Value of impact microindentation in the evaluation of bone fragility in clinical practice

Schoeb, M.

Chapter 9

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

An increasing body of evidence that has accumulated over the past two decades suggests a promising added value of Impact Microindentation using the OsteoProbe® in the evaluation of the contribution of bone tissue-level properties to bone strength. During this time span, it has also become clear that these features may not be captured by the sole measurement of BMD. Our Systematic Review evaluated data from all 38 published studies on the use of IMI, particularly with the use of the OsteoProbe®, up to the year 2019 (12). The review also highlighted the added value of BMSi in identifying fracture risks that were underestimated by the alone use of DXA BMD measurements. There have been only few additional publications on IMI since 2019. An important addition to the literature since then is the reporting of the results of a landmark Multicenter International study by Rufus-Membere et al (13), who set out to define reference interval data for BMSi in healthy adults by analysing *a posteriori* data collected from 479 healthy adult men and women aged 25 to 98 years, from seven research centers from Europe, Australia and the United States of America, including healthy subjects who participated in our IMI studies at the LUMC. Associations between BMSi, age, sex and areal BMD were examined. This study provided the so far missing healthy reference data values that can be used in the calculation of T- and Z-scores for BMSi and thus help confirm the ability of BMSi in predicting fracture risk beyond BMD. However, these data still need to be confirmed in larger prospective studies including populations from additional different geographic regions, as geographical differences are likely to influence BMSi values (12, 14). As discussed in our Systematic Review article, age-matched non-fractured women from Sweden had strikingly lower BMSi values compared with those from The Netherlands or Spain. These variations may also be reflected in differences in fracture risk and should thus be considered when establishing future national reference values, or when comparing data from studies conducted in different geographical areas. Optimal cut-off values to identify those at high fracture risk who might benefit from treatment also remain to be defined.

Importantly, evidence for a diagnostic association between BMSi and prevalent fractures should be distinguished from evidence for the prospective prediction of future fractures. The value of IMI in predicting future fractures also needs to be established. Almost all studies to date used a cross-sectional study design measuring BMSi in patients with prevalent low-energy trauma fractures, also from our group (7, 8, 15-18). These studies showed lower BMSi values in patients who sustained a fracture compared to non-fracture controls. Very few studies used a longitudinal study design such as ours measuring BMSi in treatment-naive patients receiving antiresorptive drugs or calcium and/or Vitamin D alone. These studies were not powered with a fracture endpoint. In the longitudinal study reported in Chapter 4 we also include anecdotal data of two patients in whom fragility fractures occurred during the period of observation. Neither of the two patients was treated with antiresorp-

tive agents, as per the nationally adopted treatment protocols. Both demonstrated a significant decline of 8.5% and 8.9% in their BMSi values at follow-up compared to pre-treatment baseline values. To date, there is only one recently published prospective study from a Swedish group, which investigates the association between baseline BMSi measurements and incident osteoporotic fractures in a population-based cohort of 647 older women with a narrow age range of 75 to 80 years (19). During a median follow-up time of 6 years, 151 of these women sustained an incident fracture. An unexpected significant association was found between a higher and thus better baseline BMSi and an increased risk for incident fractures, also after adjusting for various confounders, or when considering the competing risk of death. This finding is intriguing given that most cross-sectional studies including some of ours have reported lower BMSi in subjects with prevalent fractures (12). However, earlier cross-sectional studies performed by the same Swedish group investigating a smaller subsample of the same cohort also didn't reveal an association between BMSi and prevalent fractures (20, 21). The missing association between BMSi and fractures not only in their earlier studies but also in this prospective study might possibly be explained by the unspecified potential inclusion of incident fractures irrespective of trauma type. It is possible that the inclusion of subjects with high-energy trauma fractures who we have shown to have higher BMSi values than those with low-energy trauma fractures might have diluted the results. Furthermore, data from our systematic review included in this thesis suggest that the measurement of BMSi might not be of much added value in assessing bone fragility in the presence of severely reduced BMD, which is in itself highly predictive of future fractures. Older women included in the Swedish cohort studies actually show some of the lowest reported BMD results among all published IMI studies, which might also partly explain the lack of association between BMSi and incident fractures during the period of observation. On the other hand, findings from our systematic review suggest that tissue material properties, as measured by BMSi using Impact Microindentation, may become more relevant in patients with less severely affected BMD, where bone quality rather than bone quantity is likely to have a greater impact on fracture risk. This hypothesis is further supported by findings from the two studies conducted in this thesis in patients with primary hyperparathyroidism and in patients with Cushing's syndrome in permanent remission.

Notwithstanding, there is still an unmet need for larger-scale prospective trials to be conducted using standardised operating protocols, and including patients with larger age and BMD ranges, to further investigate the value of IMI in predicting future fractures. This is particularly relevant in patients diagnosed with osteopenia, given that more than 50% of fragility fractures occur in patients with osteopenia (22-26) and that most patients with T-scores in that range are currently not being of-

fered treatment with bone-modifying agents according to most nationwide adopted treatment protocols.

Another aspect that needs to be investigated is the value of IMI in predicting outcome of bone-modifying treatments. Our findings from this thesis suggest that in patients with a BMD- or fracture-determined increased fracture risk, treatment with bisphosphonates or denosumab induced BMD-independent increases in BMSi values. The magnitude of treatment-induced BMSi increases depended on pretreatment BMSi values, with the larger increases observed in patients with the lower baseline BMSi values. Similar results were reported in an early prospective longitudinal IMI study in 52 patients receiving glucocorticoids for various underlying disorders concurrently treated with prophylactic anti-osteoporotic medication or calcium/vitamin D alone (10). A further cross-sectional study found that BMSi values were significantly lower in patients treated with bisphosphonates who had incident fractures during treatment compared to patients who did not sustain fractures during treatment (27). However, there are to date no data available from prospective studies powered for fracture endpoints. The threshold at which BMSi values are associated with increased fracture risk thus remains an open question, as does the BMSi threshold achieved during treatment above which the likelihood of a new fracture is lowest. Determining this threshold will help establish, in a treat to target approach, when treatment may be safely discontinued.

Taken together, results of this thesis suggest that IMI may be a valuable and safe tool not only for assessing bone fragility but also for monitoring patients, particularly those with a potentially underestimated fracture risk. BMSi is not a measure of bone mass and no clear relationship between BMSi and BMD has been established. Results of this thesis thus strengthen the notion that measurements of BMSi may be a valuable addition to currently available tools for the assessment of fracture risk, rather than a replacement for individual patient assessments.

However, despite these promising results, some issues with the use of IMI remain to be addressed. On the practical side the IMI technique requires the skills of an experienced operator, and although increasing numbers of young doctors are being trained with its use, this is currently limited to a few expertise centers. There are currently no Clinical Practice Guidelines for the use of the OsteoProbe®. The ability of BMSi to predict future fractures and treatment outcomes, as well as its added value beyond established fracture risk assessment, still needs to be validated in prospective multicenter trials using standardized operating protocols and harmonized operator training before IMI can be recommended for routine clinical use. In selected clinical scenarios in which fracture risk appears to be underestimated by

BMD measurements alone, IMI may provide complementary, BMD-independent information when performed by an experienced operator.