdy, N., Papapoulos, S., Appelman-Dijkstra, N., 2017a. Bone material strength index as measured by impact microindentation is low in patients with fractures irrespective of fracture site. Osteoporos. Int. 28, 2433–2437. https://doi.org/10.1007/s00198-017-4054-8.

Malgo, F., Hamdy, N.A.T., Papapoulos, S.E., Appelman-Dijkstra, N.M., 2017b. Impact microindentation: consistency of serial measurements and alterations in patients with Paget's disease of the tibia. J. Bone Miner. Res. 32, 2375–2380. https://doi.org/10.1002/jbmr.3239.

Nirody, J.A., Cheng, K.P., Parrish, R.M., et al., 2015. Spatial distribution of intracortical porosity varies across age and sex. Bone 75, 88–95. https://doi.org/10.1016/j.bone.2015.02.006.

Pasco, J.A., Nicholson, G.C., Kotowicz, M.A., 2012. Cohort profile: Geelong osteoporosis study. Int. J. Epidemiol. 41, 1565–1575. https://doi.org/10.1093/ije/dyr148.

Randall, C., Bridges, D., Guerri, R., et al., 2013. Applications of a new handheld reference point indentation instrument measuring bone material strength. J. Med. Device 7, 410051–410056. https://doi.org/10.1115/1.4024829.

Rokidi, S., Bravenboer, N., Gamsjaeger, S., et al., 2020. Impact microindentation assesses subperiosteal bone material properties in humans. Bone 131, 115110. https://doi.org/10.1016/j.bone.2019.115110.

Rudäng, R., Zoulakis, M., Sundh, D., et al., 2016. Bone material strength is associated with areal BMD but not with prevalent fractures in older women. Osteoporos. Int. 27, 1585–1592. https://doi.org/10.1007/s00198-015-3419-0.

Rufus-Membere, P., Holloway-Kew, K.L., Diez-Perez, A., et al., 2018. Feasibility and tolerability of bone impact microindentation testing: a cross-sectional, population-based study in Australia. BMJ Open 8, 1–5. https://doi.org/10.1136/bmjopen-2018-023959.

Rufus-Membere, P., Holloway-Kew, K.L., Diez-Perez, A., et al., 2019. Associations between bone impact microindentation and clinical risk factors for fracture. Endocrinology 160, 2143–2150. https://doi.org/10.1210/en.2019-00415.

Rufus-Membere, P., Holloway-Kew, K.L., Kotowicz, M.A., et al., 2020. Normative data for impact microindentation for Australian men: cross-sectional data from the Geelong osteoporosis study. JBMR Plus 4, 4–9. https://doi.org/10.1002/jbm4.10384.

Rufus-Membere, P., Holloway-Kew, K.L., Diez-Perez, A., et al., 2023. Reference intervals for bone impact microindentation in healthy adults: a multi-centre international study. Calcif. Tissue Int. 112, 338–349. https://doi.org/10.1007/s00223-022-01047-y.

Wang, X., Puram, S., 2004. The toughness of cortical bone and its relationship with age. Ann. Biomed. Eng. 32, 123–135. https://doi.org/10.1023/B:ABME.0000007797.92559.5e.