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Impact Microindentation: Consistency of Serial Measurements and Alterations in Patients With Paget's Disease of the Tibia

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ABSTRACT

Impact microindentation (IMI) is a new technique for the in vivo measurement of tissue-level properties of cortical bone in humans. To address issues related to the proper application of IMI in clinical practice and to directly examine cortical bone properties in patients with tibia pathology, we studied 11 subjects without tibia pathology and nine patients with Paget's disease of the tibia in biochemical remission after bisphosphonate treatment. Serial indentations in the tibias of both legs were performed in all subjects by a single operator until 10 adequate measurements were obtained in each tibia. In patients without Paget's disease (7 men and 4 women; mean age, 61.9 years; range, 51 to 72 years), there was no difference in mean bone material strength index (BMSi) between the dominant and nondominant leg (82.1 ± 1.3 and 81.4 ± 1.3 , respectively; $p = 0.606$). In each individual subject studied, sequential indentations in both legs showed no trends for higher or lower values with time. The standard deviation of unnormalized bone material strength (BMSu) was also comparable between the dominant and nondominant tibia (5.3 and 4.5, respectively; $p = 0.657$). In patients with Paget's disease (4 men and 5 women; mean age, 69.5 years; range, 55 to 87 years), mean BMSi of the Pagetic tibia was lower, albeit nonsignificantly, than that of the contralateral nonaffected tibia (74.7 ± 1.7 and 78.7 ± 1.3 , respectively; $p = 0.120$). In contrast to subjects without Paget's disease, the SD of adequate BMSu values was significantly larger in the Pagetic tibia compared to that of the non-Pagetic tibia (7.6 versus 5.0, respectively, $p = 0.008$). These results highlight the consistency of serial IMI measurements as performed by a single operator in the presence as well as absence of tibia pathology and illustrate that the method is able to capture alterations of tissue-level cortical bone properties in patients with Paget's disease of the tibia. © 2017 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals Inc.

KEY WORDS: REFERENCE POINT INDENTATION; IMPACT MICROINDENTATION; OSTEOPROBE; PAGET'S DISEASE OF BONE

Introduction

Impact microindentation (IMI) is a new reference point indentation technique that measures tissue-level properties of cortical bone in humans in vivo at the mid-shaft of the tibia. The tool used to perform IMI is a hand-held device (OsteoProbe; Active Life Scientific, Santa Barbara, CA, USA) that imparts a single impact load to the bone surface. The methodology and clinical value of the method have been recently reviewed.^(1–3) In the course of the investigation, repeated indentations are performed on the tibia until a minimum number of adequate measurements is obtained. The manufacturer of the device does not provide an algorithm to automatically flag inadequate measurements, the evaluation of which is left to the judgment of the operator during the procedure. To our knowledge, the variance of measurements obtained in an individual subject by sequential adequate indentations has not been previously reported. Moreover, whereas the nondominant leg is

recommended as the preferred investigation site,⁽³⁾ data supporting this recommendation are not available. An important, clinically relevant question is whether the application of IMI is informative and reliable in patients with tibia pathology, particularly as pathology at this site has so far been considered as an exclusion criterion. IMI measurements may indeed provide valuable information not only on the tissue-level properties of the diseased tibia, but also on the performance of the technique in general.

To address these questions and to obtain more insight into the value of IMI in clinical practice, we examined tissue-level properties of cortical bone of both legs in individuals without tibia pathology and in patients with Paget's disease of the tibia. Localizations of Pagetic lesions in the tibia can be found in the original description of the disease by Sir James Paget in 1887,⁽⁴⁾ and we have previously reported that lesions of the tibia comprised 7% of all Pagetic lesions in 180 consecutive patients from our cohort of patients with Paget's disease of bone.⁽⁵⁾

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Fig. 1. Characteristic radiographic features of the tibiae of two patients with Paget's disease of bone included in the study.

Paget's disease of the tibia has characteristic radiologic features such as cortical thickening and abnormal bone texture (Fig. 1) and may be associated with significant deformity, pain, and increased risk of stress and complete fractures.⁽⁶⁾

Patients and Methods

IMI was performed in all subjects by a single operator (FM) in the Out-Patient Clinic of the Center for Bone Quality of the Leiden University Medical Center (LUMC). The group of patients without tibia pathology included in this study consisted of consecutive patients attending our Out-Patient Clinic who participated in our studies of tissue-level properties of cortical bone in patients with and without fractures and with well-controlled acromegaly and who consented to having further IMI measurements undertaken in both legs. Details of the characteristics and selection of these patients have been published.^(7,8) Exclusion criteria included localized infection of the tibia, metabolic bone disease other than osteoporosis, any untreated endocrine disorder, bilateral hip replacement, severe liver insufficiency, chronic kidney disease stage IV or V, and current or past use of glucocorticoids with the exception of hydrocortisone supplementation for secondary adrenal insufficiency in patients with acromegaly and inability to provide informed consent. All patients with radiologically confirmed Paget's disease of the tibia who were followed regularly in our Center and were in remission after treatment with bisphosphonates were also studied. The study was approved by the Medical Ethics Committee of the LUMC and all participants provided written informed consent.

Data on age, gender, height and weight, history of fractures, and use of medications (current and previous) were documented in all patients included in the study. In subjects without

Paget's disease, the presence of morphometric vertebral fractures was examined by spine radiographs and bone mineral density was measured by DXA. In patients with Paget's disease the date of diagnosis of the disease and dates, type, and number of bisphosphonate treatments were recorded and radiographs of the tibiae were reviewed to confirm the presence of a Pagetic lesion of the tibia.

Laboratory investigations

Blood was collected and serum measured for calcium, phosphate, albumin, and creatinine using semiautomated techniques, for alkaline phosphatase (ALP) using a fully-automated P800 modulator system (Roche Diagnostics), for procollagen type 1 amino-terminal propeptide (P1NP) using an electrochemiluminescent immunoassay with a Modular Analytics E-170 system (Roche Diagnostics) and for 25-hydroxyvitamin D using the 25-OH-vitamin D TOTAL assay (DiaSorin D.A./N.V.). Plasma was measured for intact PTH using the Immulite 2500 assay (Siemens Diagnostics).

IMI

Bone material strength index (BMSi) was measured in all subjects by IMI applied to the mid-shaft of the tibia by a single operator (FM) using a hand-held microindenter (OsteoProbe RUO; Active Life Scientific), as previously described and recommended by a group of experts.⁽³⁾ The patient was placed in a decubitus supine position with the tibia in external rotation to orient the flat surface of the medial tibia diaphysis in a horizontal position. Indentations of both tibiae were performed in a single session without repositioning of the patient. The measurement site was defined as the midpoint of the distance between the distal apex of the patella and medial malleolus. The operator ensured that the test probe was placed perpendicularly to the bone surface and classified the measurements as "well performed," "adequate," or "poorly performed" after the indentation and before checking the computer display according to the following criteria: "well performed" when the operator judged that the test probe was exactly perpendicular to the bone surface; "adequate" when the test probe was within acceptable deviation from the bone surface⁽⁹⁾; "poorly performed" when the operator judged that the test probe was not appropriately placed. "Poorly performed" measurements are usually due to slipping of the test probe, moving of the subject's leg or failure to place the device perpendicularly to the bone surface and are excluded from the analysis. In the present study the operator continued the protocol until 10 adequate measurements were obtained. Five additional measurements were subsequently performed on a calibration phantom, a cube of polymethylmethacrylate (PMMA), firmly secured in a holder and placed on a stable surface. BMSi is calculated as 100 times the harmonic mean of the indentation distance increase from impact into the PMMA material divided by the indentation distance increase from impact into the bone.⁽³⁾ Another parameter, unnormalized bone material strength (BMSu), has been used in the original description of the method to describe the effects of instrument variables on measurements.⁽⁹⁾ We concluded that BMSu directly obtained by measurement of individual sequential indentations is more suitable for the analysis of variability of the procedure than BMSi, which is the final result of all sequential measurements in a single patient after correction with the PMMA calibration phantom. Normalization of the measured values to the calibration phantom, as done in the standard calculation of

BMSi, would remain relatively consistent when a variable, such as probe sharpness or indentation angle, is changed. BMSu is defined as 100 times the ratio of the ideal indentation distance increase from the impact into PMMA (150 μm) divided by the indentation distance increase from the impact into the bone sample. We used this parameter for the calculation of variability of sequential measurements in the same subject and we arbitrarily defined it BMSu as opposed to BMSi.

The intraobserver coefficient of variation (CV) of the technique was calculated to be 2.2% in a previous study of patients with low bone mass with or without fractures by measuring BMSi twice in the right leg according to the above mentioned protocol with the second investigation performed 2 cm below the first measurement site in 10 subjects.⁽¹⁰⁾ Mean \pm SD BMSi of the two measurements was 75.9 ± 5.7 and 76.6 ± 4.9 , respectively.

Statistical analysis

Indentations judged “poorly performed” by the operator were not included in the calculation of the final BMSi or in the variation analyses. Results are reported as mean \pm SE unless otherwise stated. Between-group differences in baseline characteristics were assessed using a Student’s *t* test, a chi-square test, or a Mann-Whitney *U* test for non-normally distributed variables. Pearson’s and Spearman’s correlations were used to assess correlations between BMSi and patients’ parameters that were normally and not normally distributed. A paired *t* test was used to compare BMSi values between both tibias. A Wilcoxon signed ranks test was used to compare the standard deviation of the 10 adequate BMSu values between both tibias. Differences were considered to be significant at $p < 0.05$. All analyses were performed using SPSS software for Windows (version 23.0; IBM Corp, Armonk, NY, USA). Scatterplots were constructed with Graphpad Prism (version 7.0; Graphpad Software Inc., La Jolla, CA, USA); BMSu values were plotted in the sequence they were obtained from the first to the last.

Results

We studied 11 consecutively presenting individuals (7 men) aged 61.9 years (range, 51 to 72 years) and BMI 27.3 ± 1.7 , without pathology of the lower extremities and who consented to bilateral IMI measurements. Four had osteoporosis, five had osteopenia, and two had normal bone mineral density. Two patients with osteoporosis had a history of a clinical vertebral fracture and one with osteopenia of a distal radius fracture. Five patients from the acromegaly cohort had morphometric vertebral fractures. In all subjects studied biochemical parameters of bone and mineral metabolism were within the normal laboratory reference ranges (not shown). Nine patients (4 men) with Paget’s disease of the tibia with a mean age of 69.5 years (range, 55 to 87 years), and BMI 27.5 ± 1.1 , who were in biochemical remission for at least 1 year after treatment with bisphosphonates (median, 5.5 years; range, 1 to 30 years) were also studied. At the time of the investigation mean serum alkaline phosphatase activity was 76.7 ± 5.7 IU/L (reference range, 40 to 120 IU/L) and serum P1NP was 41.8 ± 4.6 ng/mL (reference range < 65 ng/mL).

IMI in subjects without tibia pathology

In subjects without Paget’s disease a mean of 12 indentations (range, 11 to 15) were performed in the dominant leg and 12

indentations (range, 10 to 14) in the nondominant leg in order to obtain 10 adequate measurements in each tibia of all tested individuals. Inadequate measurements were evenly spread during the procedure with the exception of the first indentation that was classified as “poorly performed” by the operator in 10 of the 22 measurements (7/14 and 3/8 measurements in acromegaly and remaining patients, respectively). Mean BMSi of the dominant leg was not different from that of the nondominant leg (82.1 ± 1.3 and 81.4 ± 1.3 , respectively; $p = 0.606$). Individual adequate measurements of the same tibia generally showed minimal variations (Fig. 2A), but larger variations were also observed (Fig. 2B), which did not in any case affect the mean BMSi value. These larger variations were not operator-dependent and bore no relation to the sequence timing of the indentation. This is illustrated in Fig. 3 by the lack of a trend toward lower or higher values or alterations in the magnitude of SDs of the mean BMSu of sequential adequate indentations. Mean SDs of BMSu of the dominant and nondominant legs were overall not different (5.3 and 4.5, respectively; $p = 0.657$). Similarly, there was no difference in mean SD of BMSu of the right and left leg (5.1 and 4.7, respectively; $p = 0.657$). There was no difference in BMSi values after five or 10 adequate measurements in either investigated leg (82.7 ± 1.2 versus 82.1 ± 1.3 and 81.1 ± 1.3 versus 81.4 ± 1.3 for the dominant and nondominant leg, respectively).

IMI in patients with Paget’s disease of the tibia

In patients with Paget’s disease a mean of 11 indentations (range, 10 to 12) were performed in the affected tibias and 12 indentations (range, 10 to 16) were performed in the non-Pagetian tibia in order to obtain 10 adequate measurements of each tibia. Mean BMSi of Pagetic bone was lower, albeit nonsignificantly, than that of the contralateral nonaffected bone (74.7 ± 1.7 and 78.7 ± 1.3 , respectively; $p = 0.120$). In contrast to the observations in subjects without Paget’s disease, the variability of measured BMSu values of the Pagetic tibia was greater than that of the contralateral tibia (Figs. 4A,B and 5). This was confirmed by the significant difference in mean SDs of BMSu measurements between Pagetic and non-Pagetian bones (7.6 versus 5.0, respectively, $p = 0.008$). In none of the patients with Paget’s disease was the SD of BMSu larger in the unaffected bone compared to the affected one.

Discussion

The *in vivo* measurement of IMI in the tibia of humans using the OsteoProbe is a new technique that provides information about tissue-level material properties of cortical bone. Although the relationship between measured properties of bone and its traditional mechanical properties still needs to be determined, clinical studies have demonstrated that the method could differentiate patient groups at increased risk for fracture from control groups independently of BMD values, suggesting that the method measures aspects of bone fragility not captured by BMD.^(7,11–13) In the present study we report for the first time serial indentations of both legs in all tested subjects to address issues related to the proper application of this technique in clinical practice and to directly examine properties of cortical bone in patients with Paget’s disease of the tibia compared to cortical bone of nonpathologic tibias.

Results obtained by *in vivo*, non-automated methods of investigation are subject to variations that depend on the

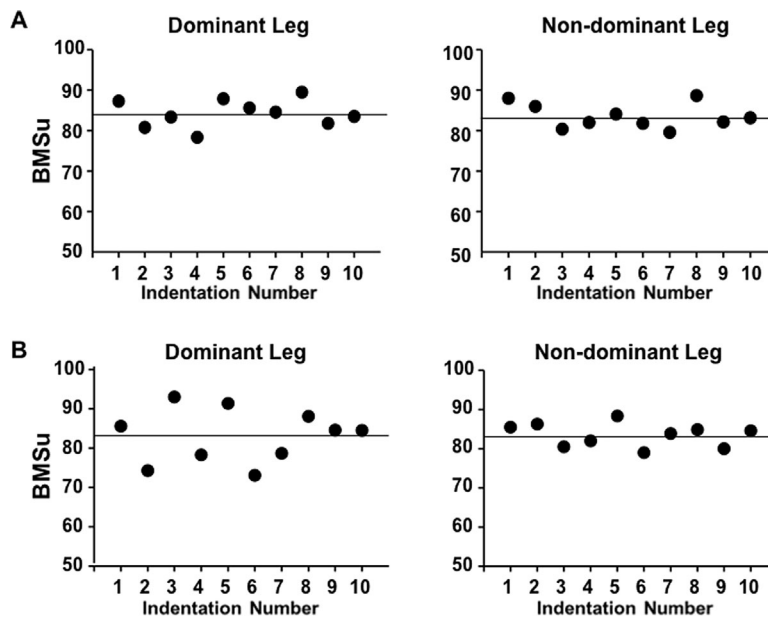


Fig. 2. Scatterplot of 10 sequential adequate indentations of both legs in two subjects (A, B) without tibia pathology.

operator, on the performance of the procedure and on underlying individual biological variance. Results obtained using the OsteoProbe may be affected by all these factors and adequate evaluation of these factors may help in explaining some discrepancies in reported results between different groups that raised questions regarding the value of this method in the clinic.⁽²⁾

The IMI method used in the present study does not automatically exclude inadequate measurements, a task which is left to the judgment of the operator. This has been an issue of critique, particularly because there has been no specific reference to flagged results in most reported studies so far. Our data from this study show that in the hands of an experienced operator, who applied exclusion of inadequate indentations without knowledge of the result, up to 16 indentations was needed in order to obtain 10 adequate measurements. Although we have no data to compare the performance of different operators, our previous results with a single operator showing minimal intraobserver variation are

clearly at odds with studies reporting results obtained by different operators, which showed large and significant variations in measured BMSi values requiring statistical adjustment of the results.⁽¹⁴⁾ This confirms the notion that an experienced operator is a sine qua non for the successful clinical application of the technique. If this is not feasible, additional operators should undergo a period of training with continuous comparison of their performance with that of an experienced operator. Relevant to this issue is the variable number of indentations required for the final results in different studies that ranged from five adequate to 15 in total.^(7,11,14-16) In the recent technical report of the application of OsteoProbe in human studies, five adequate indentations are recommended to be performed in each tested subject.⁽³⁾ We found no difference in final BMSi values between five and 10 adequate indentations, a result that is in agreement with the recommendation. However, more than five indentations may be required when an intrinsic, operator-independent variability in values is expected. The exclusion of the result of the first indentation

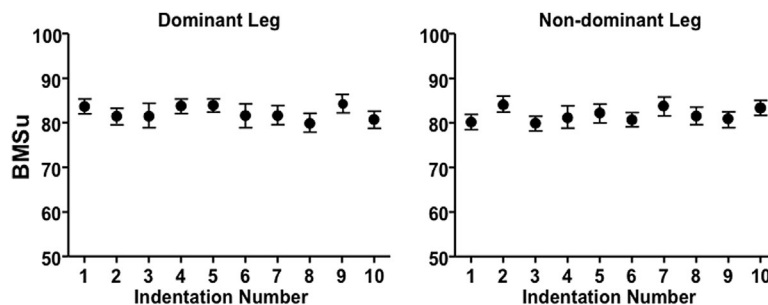


Fig. 3. Scatterplot of standard deviations of mean BMSu of sequential adequate indentations. BMSu = unnormalized bone material strength.

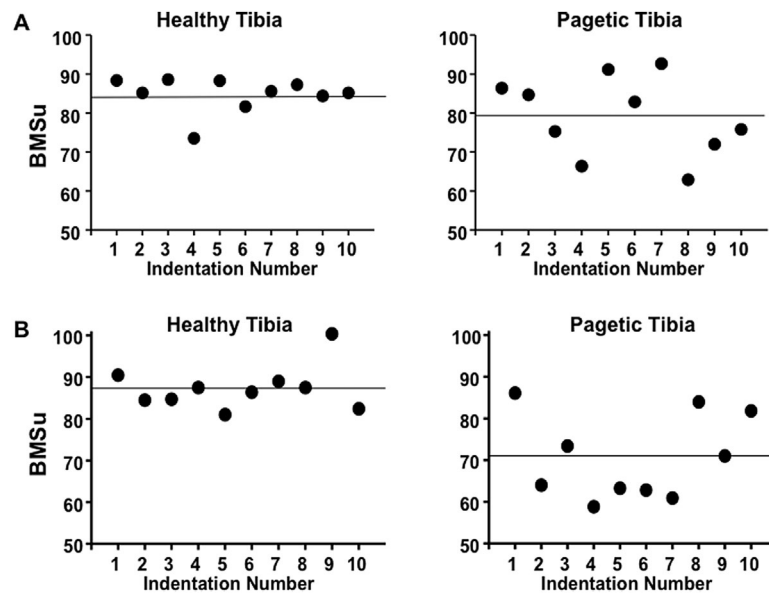


Fig. 4. Scatterplot of 10 sequential adequate indentations of the healthy and of the affected tibia in 2 patients (A, B) with Paget's disease of bone.

routinely and independently of the operator's evaluation, as used by some investigators, has also been recommended.⁽³⁾ In our study flagged measurements were evenly distributed among sequential indentations for up to 16 indentations with the exception of the first indentation that had to be flagged by the operator in 10 of the 22 measurements in subjects without Paget's disease. This high number of inadequate first indentations justifies the recommendation of routinely excluding the first indentation value from the measurements. On the other hand, a remarkable consistency of sequential results and minimal variability in mean values was observed indicating a robust method. Although variability may be greater in individual subjects this did not seem to affect the final outcome. These findings, together with the overlap of values between tested control and patient groups in reported studies, suggest that whereas the method can currently provide valid information in groups of individuals, it cannot be recommended as yet for drawing firm conclusions about tissue material properties of

cortical bone in individual patients. Finally, we show here that in the absence of tibia pathology, there is no difference in measured BMSi between the two legs. Although the harmonized use of the nondominant leg is recommended for consistency of data acquisition and for comparison of outcomes obtained with the use of the OsteoProbe between different centers,⁽³⁾ our bilaterally obtained data do suggest that the investigator's choice of the most suitable leg for testing may be allowed as this does not compromise the outcome of the procedure.

Taken at face value, our first ever reported results of IMI in patients with Paget's disease of the tibia unexpectedly showing no significant decrease in BMSi in the affected compared to the normal tibia may seem surprising and perhaps disappointing about the value of IMI in discerning abnormal tissue level properties of cortical bone in Pagetic tibias.⁽¹⁷⁾ However, a caveat in the interpretation of these results as well as of the absence of complications of the procedure in pathological tibias, may be because of the small number of patients studied, limiting the power of the study to detect significant differences between healthy and pathological bone or to capture complications. It is also of note that all nine patients with Paget's disease were in biochemical remission for longer than 1 year following treatment with bisphosphonates and none had sustained a stress or complete fracture of the tibia or had been subjected to a corrective surgical procedure. Whereas the finding of no significant BMSi difference between pathological and healthy tibias in patients with Paget's disease in our study may well have been related to bisphosphonate treatment and long-term remission of the disease, our data cannot address this assumption, because we did not investigate treatment-naive patients. Interestingly, Mellibovsky and colleagues⁽¹⁵⁾ recently reported that risedronate treatment given for 20 weeks to patients treated with glucocorticoids significantly improved BMSi before any measurable change in BMD could be observed.

The most important novel finding in our study was the wide variability of adequate measurements of BMSu of the affected Pagetic tibia indicating a heterogeneity of tissue properties

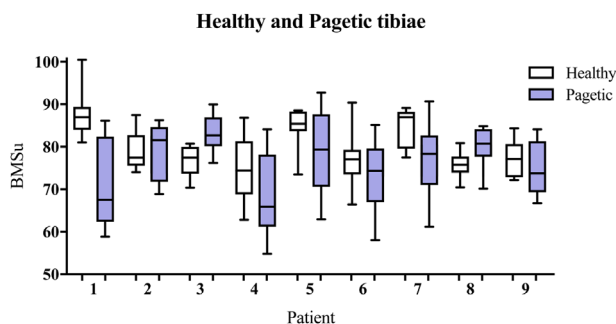


Fig. 5. Box-plots of BMSu values of healthy and affected tibias of all patients with Paget's disease of bone included in the study. BMSu = unnormalized bone material strength.

associated with the bone pathology of the disease. In this disorder, the localized accelerated bone remodeling results in the deposition of a disorganized mosaic of woven and lamellar bone leading to heterogeneous structural changes at affected skeletal sites. The BMSu values we recorded were very variable: within or higher than the range of values of the contralateral non-Pagetian tibia, interspersed with very low measured values. The variability of these measurements reveals a new, previously unreported, heterogeneous pattern of tissue level properties of pathological bone that is not due to methodological inadequacies and cannot be readily explained. This finding raises, in addition, the question whether variability of adequately performed indentations in individual subjects may enable the identification of aspects of biological variance of bone properties that are not captured by mean BMSi values. This issue warrants further investigation in appropriately selected patients or groups of patients.

Disclosures

SEP is an unpaid member of the Scientific Board of Active Life Scientific, manufacturer of the Osteoprobe.

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Authors' roles: Study design: FM, SEP, and NMAD. Study conduct: FM and NMAD. Data collection: FM. Data analysis: FM, SEP, and NMAD. Data interpretation: FM, NATH, SEP, and NMAD. Drafting manuscript: FM, NATH, SEP, and NMAD. Revising manuscript content: FM, NATH, SEP, and NMAD. Approving final version of manuscript: FM, NATH, SEP, and NMAD. FM and NMAD take responsibility for the integrity of the data analysis.

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