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

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A full-page background image featuring a sunset over a beach. The sun is low on the horizon, casting a warm orange and yellow glow across the sky and reflecting on the water. The sky is filled with soft, pinkish-purple clouds. In the background, a range of rugged mountains is visible. The foreground shows a sandy beach with small pebbles and a large, deep, circular crater or hole dug into the sand.

SUMMARY AND GENERAL DISCUSSION



Chapter 8

SUMMARY OF THIS THESIS

Identifying the patient at increased risk for a fragility fracture remains challenging, especially in patients with secondary causes for osteoporosis, as BMD measurements using DXA have been shown to underestimate true fracture risk not only in secondary but also in primary osteoporosis (1-5). Over the past two decades, evidence has been accumulating for the need to evaluate bone strength beyond DXA BMD values in the assessment of true fracture risk. The Impact Microindentation technique has been demonstrated to be valuable in this respect by allowing the in vivo assessment of tissue-level material properties of bone, which significantly contribute to bone strength, in addition to the contribution of BMD.

Although several studies using the handheld OsteoProbe® device at the location of the mid-shaft of the tibia have demonstrated that measurements of BMSi are independent of measurements of BMD in the prediction of bone fragility, there are still questions to be addressed about the added value of its use in addition to DXA in the clinic, particularly in secondary osteoporosis, and of the general short- and longer-term safety of the technique.

The main findings of the studies included in this thesis are briefly summarized in this chapter.

PART I: INTRODUCTION

In Part I of this thesis, we set the scene for exploring the broader added value of IMI in the evaluation of bone strength in clinical practice by conducting a comprehensive systematic review of all published literature on the topic up to the year 2019. In **Chapter 2** we provide the results of data obtained from all 38 clinical studies using the IMI technique in vivo in humans up to this year, also addressing practical aspects of the technique. We also identified gaps and inconsistencies in the methodology and interpretation of data, mainly related to the lack of a standard operating procedure for the technique up to its publication in 2016 (6). Data from these 38 studies highlight the ability of IMI in identifying patients with increased bone fragility. This includes patients with primary osteoporosis with prevalent fragility fractures, especially those with osteopenia, most of whom are not currently being treated with bone-modifying agents under commonly adopted nationwide protocols. Findings from this systematic review consolidate the view that IMI may indeed represent a valuable tool for identifying patients with primary osteoporosis at increased fracture risk, particularly those with osteopenia, in whom DXA fails to adequately evaluate that risk. Although limited to three smaller studies, the review also suggests the ability of the technique in detecting changes in BMSi in patients on bone-modifying therapies thus highlighting the potential role of IMI in monitoring patients with

elevated fracture risk. Results further underscore the value of IMI in patients with or at risk for secondary osteoporosis due to various systemic disorders including endocrine conditions such as diabetes mellitus or acromegaly. From safety data gathered for our systematic review, IMI is reported to be well tolerated during and immediately after the investigation, but there are so far no published data on the longer-term safety and acceptability of IMI measurements performed with the handheld OsteoProbe® device.

PART II: EVALUATION OF BONE FRAGILITY USING IMPACT MICROINDENTATION IN PRIMARY AND SECONDARY OSTEOPOROSIS

Part II of this thesis addresses the value of IMI in the assessment of bone strength not only in patients with low-energy trauma fractures, in the majority of whom BMSi values have been previously documented to be lower compared to non-fracture controls, but also in subjects with high-energy trauma fractures in whom this has never been previously investigated. In addition, this part explores the ability of IMI to detect longitudinal changes in BMSi in response to anti-osteoporotic treatment and its contribution to the evaluation of bone fragility in secondary osteoporosis due to endocrine disorders, specifically primary hyperparathyroidism and endogenous Cushing's syndrome (CS).

In Chapter 3, results of BMSi measured in forty patients with high-energy trauma fractures, who were attending our fracture liaison service (FLS) or the outpatient clinic of the Center for Bone Quality of the LUMC, were compared with those of gender- and age-matched patients with comparable fractures due to low-energy trauma also attending the FLS. Patients who had sustained one or more high-energy trauma fracture(s) were found to have significantly higher BMSi than their matched controls who sustained a low-energy trauma fracture. Data from this study also show that BMSi values did not differ between patients with osteopenia and those with osteoporosis within each trauma group. BMSi values of patients with high-energy trauma fractures were otherwise comparable to those previously reported in subjects without a fracture (7, 8). These data suggest that tissue-level properties of cortical bone are not impaired in patients with high-energy trauma fractures.

In Chapter 4, we address the issue whether changes in BMSi values are observed over time in patients receiving anti-osteoporotic treatments. We also assessed whether any observed changes in BMSi might provide additional information to that provided by changes in BMD measurements. To this effect, we assessed the longitudinal changes in BMSi and in BMD in treatment-naïve patients with osteopenia or

osteoporosis with or without fractures who were treated with either antiresorptive agents in the form of bisphosphonates or Denosumab with vitamin D $\pm$ calcium supplements, or with only vitamin D $\pm$ calcium supplements (control group) following Dutch national guidelines for the management of osteoporosis. Our results show that treatment with bisphosphonates or denosumab for a mean period of 2 years, increases BMSi values in patients with low bone mass and increased risk of fracture, while they remain unchanged in the control group. The values of BMSi reached with antiresorptive treatment were comparable to the baseline values of the control group, as well as to those previously reported in patients with low bone mass without fractures (7, 8). The magnitude of BMSi changes depended on baseline values with larger increases observed in patients with the lower baseline values. Lumbar spine and total hip BMD values also increased in patients treated with bisphosphonates or denosumab, but the observed increases in BMD values were not associated with changes in BMSi values. Findings from this study thus suggest that IMI can capture BMD-independent, treatment-induced changes in BMSi, and may further be a useful addition to currently available tools for the assessment and follow-up of patients at increased fracture risk.

The assessment of BMSi using IMI is of particular interest in the evaluation of patients with secondary osteoporosis due to endocrine diseases, in which traditional measurements of BMD have been shown to underestimate fracture risk. In **Chapter 5**, we evaluated tissue-level properties of bone in 37 men and women with primary hyperparathyroidism (PHPT), and in 37 non-PHPT controls matched for gender, age and fragility fracture status. Patients and controls were studied at the outpatient clinic of the Department of Endocrinology of the LUMC which is a national expertise center for PHPT. In keeping with a preliminary report by Starr et al., published in abstract form, which demonstrated significantly lower BMSi values in 13 subjects with PHPT compared to 22 non-PHPT matched controls (9), our findings demonstrate significantly lower BMSi values in patients with PHPT compared to non-PHPT controls, independently of BMD values. Our data also show significantly lower BMSi values in patients with PHPT and prevalent fragility fractures compared to patients with PHPT without fragility fractures, and that BMSi values were inversely related to the severity of the hyperparathyroidism. These data indicate that tissue-level properties of bone are impaired in patients with PHPT, potentially contributing to the higher fracture risk observed in this population. This increased risk appears disproportionate to what would be anticipated based on BMD measurements alone and is likely to be attributable to impairments in material properties affecting both cortical and trabecular bone compartments.

In **Chapter 6**, we report the findings of a study on the value of BMSi in the assessment of fracture risk in endogenous Cushing's syndrome (CS), a markedly less

frequent endocrine disease than PHPT, although also associated with osteoporosis and fragility fractures as main clinical manifestations. In these patients, BMD has been observed to increase toward values within the normal range following successful treatment and remission of the disease, but fracture risk remains increased. At the LUMC, which is the coordinating center of the European Reference Network for Rare Endocrine conditions, and a European reference center for pituitary and adrenal diseases, we have a well-characterized cohort of patients with CS in remission after treatment. To further investigate the discrepancy between BMD data and fracture risk, we evaluated BMSi values in 60 patients with CS, a median of 6 years after achieving remission, and compared their data with 60 gender-, age- and BMD-matched controls. We found significantly lower BMSi values in patients with CS in remission than in controls, and BMSi values were also negatively correlated to BMI in patients with CS in remission compared to controls. This finding might reflect the length and severity of cortisol exposure and its deleterious effects on tissue-level properties of bone during active disease, which may persist and may be permanently impaired after complete CS remission is achieved. Strikingly, BMSi values of our CS cohort after long-term remission were comparably low as those measured in subjects treated with exogenous glucocorticoids, known to rapidly increase fracture risk, for more than 20 weeks for various underlying disorders in another study (10). These data highlight the necessity of a comprehensive evaluation of bone health in all patients with CS, both at the time of diagnosis and also after long-term remission.

PART III: EVALUATION OF THE SAFETY AND ACCEPTABILITY OF THE IMPACT MICROINDENTATION TECHNIQUE

IMI is being increasingly used in studies evaluating the contribution of tissue material properties to bone fragility in humans, and the OsteoProbe® has been approved for use in the clinic in Europe and the United States. Previous data show that IMI is well tolerated during and immediately after the procedure (11). However, it is important to establish whether this transcutaneous minimally invasive procedure is safe during and immediately after the procedure and whether it is well accepted by patients.

In **Chapter 7**, we address these issues by prospectively following patients with primary or secondary osteoporosis who participated in studies included in this thesis for 30 days after IMI measurements. The thirty-day post-IMI complication rate was found to be very low at 2.8%. No serious adverse events were observed neither immediately post-measurement, nor at the 1-week or at the 1-month follow-up time points. Only three minor adverse events were noted: one patient developed a small bruise at the indentation site, and two patients experienced very small hemato-

mas—one of whom was receiving antiplatelet therapy (Aspirin). These events were mild, described as a visible measurement spot, and had resolved by the 1-month follow-up time point. In none of the patients were clinical signs of local infection observed at any of the time points of assessment. From the acceptability point of view, all patients expressed their willingness to undergo the procedure again and rated the measurement acceptable for use in other patients. These data confirm that although minimally-invasive, IMI using the OsteoProbe® at the site of the midshaft of the tibia is a very safe and well-accepted procedure in the hands of an experienced operator, as is the case in our center.