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Clinical Research Article

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Associations between Bone Material Strength Index, Calcaneal Quantitative Ultrasound, and Bone Mineral Density in Men

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Abbreviations: 25OHD, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; BMSi, bone material strength index; BUA, broadband ultrasound attenuation; CKD, chronic kidney disease; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; IMI, impact micro-indentation; QUS, quantitative ultrasound; SOS, speed of sound; SI, stiffness index; T2DM, type 2 diabetes mellitus; TBS, trabecular bone score; UD, ultradistal.

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Abstract

Objectives: Impact micro-indentation (IMI) measures bone material strength index (BMSi) in vivo. This study investigated how IMI is associated with calcaneal quantitative ultrasound and bone densitometry parameters in men.

Methods: BMSi was measured on the tibial plateau using the OsteoProbe in 377 men (age 33-96 years) from the Geelong Osteoporosis Study. Broadband ultrasound attenuation (BUA), speed of sound (SOS), and stiffness index (SI) were assessed at the calcaneus using an ultrasonometer. Areal BMD was measured at several skeletal sites using dual-energy x-ray absorptiometry. Linear associations between parameters were tested using Pearson's correlation. Multivariable regression techniques were used to determine associations between BMSi and other measures of bone, independent of confounders.

Results: BMSi was negatively correlated with age (r = –0.171, $P = .001$), weight (r = –0.100, $P = .052$), and body mass index (r = –0.187, $P = .001$), and positively with height (r = +0.109, $P = .034$). There was some evidence to support a positive association between BMSi and BUA ($\beta = 0.052$, $P = .037$), SOS ($\beta = 0.013$, $P = .144$), and SI ($\beta = 0.036$, $P = .051$). After age adjustment, this association was attenuated. No correlations were observed between BMSi and BMD at any skeletal site (r values ranged from –0.006 to +0.079, all $P \geq .13$).

Conclusion: There was a small positive association between BMSi and quantitative ultrasound (QUS) parameters, which were not independent of age. No associations

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were detected between BMSi and BMD. This suggests that BMSi and QUS are capturing common age-dependent properties of bone. Further research on the utility of IMI alone and complementary to conventional bone testing methods for predicting fracture risk is warranted.

Key Words: impact microindentation, bone material strength index, fractures, osteoporosis, quantitative ultrasound

With an increasingly aging population, fractures constitute a major public health concern. This is because fractures are associated with significant morbidity and mortality [1-3], particularly in cases of hip fracture, with the 1-year mortality after sustaining a hip fracture estimated to be 14% to 58% [4-7].

Bone fragility is determined by bone mass, bone architecture, and bone material properties [8]. Hence, measuring both the quantity and quality of bone is important in the assessment of fracture risk. The current gold standard for assessment for fracture risk, areal bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA), provides limited information on bone quality [8, 9]. An existing complementary technique to DXA for assessing bone status is calcaneal (heel) quantitative ultrasound (QUS), which provides information about bone density, architecture, and composition [9-12].

QUS measures broadband ultrasound attenuation (BUA), which reflects bone density and architecture, and speed of sound (SOS), which reflects bone density and elasticity; BUA and SOS are combined to calculate the stiffness index (SI) [10, 13]. BUA and SOS measured at the heel have been reported to have weak correlations with DXA-derived heel BMD [14] and femoral neck BMD [13]. The QUS parameters have been associated with fracture risk, independently of BMD [15, 16].

Recently, impact micro-indentation (IMI), using the OsteoProbe, has been developed to measure bone material strength index (BMSi), a property of cortical bone material strength [17]. BMSi is defined as 100 times the ratio of the indentation distance from the impact to a calibration material, poly methyl methacrylate, divided by the indentation distance from the impact into the bone. As the probe indents the bone, microfractures are induced. The more easily the bone is fractured, the deeper the probe indents and the lower the BMSi.

Elements like microporosity, collagen and noncollagen protein properties, degree of mineralization, water content, or tissue homogeneity, among others, contribute to the mechanical properties of the bone tissue and will be reflected in the BMSi. Some of these properties of bone are more likely to be captured by QUS rather than by bone densitometry. Thus, we hypothesized that by virtue of such shared properties, BMSi, and QUS would be positively correlated. Previous reports have demonstrated an association between low BMSi and low BMD [18], high prevalence of fracture [19, 20], and increased cortical porosity [21]. Part of the evaluation of the clinical utility of the OsteoProbe for assessing bone status is an appraisal of how its outcome, BMSi, relates to conventional bone measurement techniques. There are no previously published studies investigating the associations between BMSi and QUS parameters, and only a few have investigated associations with BMD at multiple skeletal sites.

In this study, we aimed to explore the associations between BMSi and bone parameters measured with QUS and DXA. Quantifying the relationship between BMSi and other measures of bone will improve an understanding of how IMI might be used in the clinical assessment of bone fragility.

Materials and Methods

Participants

Participants were men from the Geelong Osteoporosis Study, a population-based cohort study situated in the Barwon Statistical Division, a geographically well-defined region in south-eastern Australia [22].The male arm of the Geelong Osteoporosis Study commenced in 2001 with recruitment of 1540 men aged 20 to 92 years. Participants are reassessed every few years and data for this cross-sectional analysis were generated from the first 501 men who were measured in the current follow-up phase (ages 33-96 years), which commenced in 2016. The study was approved by the Human Research Ethics Committee at Barwon Health. All participants provided written informed consent.

Measurements

IMI using the OsteoProbe RUO (Active Life Technologies, Santa Barbara, CA, USA), was conducted to measure BMSi on the anterior surface of the mid-tibia [23]. The indentation site was located by measuring the midpoint from the medial border of the tibial plateau to the distal edge of the medial malleolus. Following disinfection of the area and administration of local anesthesia, the OsteoProbe tip was inserted through the skin and periosteum until reaching the surface of the bone at the anterior face of the mid-tibia. The

right leg was measured, except in cases where some local contraindication was present, in which case the left leg was measured. Malgo et al. reported no difference in mean BMSi between the dominant and nondominant legs [24].

At least 11 indentations were performed for each participant, of which the first measurement was systematically disregarded followed by 10 valid test indentations. The first measurement was disregarded to ensure sufficient penetration of the probe tip through the periosteum. Two trained operators conducted the IMI measurements. The procedure was conducted according to internationally recognized recommendations for using the OsteoProbe [23]. We have previously reported that it is feasible to use the OsteoProbe in this research setting and that participants tolerate IMI measurements well [25].

BUA (dB/MHz), SOS (m/sec), and SI (%) were assessed for the left heel using a Lunar Achilles Insight ultrasonometer (GE Lunar, Madison, WI, USA). Areal BMD (g/cm^2) was measured at the total hip, femoral neck, Ward's triangle, trochanter, lumbar spine (posterior–anterior projection, L2-L4), whole body, ultradistal (UD) forearm, and mid-third of the forearm using DXA (GE Lunar, ProdigyPro, Madison, WI, USA). Trabecular bone score (TBS) was determined from lumbar spine scans using TBS iNsight software (Version 2.2). Quality control was maintained through daily measurements of a Lunar DXA phantom. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, and body mass index (BMI; kg/m^2) was calculated. All clinical measures were performed by trained personnel.

Questionnaire data

All participants completed comprehensive questionnaires detailing medical history, medication use, and lifestyle behaviors. A parental fracture referred to at least 1 maternal or paternal hip fracture. A participant's prior fracture was defined as any low-trauma fracture equivalent to a fall from a standing height or less, excluding fractures of the toe, skull, finger, and face, occurring during adulthood (age ≥20 years). Fractures were radiologically verified [26]. Secondary osteoporosis included current use of oral glucocorticoids (n = 3), anticonvulsants (n = 12), selective serotonin reuptake inhibitors (n = 12), androgen deprivation therapy, and history of hyperparathyroidism (n = 4), rheumatoid arthritis (n = 5), or gastrointestinal disease.

Diabetes and vitamin D status

Blood samples were collected after an overnight fast and sera analyzed for serum 25-hydroxyvitamin D (25OHD) and estimated glomerular filtration rate (eGFR) calculated. Diabetes was classified as fasting plasma glucose ≥ 7.0 mmol/L(126 mg/dL) and/or a self-report of diabetes and/or use of antihyperglycemic agents. Type 2 diabetes mellitus (T2DM) was determined by examination of medical records. Participants were classified as having chronic kidney disease (CKD) if they had eGFR <60 mL/min/1.73 m^2, as previously described [27, 28]

Statistical analysis

The distribution of continuous data was visually assessed for normality using histograms. Categorical data were considered as binary variables. Associations between BMSi values and QUS and DXA parameters were tested using Pearson's correlation. Multiple linear regression models were used to identify whether differences in BMSi were independent of other potential confounders. The models were tested for interaction terms. Age and BMI were classified as binary variables (age: <60 and ≥60 years; BMI: <30 and ≥30 kg/m^2) to test for interaction terms.

Statistical analyses were performed using Minitab V.17 (State College, Pennsylvania, USA).

Results

Of 510 participants in the current follow-up, 377 underwent IMI testing. Reasons for nonmeasurement in 153 men were needle phobia (n = 20), existing skin infections (n = 41), excessive soft tissues around the mid-tibial region (n = 82), discomfort (pressure, not pain) after the first indentation (n = 5), inability to provide informed consent (n = 2), and 2 participants did not provide any reasons for declining. Compared with participants, nonparticipants were older (mean ± SD, 70.3 ± 15.9 vs 64.2 ± 11.9 years, $P < .001$) and had greater mean BMI (30.2 ± 5.4 vs 27.0 ± 3.2 kg/m^2, $P < .001$).

Associations between BMSi, anthropometrics, and TBS

Participant characteristics are presented in Table 1. BMSi was negatively correlated with age (r = –0.171, $P = .001$), weight (r = –0.100, $P = .052$), and BMI (r = –0.187, $P = .001$), and positively correlated with height (r = +0.109, $P = .034$). A positive correlation was observed between BMSi and TBS (r = 0.200, $P < .001$). TBS was positively correlated with BUA (r = 0.370, $P < .001$), SOS (r = 0.288, $P < .001$), and SI (r = 0.345, $P < .001$).

These associations were sustained after adjusting for other factors.

Associations between BMSi, anthropometrics, QUS, and BMD parameters

There was evidence to suggest a positive correlation between BMSi and BUA (r = +0.108, *P* = .037), SI (r = +0.101, *P* = .051), and SOS (r = +0.075, *P* = .144) (Fig. 1). These associations were sustained after adjusting for potential confounders, including BMI, prior fracture, parental fracture, alcohol consumption, secondary osteoporosis, CKD, and T2DM (Table 2). After age adjustment, this association was attenuated. No interactions were identified.

No correlations were detected between BMSi and BMD at any skeletal site: spine (r = –0.027, *P* = .201), total femur (r = +0.006, *P* = .906), femoral neck (r = +0.012, *P* = .822), Ward's triangle (r = +0.036, *P* = .491), trochanter (r = –0.012; *P* = .821), UD forearm (r = +0.079, *P* = .134), and mid-forearm (r = +0.068, *P* = .197).

Discussion

Our data suggest that a higher BMSi is likely associated with higher QUS measures. This association was sustained after adjusting for most potential confounders but not independent of age. We also observed positive relationships between BMSi and TBS, and TBS and QUS parameters, independent of other factors. We found no evidence of an association between BMSi and BMD.

To our knowledge, no previous studies have reported how BMSi varies with parameters of QUS. Several studies have detected lower QUS values for people with fragility fractures [29, 30, 31]. McCloskey et al. reported a relationship between low heel QUS values and increased fracture risk, that was independent of age [29].

While some studies have shown a correlation between BMD and QUS measures [13, 14], others have reported discordant results [30]. QUS and bone densitometry capture different properties of bone. While the DXA measures BMD by analyzing both cortical and trabecular bone, it is limited in its ability to detect bone microarchitecture [32]. QUS parameters are related to properties of bone that are influenced by the proportion of cortical to trabecular bone, trabecular orientation, and composition of organic and inorganic components [31] and thus reflect bone quantity and bone quality (microarchitecture and strength) [33]. Our finding that a higher BMSi is associated with a higher TBS suggests that although TBS primarily reflects trabecular microarchitecture, it may also be able to capture differences in cortical bone.

Table 1. Participant characteristics (n = 377)

	Mean (± SD)
Age (years)	62.7 ± 13.8
Weight (kg)	81.5 ± 11.1
Height (cm)	174.2 ± 6.9
Body mass index (kg/m^2)	26.8 ± 3.2
BMSi	82.5 ± 6.8
QUS	
BUA (dB/MHz)	116.2 ± 13.9
SOS (m/sec)	1572.7 ± 40.5
SI (%)	97.2 ± 18.7
BMD (g/cm^2)	
Spine	1.314 ± 0.206
Femoral neck	0.958 ± 0.126
Ward's triangle	0.748 ± 0.142
Trochanter	0.889 ± 0.137
Total femur	1.040 ± 0.139
UD forearm	0.511 ± 0.079
Mid-forearm	0.983 ± 0.099
Whole body	1.248 ± 0.103
Serum 25OHD (nmol/L)	63.867 ± 18.64
Prior fracture, n (%)[a]	41 (10.88)
Parental fracture, n (%)	42 (11.14)
Alcohol consumption, n (%)[b]	63 (16.71)
Secondary osteoporosis, n (%)[c]	45 (11.94)
T2DM, n (%)	45 (11.94)
eGFR <60 mL/mm/1.73 m^2, n (%)[d]	52 (13.79)

Abbreviations: 25OHD, 25-hydroxyvitamin D; QUS, quantitative ultrasound; BUA, broadband ultrasound attenuation; SOS, speed of sound; SI, stiffness index; BMD, bone mineral density; UD forearm, ultradistal forearm; T2DM, type 2 diabetes mellitus.

[a]Fractures were 5 vertebra, 2 hip, 2 foot, 3 elbow, 4 ankle, 5 humerus, 8 tibia, and 12 rib.

[b]Consumes 3 or more units of alcohol daily.

[c]Current use of oral glucocorticoids, anticonvulsants, selective serotonin reuptake inhibitors, androgen deprivation therapy, and presence of hyperparathyroidism, rheumatoid arthritis, or gastrointestinal diseases.

[d]Chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

IMI is a technique designed to determine bone material properties, at a tissue level. Bone remodeling at the basic multicellular units influences the material properties of bone by replacing old mineralized bone with new matrix, increasing the heterogeneity of the skeleton, and increasing its resistance to the propagation of microdamage that ultimately leads to fracture. Additionally, the portability and absence of ionizing radiation of IMI and QUS techniques make them a practicable alternative in clinical, research settings, and in certain populations, including those in rural and remote areas where access to densitometry may be limited [34]. Bridges et al. [35] validated the use of the OsteoProbe in measuring IMI. However, as with other technologies, there are limitations. Some of the limitations of IMI include the recommendation of 2 trained operators and contraindications for the procedure such as local

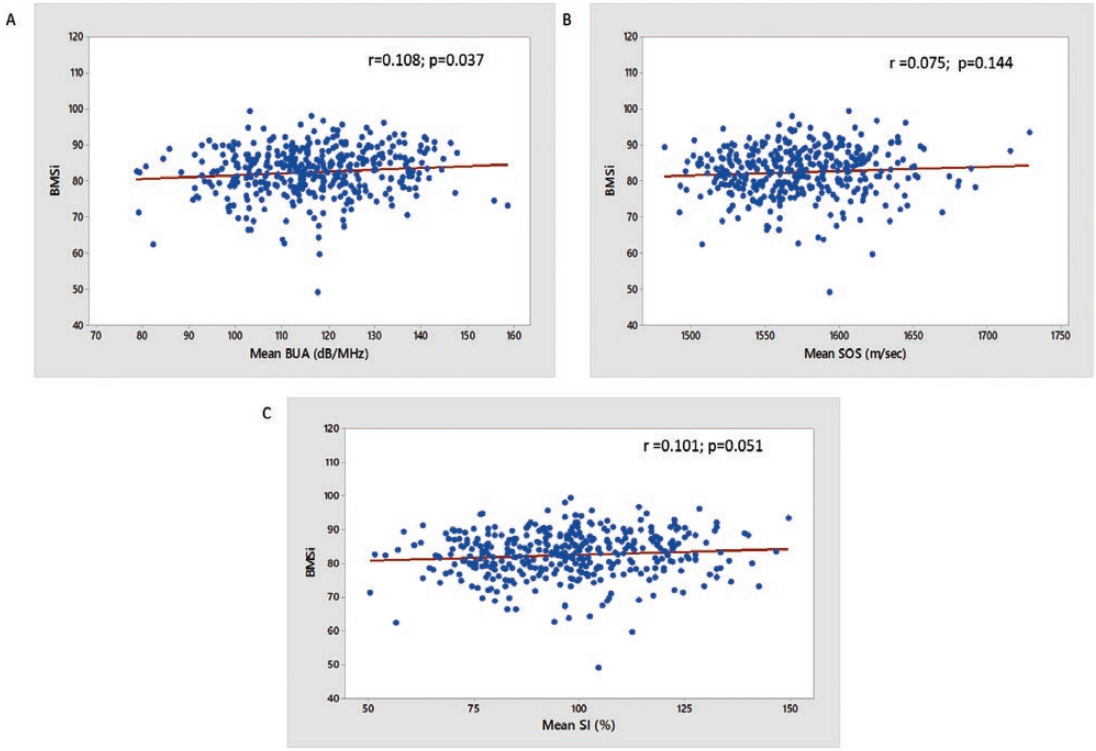

Figure 1. Associations between BMSi and (A) BUA (dB/MHz); (B) SOS (m/sec) and (C) SI (%), r- and *P* values were calculated using Pearson correlation.

oedema, severe obesity, local skin infection, and dermatological lesions in the area of measurement. Furthermore, there is a dearth of data confirming its potency in predicting fractures.

Our finding that an association between BMSi and BMD was not detected corroborates reports from some other studies. Malgo et al. [36] and Duarte Sosa et al. [37] reported no correlations between BMSi and BMD in a study involving 90 patients (aged between 40.4 and 85.5 years) with low bone mass with or without fragility fracture and in 66 women with osteoporotic fracture and 66 age- and sex-matched controls without fracture, respectively. However, Rudäng et al. [18] observed a positive association between BMSi and BMD of the total hip, femoral neck, spine, and mid-third of the nondominant radius. This lack of consistency in in the literature may reflect lifestyle and genetic differences between study populations or biases resulting from study designs and participant selection. Our study involved unselected men drawn from the general population, and with a wider age range and lower mean age than the population examined by Rudäng et al.

Our reported age-related decline in BMSi is similar to the study by Malgo et al. [36] However, Duarte Sosa et al. [37] observed no association between BMSi and age. Given that the strength of bone is inversely associated with density of microcracks in bone tissue [38, 39], and microcracks density increases with age [35], it seems plausible that the BMSi should be negatively correlated with age [40].

BMSi was negatively correlated with weight and BMI, and positively correlated with height. The association between height and risk of fracture has been explored in several studies, but the evidence is limited and inconclusive. Compston et al. [41] reported a positive association between height and vertebral fractures, but not wrist or hip fracture, while an inverse relationship was indicated between height and clavicular and upper arm/shoulder fractures. Moreover, a decreased fracture risk in most sites has been described in men with obesity [42]. At this point, we have no clear explanation for the correlations between BMSi and the anthropometric parameters in this population.

Our study has several strengths and limitations. To the best of our knowledge, this is the first study to explore the relationship between BMSi and QUS parameters and BMD at the Ward's triangle, trochanter, and UD forearm. Unlike most of the previous studies, this study is population based and unselected on the basis of disease status. However, we investigated men only and note that the sample was mainly Caucasian (~98%), and thus acknowledge that the observations may not be generalizable to women or other populations. Moreover, IMI, QUS, and DXA were measured at different parts of the skeleton and although the associations between BMSi and QUS parameters were independent of

Table 2. Results for linear regression models with BMSi as the dependent variable and the QUS parameter (BUA, SOS, SI) as the independent variable, adjusting for BMI and age

Model		BUA			SOS			SI		
1	Variable	β	SE coefficient	*P* value	β	SE coefficient	*P* value	β	SE coefficient	*P* value
	QUS	0.05	0.03	.037	0.01	0.01	.144	0.04	0.02	.051
	Constant	76.43	2.92	<.001	62.70	13.50	<.001	78.98	1.84	<.001
2	QUS	0.06	0.02	.012	0.01	0.01	.093	0.04	0.02	.024
	BMI	–0.42	0.11	<.001	–0.40	0.11	<.001	–0.41	0.11	<.001
	Constant	86.59	3.85	<.001	70.90	13.50	<.001	89.53	3.28	<.001
3	QUS	0.04	0.03	.167	0.01	0.01	.408	0.23	0.02	.225
	Age	–0.08	0.03	.003	–0.08	0.03	.002	–0.08	0.03	.003
	Constant	83.16	3.68	<.001	76.20	14.10	<.001	85.05	2.74	<.001
4	QUS	0.05	0.02	.043	0.01	0.01	.203	0.03	0.02	.069
	Previous fracture	–1.94	1.11	.082	–1.87	1.12	.096	–1.86	1.11	.095
	Constant	76.84	2.92	<.001	65.40	13.60	<.001	79.42	1.86	<.001
5	QUS	0.05	0.03	.046	0.01	0.01	.161	0.03	0.02	.06
	Parental fracture	–1.06	1.11	.338	–1.17	1.11	.292	–1.11	1.10	.316
	Constant	76.79	2.95	<.001	63.6	13.6	<.001	79.22	1.86	<.001
6	QUS	0.05	0.03	.042	0.01	0.01	.145	0.04	0.02	.054
	Alcohol consumption	–0.64	0.97	.511	–0.77	0.97	.428	–0.71	0.97	.465
	Constant	76.66	2.95	<.001	62.8	13.5	<.001	79.13	1.85	<.001
7	QUS	0.05	0.03	.04	0.02	0.01	.146	0.04	0.02	.053
	Secondary osteoporosis	–0.15	1.11	.891	–0.26	1.11	.812	–0.22	1.10	.842
	Constant	76.47	2.94	<.001	62.8	13.6	<.001	79.01	1.85	<.001
8	QUS	0.06	0.03	.044	0.02	0.01	.065	0.04	0.02	.034
	T2DM	–2.09	1.08	.054	–2.27	1.07	.035	–2.14	1.07	.047
	Constant	76.06	3.28	<.001	55.9	14.5	<.001	78.44	2.02	<.001
9	QUS	0.05	0.03	.052	0.01	0.01	.244	0.03	0.02	.087
	eGFR	–0.67	1.01	.505	–0.82	1.01	.420	–0.73	1.01	.468
	Constant	76.49	3.16	<.001	66.1	14.2	<.001	79.28	1.98	<.001
10	QUS	0.05	0.002	<.001	0.01	0.00	<.001	0.04	0.01	<.001
	Serum 25OHD	0.00	0.00	.996	0.00	0.00	.997	0.00	0.00	.996
	Constant	76.06	0.27	<.001	64.62	1.14	<.001	78.97	0.19	<.001

1, unadjusted; 2, BMI adjusted; 3, age adjusted; 4, previous fracture; 5, parental fracture; 6, alcohol consumption; 7, secondary osteoporosis; 8, type 2 diabetes mellitus; 9, chronic kidney disease; 10, serum Vitamin D.
Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; eGFR, estimated glomerular filtration rate; QUS, quantitative ultrasound.

BMI, we were not able to explore this across the full range of BMI due to exclusions involving excessive soft tissue at the measurement site.

We conclude that in this population-based sample of men, there was a small positive association between BMSi and measures of calcaneal QUS, which supports the hypothesis that BMSi and QUS are capturing common age-dependent properties of bone. The results of this study suggest that BMSi identifies unique properties of bone that are not captured by DXA. Hence, IMI may complement DXA for assessing fracture risk, predominantly in medical disorders where BMD only partially explains fracture propensity. This will be useful in targeting treatments since many patients with no or moderate deficits in BMD experience fracture and not all patients with low BMD are destined to fracture. There were no associations found between BMSi and BMD. Further studies are needed to establish the efficacy of BMSi alone, and in conjunction with other measures of bone, for predicting fractures.

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Author Contributions: P.R.-M. performed the indentation measurements in the presence of another trained observer (K.L.H.-K.) and drafted the manuscript. K.L.H.-K. assisted with taking measurements. A.D.-P. assisted with training to use the OsteoProbe device and provided advice on measurement technique. M.A.K. and J.A.P. conceived and designed the study. J.A.P. secured ethics approval. All authors interpreted the data, guided and reviewed the manuscript. All authors read and approved the final manuscript.

Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Pasco JA, Sanders KM, Hoekstra FM, Henry MJ, Nicholson GC, Kotowicz MA. The human cost of fracture. *Osteoporos Int*. 2005;**16**(12):2046-2052.
2. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. *J Bone Miner Res*. 2013;**28**(11):2317-2324.
3. Pande I, Scott DL, O'Neill TW, Pritchard C, Woolf AD, Davis MJ. Quality of life, morbidity, and mortality after low trauma hip fracture in men. *Ann Rheum Dis*. 2006;**65**(1):87-92.
4. Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL. The 1-year mortality of patients treated in a hip fracture program for elders. *Geriatr Orthop Surg Rehabil*. 2010;**1**(1):6-14.
5. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA*. 2009;**302**(14):1573-1579.
6. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ*. 2005;**331**(7529):1374.
7. Bentler SE, Liu L, Obrizan M, et al. The aftermath of hip fracture: discharge placement, functional status change, and mortality. *Am J Epidemiol*. 2009;**170**(10):1290-1299.
8. Felsenberg D, Boonen S. The bone quality framework: determinants of bone strength and their interrelationships, and implications for osteoporosis management. *Clin Ther*. 2005;**27**(1):1-11.
9. Quiros Roldan E, Brianese N, Raffetti E, et al. Comparison between the gold standard DXA with calcaneal quantitative ultrasound based-strategy (QUS) to detect osteoporosis in an HIV infected cohort. *Braz J Infect Dis*. 2017;**21**(6):581-586.
10. Baroncelli GI. Quantitative ultrasound methods to assess bone mineral status in children: technical characteristics, performance, and clinical application. *Pediatr Res*. 2008;**63**(3):220-228.
11. Marín F, González-Macías J, Díez-Pérez A, Palma S, Delgado-Rodríguez M. Relationship between bone quantitative ultrasound and fractures: a meta-analysis. *J Bone Miner Res*. 2006;**21**(7):1126-1135.
12. Pasco JA, Nicholson GC, Ng F, et al. Oxidative stress may be a common mechanism linking major depression and osteoporosis. *Acta Neuropsychiatr*. 2008;**20**(3):112-116.
13. Njeh CF, Hans D, Li J, et al. Comparison of six calcaneal quantitative ultrasound devices: precision and hip fracture discrimination. *Osteoporos Int*. 2000;**11**(12):1051-1062.
14. Bouxsein ML, Radloff SE. Quantitative ultrasound of the calcaneus reflects the mechanical properties of calcaneal trabecular bone. *J Bone Miner Res*. 1997;**12**(5):839-846.
15. Bauer DC, Glüer CC, Cauley JA, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1997;**157**(6):629-634.
16. Moayyeri A, Kaptoge S, Dalzell N, et al. The effect of including quantitative heel ultrasound in models for estimation of 10-year absolute risk of fracture. *Bone*. 2009;**45**(2):180-184.
17. Randall C, Bridges D, Guerri R, et al. Applications of a new handheld reference point indentation instrument measuring bone material strength. *J Med Device*. 2013;**7**(4):410051-410056.

18. Rudäng R, Zoulakis M, Sundh D, et al. Bone material strength is associated with areal BMD but not with prevalent fractures in older women. *Osteoporos Int*. 2016;**27**(4):1585-1592.
19. Diez-Perez A, Güerri R, Nogues X, et al. Microindentation for in vivo measurement of bone tissue mechanical properties in humans. *J Bone Miner Res*. 2010;**25**(8):1877-1885.
20. Sosa DD, Eriksen EF. Reduced bone material strength is associated with increased risk and severity of osteoporotic fractures. An impact microindentation study. *Calcif Tissue Int*. 2017;**101**(1):34-42.
21. Sundh D, Rudäng R, Zoulakis M, Nilsson AG, Darelid A, Lorentzon M. A high amount of local adipose tissue is associated with high cortical porosity and low bone material strength in older women. *J Bone Miner Res*. 2016;**31**(4):749-757.
22. Pasco JA, Nicholson GC, Kotowicz MA. Cohort profile: Geelong osteoporosis study. *Int J Epidemiol*. 2012;**41**(6):1565-1575.
23. Diez-Perez A, Bouxsein ML, Eriksen EF, et al. Technical note: recommendations for a standard procedure to assess cortical bone at the tissue-level in vivo using impact microindentation. *Bone Rep*. 2016;**5**:181-185.
24. Malgo F, Hamdy NT, Papapoulous SE, Appelman-Dijkstra. Impact Microindentation: Consistency of serial measurements and alterations in patients with Paget's Disease of the Tibia. *J Bone Miner Res*. 2017;**32**(12):2375-2380.
25. Rufus-Membere P, Holloway-Kew KL, Diez-Perez A, Kotowicz MA, Pasco JA. Feasibility and tolerability of bone impact microindentation testing: a cross-sectional, population-based study in Australia. *BMJ Open*. 2018;**8**(12):e023959.
26. Pasco JA, Henry MJ, Gaudry TM, Nicholson GC, Kotowicz MA. Identification of incident fractures: the Geelong Osteoporosis Study. *Aust N Z J Med*. 1999;**29**(2):203-206.
27. Holloway-Kew KL, Betson A, Rufus PG, et al. Impact microindentation in men with impaired fasting glucose and type 2 diabetes. *Bone*. 2021;**142**:115685.
28. Holloway-Kew KL, Rufus-Membere P, Anderson KB, et al. Bone material strength index is associated with prior fracture in men with and without moderate chronic kidney disease. *Bone*. 2020;**133**:115241.
29. McCloskey EV, Kanis JA, Odén A, et al. Predictive ability of heel quantitative ultrasound for incident fractures: an individual-level meta-analysis. *Osteoporos Int*. 2015;**26**(7):1979-1987.
30. Flöter M, Bittar CK, Zabeu JL, Carneiro AC. Review of comparative studies between bone densitometry and quantitative ultrasound of the calcaneus in osteoporosis. *Acta Reumatol Port*. 2011;**36**(4):327-335.
31. Glüer CC, Wu CY, Jergas M, Goldstein SA, Genant HK. Three quantitative ultrasound parameters reflect bone structure. *Calcif Tissue Int*. 1994;**55**(1):46-52.
32. Schuit SC, Van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone*. 2004;**34**(1):195-202.
33. Chin KY, Ima-Nirwana S. Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? *Int J Med Sci*. 2013;**10**(12):1778-1783.
34. Tucker KN, Schultz CG, Chatterton BE. Mobile bone densitometry service in rural South Australia. *ANZ Nuclear Medicine*. 1997;**28**(3):41.
35. Bridges D, Randall C, Hansma PK. A new device for performing reference point indentation without a reference probe. *Rev Sci Instrum*. 2012;**83**(4):044301.
36. Malgo F, Hamdy NA, Papapoulos SE, Appelman-Dijkstra NM. Bone material strength as measured by microindentation in vivo is decreased in patients with fragility fractures independently of bone mineral density. *J Clin Endocrinol Metab*. 2015;**100**(5):2039-2045.
37. Duarte Sosa D, Vilaplana L, Güerri R, et al. Are the high hip fracture rates among Norwegian women explained by impaired bone material properties? *J Bone Miner Res*. 2015;**30**(10):1784-1789.
38. Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. *J Bone Miner Res*. 1997;**12**(1):6-15.
39. Zioupos P. Accumulation of in-vivo fatigue microdamage and its relation to biomechanical properties in ageing human cortical bone. *J Microsc*. 2001;**201**(Pt 2):270-278.
40. Schaffler MB, Choi K, Milgrom C. Aging and matrix microdamage accumulation in human compact bone. *Bone*. 1995;**17**(6):521-525.
41. Compston JE, Flahive J, Hosmer DW, et al.; GLOW Investigators. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *J Bone Miner Res*. 2014;**29**(2):487-493.
42. Premaor MO, Compston JE, Fina Avilés F, et al. The association between fracture site and obesity in men: a population-based cohort study. *J Bone Miner Res*. 2013;**28**(8):1771-1777.