



Bone quality in endocrine diseases: determinants and clinical relevance

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Abstract

Purpose Bone is one of the main targets of hormones and endocrine diseases are frequent causes of secondary osteoporosis and fractures in real-world clinical practice. However, diagnosis of skeletal fragility and prediction of fractures in this setting could be a challenge, since the skeletal alterations induced by endocrine disorders are not generally captured by dual-energy X-ray absorptiometry (DXA) measurement of bone mineral density (BMD), that is the gold standard for diagnosis of osteoporosis in the general population. The aim of this paper is to review the existing evidence related to bone quality features in endocrine diseases, proposing assessment with new techniques in the future.

Methods A comprehensive search within electronic databases was performed to collect reports of bone quality in primary hyperparathyroidism, hypoparathyroidism, hyperthyroidism, hypercortisolism, growth hormone deficiency, acromegaly, male hypogonadism and diabetes mellitus.

Results Using invasive and non-invasive techniques, such as high-resolution peripheral quantitative computed tomography or DXA measurement of trabecular bone score (TBS), several studies consistently reported altered bone quality as predominant determinant of fragility fractures in subjects affected by chronic endocrine disorders.

Conclusions Assessment of skeletal fragility in endocrine diseases might take advantage from the use of techniques to detect perturbation in bone architecture with the aim of best identifying patients at high risk of fractures.

Keywords Bone quality · Hormones · Bone structure · Hyperparathyroidism · Diabetes · Hyperthyroidism · Cushing syndrome · Acromegaly · Growth hormone deficiency · Hypogonadism · TBS REMS

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Introduction

The silent pandemic of osteoporosis and its logical consequence, i.e. fragility fractures, are globally spreading, constituting a challenge for the majority of health systems [1]. Assessment and treatment of osteoporosis is mandatory in both sexes, in order to decrease the risk of fracture and the burden of osteoporotic fractures worldwide [2]. Up to 40% of osteoporotic postmenopausal women and 60% of osteoporotic men can harbor a secondary cause of bone loss, including rheumatological, gastrointestinal, hematological, neurological and endocrine diseases [3]. Thus, in the diagnostic work-up of a patient with osteoporosis, secondary causes of osteoporosis, most of all of endocrine nature, must always be ruled out [4]. Conversely, bone assessment and evaluation of fracture risk is mandatory for a comprehensive evaluation of patients with most endocrinopathies before and after treatment. Indeed, bone is a target organ of major hormones and bone remodeling is deeply influenced by pathological changes in their levels. The evaluation of bone mineral density (BMD) by means of dual-energy X-ray absorptiometry (DXA) with its incorporation into prediction algorithms, constitutes a mainstay in the evaluation of the risk of fragility fractures and has provided the practical definition of osteoporosis, as based on the *T*-score less than -2.5 standard deviation, originally established for postmenopausal women [5]. Nonetheless, the majority of patients with fragility fractures show *T*-scores above -2.5 standard deviation, especially in the setting of secondary osteoporosis and, in particular, endocrine diseases. Several reports in the last years have shown that endocrinopathies are associated with altered bone strength leading to increased fracture risk, at least in part independent of bone quantity as derived from DXA parameters, but mainly relying on hampering of bone quality as directly or indirectly assessed by different techniques [3].

To our knowledge, so far, no study has focused on available data on bone quality in major endocrinopathies affecting skeletal tissue in adults. The aim of this paper is to review the existing evidence related to bone quality features in diseases characterized by hyperfunction or hypofunction of major endocrine glands, namely parathyroid and thyroid disorders, hypercortisolism, growth hormone disorders, male hypogonadism and diabetes, starting from the definition and assessment of bone quality in clinical practice. For this purpose, a PubMed search up to December 2022 has been performed using the terms: “bone quality/qualities”, “trabecular bone score/TBS”, “bone strength index/BSI”, “central quantitative computed tomography/cQCT”, “peripheral quantitative computed tomography/pQCT”, “high resolution peripheral QCT/HR-pQCT”, “radiofrequency echographic multispectrometry/REMS”,

“magnetic resonance imaging/MRI”, “histomorphometry”, “microindentation”, “fractures”, “meta-analysis” and major endocrinopathies (“hyperparathyroidism”, “hypoparathyroidism”, “hyperthyroidism”, “hypothyroidism”, “GH excess/acromegaly”, “GH deficiency”, “hypercortisolism/Cushing syndrome”, “hypogonadism”, “diabetes”), with a main focus on in vivo results.

Bone quality or bone qualities: definition and clinical significance

In major endocrinopathies, bone is a target organ for altered bone quantity and quality, both leading to a decrease in its strength, as demonstrated by the increased rate of prevalent vertebral fractures, as assessed by vertebral morphometry, and previous/incident clinical fractures, regardless of BMD values [4, 6]. Indeed, although BMD as determined by DXA is one of the major determinants of fracture risk, reducing a 3-D structure to a 2-dimensional analysis poses great limit for the assessment of the complexity of bone structure.

Total bone mass, bone geometry and design, and material composition contributes to structural integrity of bones, shaped and constantly re-cycled by modeling and remodeling processes, respectively [7, 8].

In the last two decades, the concept of bone quality and its assessment has acquired a major role in the understanding and proper estimating bone fragility and explain the reduction of fracture risk as obtained by anti-osteoporotic treatments. Bone quality is a complex term and refers to the multifaceted properties of bone tissues, first of all micro-architecture, as determinants of bone competence to resist to fracture [9].

Bone quality, as distinct from bone quantity, stands for the intrinsic biomechanical characteristics, conferring strength and stiffness to the skeletal tissue, which are not accounted for bone mass (quantity) determination by DXA, which provide areal bone mineral density. Indeed, the knowledge of bone quality ensues from integrated competencies of a number of disciplines such as clinicians, biologists, physicists, and engineers and refers to the essential or distinctive characteristics, properties, or attributes of bone [10]. These features, whose integrity is needed for bone resistance, reflect the hierarchical macro-to-nanoscale structure of the bone tissue, which can be mainly assessed in research settings [11] (Fig. 1).

The balance between toughness and stiffness must be preserved in the skeleton to maintain structural strength. Collagen fibrils organized in triple helixes appropriately cross-linked together, confer strength in tightness, nevertheless allowing flexibility. The addition of hydroxyapatite crystals to the matrix confers stiffness. Nonetheless, since

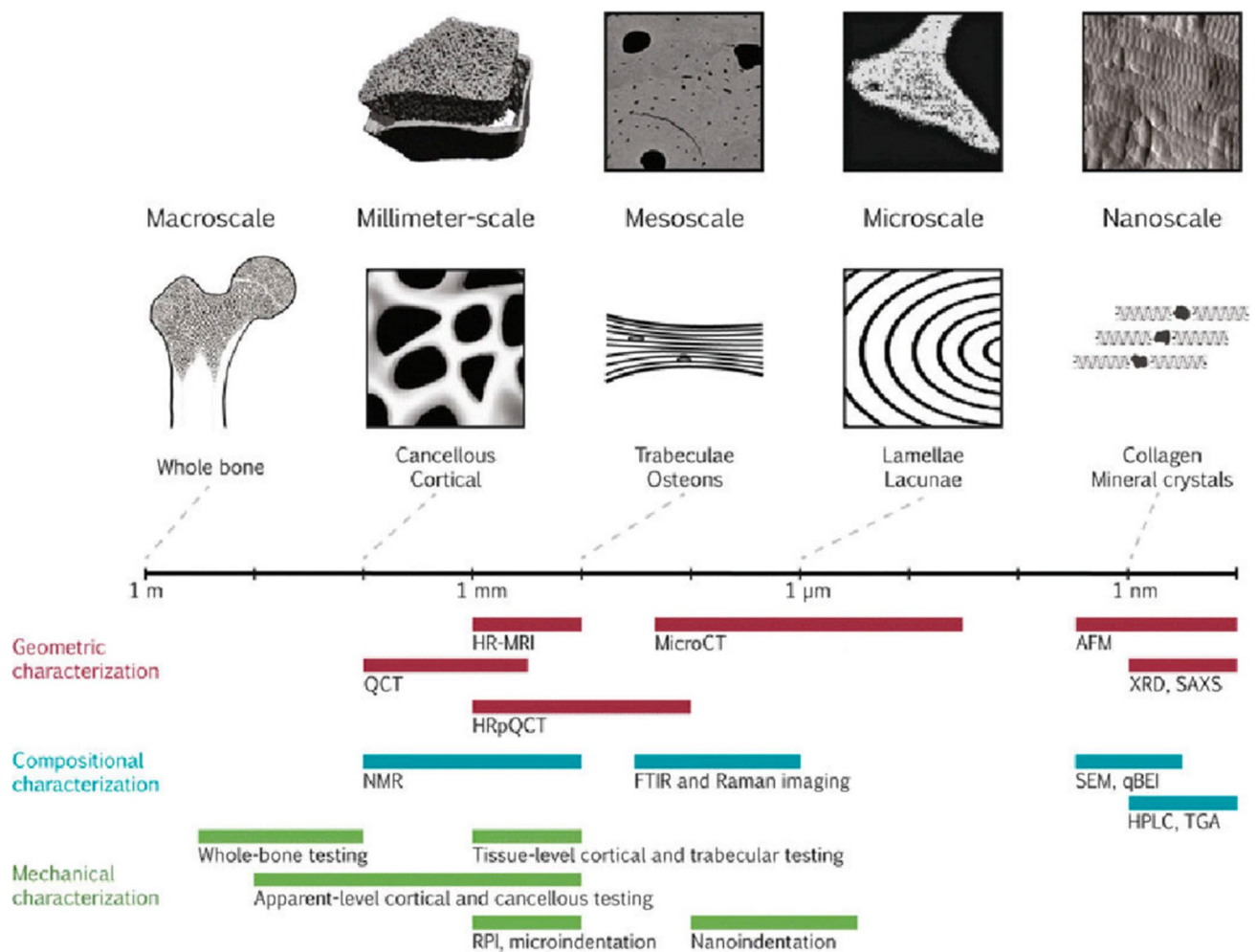


Fig. 1 Bone quality measurement techniques depicted on a logarithmic scale of the hierarchical structure of bone. Each characterization technique is categorized as geometric, compositional, or mechanical and is depicted by a bar showing the approximate range of resolutions currently achievable. *AFM* atomic force microscopy; *FTIR* Fourier transform infrared; *HPLC* high-performance liquid chromatography; *HR-MRI* high resolution magnetic resonance imaging; *HR-pQCT*

high-resolution peripheral quantitative computed tomography; *micro-CT* micro-computed tomography; *NMR* nuclear magnetic resonance imaging; *qBEI* quantitative back scattered electronic imaging; *QCT* quantitative computed tomography; *RPI* reference point indentation; *SAXS* small-angle scattering; *SEM* scanning electron microscopy; *TGA* thermogravimetric analysis; *XRD* x-ray diffraction (reproduced with permission from Ref. [11])

human skeletal tissue is about 60% mineralized, flexibility and lightness are preserved to deform to bending or compression forces without breaking and to allow movement, respectively. The complexity of the architecture of the skeletal tissue at a microscopic level, i.e., the number of osteons in cortical bone, contributes to limit the propagation of microcracks in the bone, allowing remodeling process to resorb and substitute the damaged tissue with new bone [12].

At a macroscopic level, trabecular and cortical bone are shaped to display a structure specifically suitable to the purpose of sustain, absorb forces and resist to fracture. In trabecular bone, the connectivity of the trabeculae as determined by their thickness and number ensure lightness and flexibility. Diameter and thickness of cortical bone, shaped by periosteal apposition and endosteal resorption, especially

during modeling, contribute to the resistance of long bone to bending. Adaptation in size and shape during modeling occur in response to load [12].

Negative balance in the bone multicellular unit between bone formation and resorption observed during aging or diseases, somehow combined with a higher remodeling rate lead to bone loss, deterioration of bone qualities and increased fracture risk. In cancellous bone this is reflected by a decrease in the number and thickness, and an increase in trabecular perforation, all leading to loss of connectivity of trabecular plates. In cortical bone, the increased intracortical and endocortical remodeling causes the trabecularization of the cortex. Moreover, a decreased periosteal apposition contributes to the thinning of the bone cortex together with the increased endocortical reabsorption [9, 13].

These changes in the macroscopic structure of the bone are nowadays recognized as some of the main culprits of bone fragility during the aging process or diseases affecting bone and can even precede or occur in the absence of modifications of areal bone mineral density as identified by DXA [14]. Moreover, all the listed properties, which can be also affected during endocrine malfunction, cannot be merely reconducted just to the 2-dimensional DXA report, so that other tools have been developed to assess these features and provide better estimate of bone fragility.

Assessment of bone quality in clinical practice and research

Despite BMD derived by DXA is not able to fully evaluate the above-mentioned bone qualitative aspects that predispose to fragility fractures, this technique is still considered the standard of reference in clinical practice for bone densitometry. This is because of its several strengths over more advanced techniques, such as the extremely low radiation dose to patients, the evaluation of central skeletal sites, its low costs and wide availability [15]. Therefore, many DXA-based tools have been developed during time to explore skeletal features of bone quality, to refine fracture risk prediction.

In the early 2010s, the Trabecular Bone Score (TBS) has been developed as a DXA-based software applied to lumbar spine images, and represents one of the most successful

and well-known experiments in this field. The software can discriminate gray-level variations in the DXA image pixels; despite TBS does not provide a direct measurement of trabecular microarchitecture (due to technical constraints related to the pixel width of DXA image, which is about four time larger the mean size of trabeculae), ex-vivo and in-vivo studies showed how TBS can predict fracture risk independently of BMD [16]. It is now recognized that TBS provides indirect information about trabecular microarchitecture by means of a textural analysis: higher TBS values (> 1.310) are associated with normal microarchitecture, while lower TBS values (< 1.230) are associated with degraded microarchitecture [17] (Fig. 2). TBS report can be easily obtained on the same DXA region of interest. Other advantages of TBS are that, compared to BMD, is less affected by degenerative spinal changes, but also that it can be incorporated into the FRAX[®] to adjust a 10-year fracture probability [18, 19]. Adjustment of BMD *T*-score according to TBS values was recently proposed as a new approach for using TBS in clinical practice and enhancing fracture risk prediction independently of BMD [17]. TBS adjustment to the BMD *T*-score was based upon the change in TBS that would give the same predicted risk as a unit change in the BMD *T*-score. The Cox proportional hazards model used for TBS adjustment of BMD *T*-score paralleled the approach used for developing the TBS-adjustment to FRAX [19]. Interestingly, high agreement was found between probabilities of major osteoporotic fractures estimated by TBS-adjusted FRAX and those estimated by TBS-adjusted BMD [17].

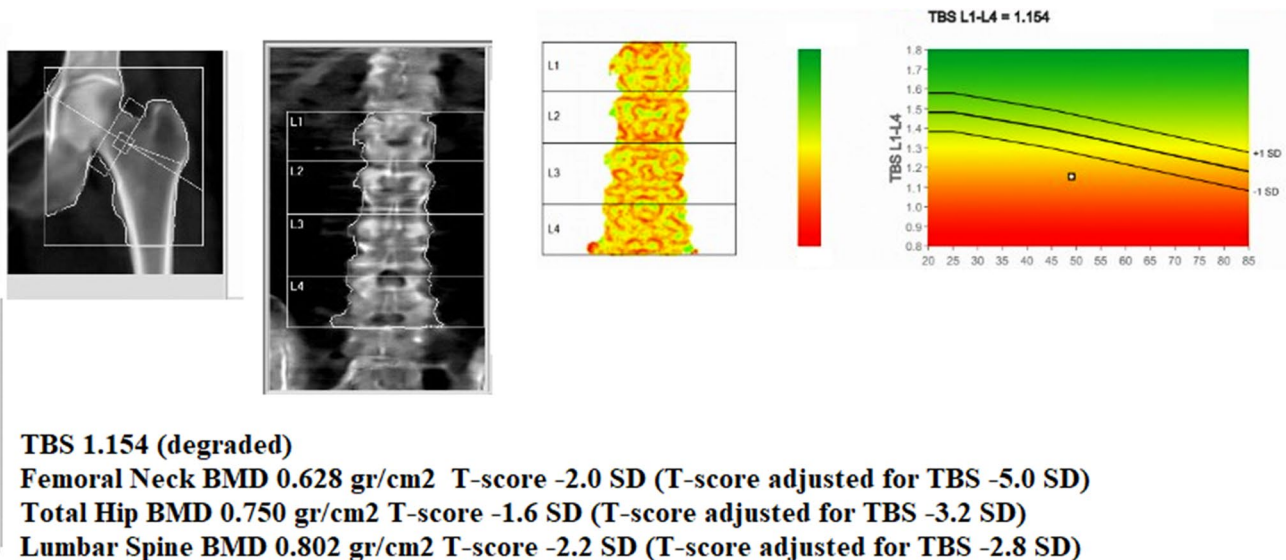


Fig. 2 Dual-energy X-ray absorptiometry (DXA) measurement of bone mineral density (BMD) and trabecular bone score (TBS) in a 49 years old post-menopausal woman with Cushing syndrome. This is a paradigmatic clinical case in which TBS was degraded notwithstanding BMD values were in the range of osteopenia. Noteworthy,

the BMD *T*-score values moved in the range of osteoporosis after adjustment for TBS, according to the mathematical model proposed by Leslie et al. [17], which parallels the approach used for developing the TBS-adjustment to FRAX [19]

A more recent DXA-based software has been introduced in 2019 with the name of Bone Strain Index (BSI) and relies on the application of finite element analysis (FEA) mathematical model to DXA images [20]. The principle beyond FEA is that the analysis of a complex object can be made simple by dividing it into a model of many smaller elements (the so-called “finite elements”), and then simulate on this model any specific conditions. BSI analysis can be done both at lumbar spine and proximal femur, with the aim of identifying those regions of the bone at higher mechanical stress, hence easier to fracture [20]. BSI software divides DXA area of analysis into small triangles, to generate a specific FEA mathematical model both for lumbar spine and proximal femur. At the spine, the load is applied to the upper vertebral plate simulating the gravity, while at the femur the load is applied to the greater trochanter simulating a lateral fall. The supposed bone load is obtained from patient-specific simulated forces, as well as patient’s body mass index. Higher BSI values indicate higher strain and fracture risk, while lower BSI values indicate less strain to the bone and lower fracture risk. Proposed BSI threshold values for the Italian population indicate normal resistance to strain for $BSI \leq 1.7$, and poor resistance for $BSI \geq 2.5$ [21].

As for DXA, computed tomography (CT) based techniques relies on X-rays, but the latter offer a cross-sectional visualization of bony structures. Therefore, with CT is possible to get measurements of trabecular and cortical bone separately. Quantitative CT (QCT) and high-resolution peripheral quantitative CT (HR-pQCT) are the two most used CT techniques for bone evaluation. They differ, among the others, for spatial resolution, and this is reflected in the type and size of bone they can measure. QCT, with a namely resolution of 250–300 μm , is typically applied to lumbar spine and proximal femur using whole body scanners [15, 22]. To obtain volumetric BMD (vBMD) values, a calibration of CT Hounsfield Unit (HU) is needed, and this is done with the use of phantoms containing a set of known density values of hydroxyapatite samples. In the case of synchronous calibration, such phantoms are placed under the patients inside the CT table. For asynchronous calibration, the phantom is scanned periodically allowing vBMD values to be obtained during routine CT exams in the absence of a phantom. The International Society for Clinical Densitometry (ISCD) indicates that *T*-score values obtained from QCT can be used for osteoporosis diagnosis only at femoral neck and total hip, as they are equivalent to DXA *T*-score [23]. At the spine, however, there is discordance between *T*-scores obtained by DXA and QCT [24], that could be more evident in presence of artifacts due to degenerative diseases or vertebral fractures (Fig. 3). To avoid diagnostic confusion that could result from different *T*-scores and facilitate the interpretation of QCT spine results, diagnostic cut points (120 mg/cm^3 and

80 mg/cm^3) were used to assign a diagnostic category based on QCT measurements [25].

HR-pQCT is currently the most powerful tool for the evaluation of bone quality. Thanks to its very high spatial resolution (82 μm , very close to the *in-vivo* range of trabecular scale) HR-pQCT can measure total, trabecular and cortical vBMD, also providing several parameters related to bone microarchitecture and quality. Among the various parameters, cortical vBMD, trabecular thickness (a measure of the mean thickness of trabeculae) and bone stiffness (a measure of bone strength derived by HR-pQCT) are reported to be the best predictor of fragility fracture, especially when measured at the distal radius [26]. Advantages of HR-pQCT are the short acquisition time (about 3 min) and the very low radiation exposure to patient. Drawbacks are the need for small field of views that limit HR-pQCT applicability to non-central sites (distal ulna and radius), as well the fact that it remains a rather expensive technique with limited clinical applicability.

Radiomics analysis on opportunistic CT scan has been proposed as promising technique for analyzing the textures and spatial heterogeneity in subjects with skeletal fragility at risk of vertebral fractures [27, 28]. Radiomics refers to comprehensive, automated high-throughput mining of quantitative medical image features to capture disease characteristics that are difficult to identify by the human eye; in turn, this supports clinical decision making with improved diagnostic and/or predictive performance [29, 30].

The last *in-vivo* technique that can provide information about cortical and trabecular parameters is high-resolution MRI (HR-MRI), which of course has the advantages over CT of being a non-ionizing technique that can be used both at central and peripheral sites. MRI image relies on the fact that cortical and trabecular bone do not produce signal, compared to the fatty replaced marrow spaces. Despite HR-MRI sequences can reach very high spatial resolution, its use is still mainly limited to research practice because it is technically difficult to perform and requires long post-processing time from experienced operators, resulting in limited availability and consistency of measurements between different scanners [22].

Another non-ionizing technique recently introduced is the Radiofrequency Echographic Multi-Spectrometry (REMS), which uses an ultrasound device to obtain spectral analysis of the raw unfiltered ultrasound signals reflected by bones. REMS is applied to lumbar spine and femur and is able to obtain -similarly to DXA- ultrasound BMD value expressed as g/cm^2 . A significant correlation between BMD measured by REMS and DXA has been reported, together with very good precision values [31]. A recent REMS-derived “fragility score” has been developed as indicator of bone quality that is independent of BMD: low values of fragility score are associated with higher quality of the evaluated bone [32].

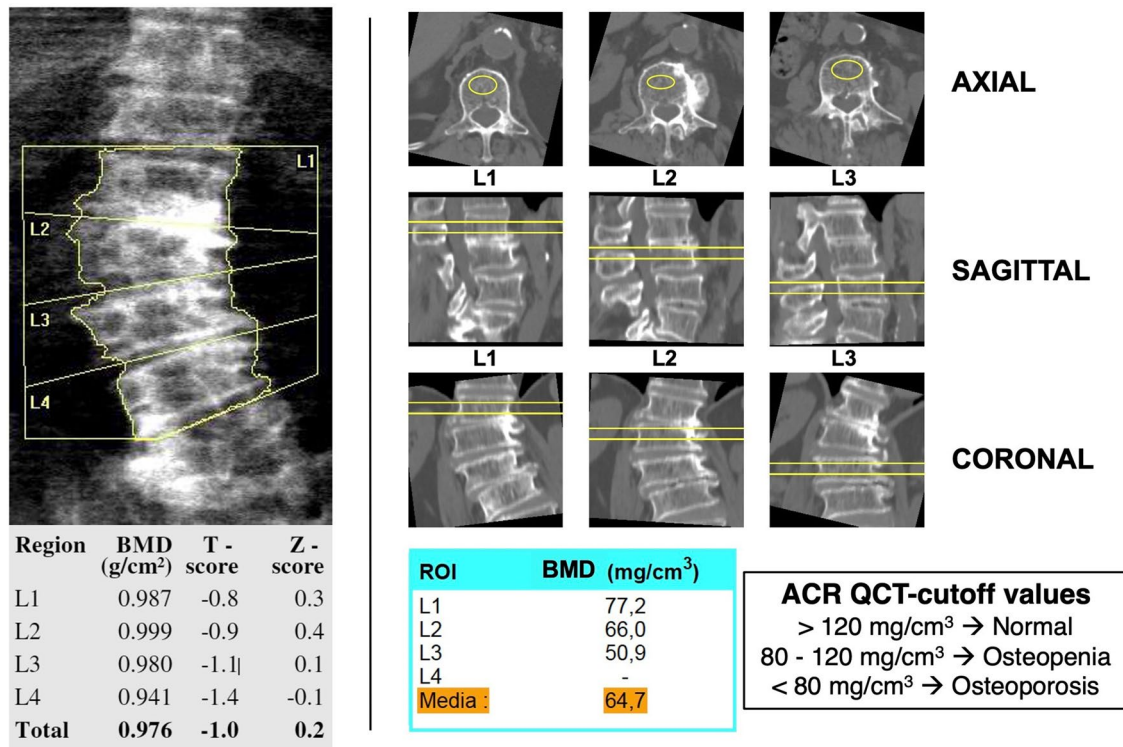


Fig. 3 Image showing the added value of QCT analysis in a female subject of 82 years old with severe osteoarthritis at lumbar spine. The DXA scan on the left side has poor diagnostic value due to extensive arthrosis related to degenerative scoliosis, and normal T-score values. The corresponding QCT analysis on the right side

allows for selective selection of trabecular region of interests, avoiding areas of bone sclerosis, with volumetric BMD values (mg/cm³) in the range of osteoporosis. QCT thresholds are expressed according to the American College of Radiology (ACR) classification [25]

Techniques to be exploited in the future to directly assess bone resistance to applied forces include impact microindentation, a method to directly assess tissue-level material properties of cortical bone *in vivo* in humans, also referred to as Reference Point Indentation (RPI). This method employs a single hand-held RPI device, i.e. a stainless-steel probe with sphericoconical tip (Osteoprobe[®]) which imparts a single impact load to the bone surface and receiving a feedback from the bone proportional to its resistance, defined as bone material strength index (BMSi) [33]. To date, no reference range has been published and no data are available in patients with endocrine diseases.

Ex vivo techniques such as back scattering electron imaging (BSEI) to assess mineralization, both static and dynamic histomorphometry on bone specimens, and vibrational spectroscopic techniques are additional systems to assess skeletal microstructure. Nonetheless, they have been left out of this paper since they are referred mainly to research settings and not routinely performed in clinical practice.

Bone quality in parathyroid disorders

Besides the effects on calcium homeostasis, parathyroid hormone (PTH) directly influences bone remodeling with significant effect on BMD and bone quality exerted by both chronic hormone excess and deficiency.

Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is defined as hypercalcemia and concomitant hyperparathyroidism or inappropriately elevated PTH secretion. It is the third most common endocrine disorder, after diabetes and thyroid diseases, in postmenopausal women. It is sustained by parathyroid cells proliferations, mainly as benign adenomas or multiglandular hyperplasia, rarely as carcinomas. PTH is deeply involved in bone metabolism by promoting both bone resorption and formation. Therefore, bone is a main target of PHPT. In the rare classical PHPT

phenotype, osteitis fibrosa cystica (OFC), was the hallmark of the disease [34]. It was characterized by brown tumors on long bones, evidence of subperiosteal bone resorption, "salt and pepper" radiographic erosions of the skull bones, and tapering of the distal portions of the finger bones and clavicles [34]. However, it has been reported that prevalence of milder signs of OFC, such as subperiosteal bone resorption in the fingers and skull mottling, are not uncommon in current PHPT clinical presentation [35].

The current most common clinical presentation of PHPT is characterized by mild disease with an increased risk of fragility fractures. PHPT predominantly occurs in post-menopausal women, who have an increased risk of osteoporosis and fractures due to ageing and loss of the protective effects of estrogen, and PHPT further increases this risk.

Early studies assessing BMD by DXA in PHPT patients demonstrated preferential reduction of BMD at sites with predominantly cortical bone such as the radius, with relative sparing of sites with predominantly trabecular bone such as the lumbar spine [36, 37].

Histomorphometry from iliac crest biopsies of patients with PHPT demonstrated increased bone turnover, thinning of cortical bone, and increased cancellous bone volume, suggesting preservation and even an increase in trabecular bone volume in PHPT patients [38].

Despite the preserved BMD at the lumbar spine by DXA, individuals with PHPT have an increased incidence of both vertebral and non-vertebral fractures [39–41], suggesting an impairment of bone microarchitecture in PHPT patients. Consequently, non-invasive techniques assessing trabecular and cortical microstructure, such as peripheral QCT, HRpQCT and TBS have been considered of interest. By pQCT and HRpQCT, abnormalities were observed at both trabecular and cortical sites in postmenopausal women with PHPT [42–44]. In adults with PHPT, a good correlation between HRpQCT and TBS has been found [45]. TBS has been shown to be reduced in more than a half of PHPT patients [46] and significantly associated with vertebral fractures in postmenopausal women and in older men with PHPT, independently of lumbar spine BMD, with less evidence of correlation with non-vertebral or total fractures [47, 48]. Recently, in a small cohort of adult Australian PHPT patients follow up for 10 years, the addition of TBS to BMD showed a trend to improve fracture prediction without reaching statistical significance [46].

Besides low TBS, there is evidence that PHPT might be associated also with high BSI values that resulted to have moderate accuracy in identifying subjects with vertebral fractures [49].

A clue of the outcome of surgical resolution of PHPT by parathyroidectomy is related to the reduction of the risk of fractures [50]. However, studies examining changes in TBS after parathyroidectomy are conflicting, with some

showing improvement in TBS [48, 51] and others showing no change [46, 52, 53], which may be related to differences in the population studied, disease severity, or sample size. Using HRpQCT, 1- and 2-year studies showed improvements in cortical and trabecular compartments after surgical cure of primary PHPT [54, 55]. It is still unknown whether cinacalcet might induce effects on bone quality in subjects with PHPT [56].

In conclusion, bone quality assessment by HRpQCT or TBS may improve the fracture risk estimation in PHPT patients and can be useful in the indication of parathyroidectomy; however, further robust studies are advisable.

Hypoparathyroidism

Hypoparathyroidism (HypoPT) is characterized by absence or deficient PTH secretion causing hypocalcemia. It is a rare disorder, whose clinical expression depends on the etiology [57]; genetic, idiopathic and autoimmune disorders are by definition chronic conditions, while chronic postsurgical HypoPT is defined when the disorder persists 6 months after neck surgery [58]. As in PHPT, complications of persistently deficient or absent PTH secretion involve the skeleton.

Bone remodeling is persistently low in HypoPT, as demonstrated by histomorphometric studies [59, 60]. The assessment of bone formation rate by tetracycline labeling showed lower values in HypoPT compared to control subjects on the cancellous, endocortical and intracortical surfaces [59, 60]. Mineral apposition rate and mineralizing surface, as well as osteoid width and surface are reduced, concomitantly with a significant lower bone resorption rate [59, 60]. As a consequence, higher, unmineralized, bone tissue is made [59, 60]. Trabecular bone volume is increased in HypoPT, mostly in association with higher trabecular width, and there is a trend towards an increase in cortical width and decreased cortical porosity [60, 61]. The low bone remodeling and the increased bone volume described in histomorphometric studies are concordant with the assessment of biochemical markers of bone turnover, that are typically in the low range of normal, and the high BMD by DXA observed in HypoPT [60, 62].

Assessment of trabecular microarchitecture by TBS was performed in five clinical studies with a total of 317 patients [52, 63–66]. Overall, they were concordant in illustrating that the degraded trabecular microarchitecture is evident in HypoPT postmenopausal women with postsurgical HypoPT [64, 66]. Sakane et al. studied a cohort of patients with postsurgical HypoPT (85.4% female, 68.6% postmenopausal) and found that more than 30% (mostly postmenopausal women) had TBS values below the normal cutoff value (1.31) [64]. In an Italian cohort of 50 postmenopausal women with postsurgical hypoparathyroidism, mean TBS values were well below the normal range and were not

different compared to healthy age- and sex-matched controls [66]. Conversely, mean TBS values are above the normal range in HypoPT cohorts including non-surgical patients [52, 63, 65]. As far as the effect of menopause on TBS in this group, results are not concordant [63, 65]. Similar values in pre- and post-menopausal HypoPT women are described in one study [63], while lower TBS values and higher rate of values within the “degraded microarchitecture” pattern in postmenopausal compared to the pre-menopausal counterpart are reported in another cohort [65].

Results on the role of TBS as determinant of vertebral fractures risk are not concordant among studies; two of them excluded [65, 66], while one confirmed [64] that TBS could be considered as predictor of vertebral fractures in HypoPT subjects. Non definitive results were observed in terms of TBS changes during recombinant human (rh) PTH(1–84) therapy; a trend towards an increase in TBS values, although not significant in some cases, was observed [52, 63].

Noninvasive assessment of bone quality by pQCT showed higher trabecular vBMD values in HypoPT compared to healthy subjects [67]. By HRpQCT, trabecular vBMD and trabecular number are higher in younger HypoPT compared to age and sex-matched controls [68, 69]. Trabecular thickness and separation was lower at the tibia in post-surgical and nonsurgical HypoPT of different age classes [68–70]. As far as the cortical compartment, different results are reported by clinical studies [68–70]. Cortical volumetric density was reported as higher, comparable and lower in HypoPT compared to controls, according to different population studied and methodologies used [62, 68–70]. Cortical porosity was lower at the radius and tibia in HypoPT [68–70]. During rhPTH(1–84) therapy, trabecular vBMD declines after 5 years and returned to baseline values afterwards; conversely, there is a continuous decline in cortical vBMD up to 12 years [71].

The overall evidence shows that bone quality may be impaired in HypoPT, particularly at the trabecular sites, with potential higher risk of vertebral fractures in postmenopausal women. More data are definitely needed to assess eventual differences in bone quality between different age groups and etiologies of the disease, as well as the association with fracture risk.

Bone quality in thyroid disorders

Thyroid hormones have physiological stimulatory effects on bone remodeling and bone mineralization, and normal euthyroid status during childhood and adolescence is required for acquisition of peak bone mass [72]. Interestingly, also thyrotropin (TSH) can act directly on bone cells possibly modulating the skeletal effects of thyroid hormones. Specifically, in pre-clinical and clinical studies, TSH was

shown to inhibit osteoclastogenesis and bone resorption [73]. Indeed, low TSH values might contribute to bone loss in subjects with hyperthyroidism [74].

Both excess and defect of thyroid hormones have been linked to bone fragility with various degree of evidence [75].

Prolonged, overt endogenous or exogenous thyrotoxicosis is a known cause risk of secondary osteoporosis and fragility fractures [76]. For this reason, long-standing hyperthyroidism is included in fracture-risk assessment of major algorithms such as FRAX®.

The treatment of hyperthyroidism with the achievement of a euthyroid status is well documented to significantly increase BMD in the medium-long term along with a reversion to normal of fracture risk which is increased at baseline [76]. Also TBS has been shown to improve in a group of young adults of both sexes with Graves' disease under anti-thyroid treatment even in the short-medium term in a retrospective study [77]. The effects of hyperthyroidism on bone quality have been assessed in a recent paper comparing in a case–control study 61 women with a similar number of euthyroid women matched for age and menopause status by means of HR-pQCT [78]. While no DXA changes at the lumbar spine and the hip were detected, lower vBMD and estimated bone strength, and compromised cortical microarchitecture at the radius were demonstrated at baseline [78]. These results confirmed in vivo for the first time old histomorphometric analyses on bone biopsies, which showed reduction in cortical thickness and increased cortical porosity as effects of increased bone turnover [79]. In the longitudinal study, a significant improvement in vBMD and cortical microstructural parameters (cortical thickness and cortical area, as assessed at the radius and tibia) were observed 1 year after restoration of euthyroidism and independently of bone specific treatments, underlining the need to treat hyperthyroidism for bone quality improvement [78].

Studies assessing the effect on BMD of Levo-thyroxine (L-T4)-mediated TSH suppression, also referred to as subclinical thyrotoxicosis, have shown bone detrimental outcomes with increased risk of major osteoporotic fractures especially in postmenopausal women and older males [80], with contradictory results in premenopausal women or younger men [75]. Nonetheless, a meta-analysis including 13 prospective international cohorts has shown that in age- and sex-adjusted analyses subclinical thyrotoxicosis is associated with increased risk of hip fracture and other major osteoporotic fractures, particularly if TSH levels are less than 0,1 mIU/ml [81].

The effects of subclinical thyrotoxicosis (i.e. suppressed TSH and normal free thyroid hormones levels) on bone quality have been mainly analyzed in patients with differentiated thyroid cancer (DTC) receiving L-T4 therapy at a dosage able to suppress TSH levels, generally assessing TBS [80]. The finding that lower TSH is associated with a deterioration

of bone quality in postmenopausal women, as assessed by TBS has been highlighted by various studies [80, 82, 83].

In particular, Chung et al. have shown in a retrospective study that in a large group of thyroidectomized postmenopausal women with DTC treated with suppressive doses of L-T4, TBS was markedly decreased, while no significant difference was evidenced as compared to the ones receiving L-T4 non-suppressing TSH [82]. In patients receiving anti-osteoporotic medications, positive significant changes in TBS were observed just in the group receiving non-suppressive L-T4 therapy [82].

The duration of TSH suppression was shown to be linked to higher risk of fragility fractures and deterioration of TBS in postmenopausal women with DTC, while no changes in microarchitecture was detected in premenopausal women in the long-term, as demonstrated in several retrospective studies [84–87]. These findings were recently confirmed in a following study group mainly composed of postmenopausal women with DTC with TSH constantly below 0.1 mIU/ml [88].

Better detection of osteopenia or osteoporosis was obtained by means of cQCT versus DXA in patients with DTC under TSH suppressive therapy, despite no control group was included [89]. vBMD and bone geometry (i.e. trabecular bone mineral content and cortical thickness) only at a non-bearing site (distal radius) were found to be altered in postmenopausal women with DTC under TSH suppression as compared to premenopausal patients, although pQCT scans were obtained just once in a cross-sectional design study [90].

The influence of either TSH levels or FT4 levels on bone quality as assessed by TBS has been tried to be dissected in studies in cohorts composed of euthyroid subjects.

An analysis in a large group of 1475 women, a subgroup belonging to an ongoing prospective study carried out in Switzerland looking at the relationship between cardiovascular diseases and osteoporosis (CoLaus/OsteoLaus cohort) has been performed. While no association was found between TSH and DXA parameters, a positive association was described between TSH and TBS at baseline (cross-sectional study) and a negative association between TSH and incident fractures in the 5-year follow-up period (longitudinal study) [91]. Nonetheless, in a previous study in euthyroid patients of both sexes (n. 1648 patients, 648 postmenopausal women and 728 men), an independent association between high-normal FT4 levels and TBS, irrespective of TSH levels, was found in community-dwelling, postmenopausal women [92].

Subclinical hypothyroidism does not seem to be associated with alteration on bone quantity and quality (as assessed by TBS), nor the proper replacement with L-T4 leads to any effect on bone health in a randomized nested trial [93]. Nonetheless, a small study including women with either

overt or subclinical hypothyroidism has shown that this disease is associated with increased trabecular bone area and a lower mineral density of cortical bone in the radius, as examined by HR-pQCT [94]. In this study, restoration of euthyroid state was accompanied by an increase in cortical porosity, without variations in estimated bone strength [94].

In conclusion, the results of these studies suggest that TBS should always be included in the baseline skeletal evaluation of patients receiving L-T4 therapy at TSH suppressive dosage, in particular in postmenopausal women, but even in premenopausal women lately transitioning to menopause. Therefore, TBS-adjusted FRAX should be calculated to assess fracture risk in these patients, even more so considering the long survival of these patients. Studies employing HR-pQCT as well as longitudinal/prospective studies are still needed in overt hyperthyroidism and hypothyroidism and subclinical thyrotoxicosis, with a particular focus in bone quality issues in older men.

Bone quality in hypercortisolism

Glucocorticoids in excess induce direct and indirect effects on bone remodeling and metabolism, these comprising suppression of osteoblastogenesis and bone formation, relative increase in bone resorption, inhibition of osteocyte function and survival, and alterations in calcium homeostasis by inducing negative calcium balance [73]. Moreover, cortisol hypersecretion can cause functional growth (GH) deficiency (GHD) and central hypogonadism, both contributing to skeletal fragility in this clinical setting [73].

Consistent with the aforementioned actions of glucocorticoids on bone cells [73], uncoupled bone remodeling with low bone formation and slight increase in bone resorption has been described in subjects with endogenous hypercortisolism [95]. These alterations in bone remodeling are cause of deterioration in bone structure and quality, predominantly in trabecular bone, as evidenced by HR-pQCT [96], DXA evaluation of BMD at the lumbar spine and femoral neck [97], DXA measurement of TBS [98], assessment of bone marrow fat by MRI [99, 100], and volumetric bone evaluation by forearm QCT [95]. However, also cortical bone structure can be altered in individuals with endogenous hypercortisolism [101].

A number of studies consistently documented increased incidence and prevalence of fragility fractures in endogenous hypercortisolism, with vertebrae and ribs being the skeletal sites most frequently involved [73, 102]. The relationship between decreased BMD and fractures in hypercortisolism is only partly maintained. Subjects with densitometric diagnosis of osteoporosis have the highest likelihood of developing fractures [103, 104], but a remarkable number of fragility fractures can occur even in the context of

normal or low-normal BMD [103–106]. It is still uncertain whether evaluation of bone microstructure in endogenous can improve prediction of fractures. In a cohort of 182 young subjects with hypercortisolism, fragility fractures did not result to be significantly associated with TBS [106]. In another study performed in 102 elderly subjects with “subclinical” hypercortisolism associated with adrenal incidentaloma, measurement of TBS improved prediction of incident vertebral fractures [107]. In line with this finding, a more recent study reported a significant association between vertebral fractures and increase in bone marrow fat measured by MRI in subjects with endogenous hypercortisolism and low-normal BMD [99], consistent with the pathophysiological concept that enhanced adipogenesis in bone marrow reflects the impairment of osteoblastogenesis induced by glucocorticoid excess [73].

After treatment of hypercortisolism, bone quality as assessed by TBS measurement seems to improve more rapidly compared to BMD, since more than two-thirds of 110 individuals with alterations in bone microstructure at diagnosis of Cushing syndrome were shown to have a clinically relevant improvement of TBS by 24 months after remission of hypercortisolism [98]. The impact of this improvement in bone quality on outcome of fracture risk is still uncertain, since fragility fractures can occur even in subjects with cured hypercortisolism, especially if they had experienced previous fractures [108, 109].

Bone quality in growth-hormone disorders

GH and insulin-like growth factor 1 (IGF1) are important regulators of bone remodeling and metabolism and have an essential role in the achievement and maintenance of bone mass throughout life. In experimental models and in humans diseases, both GHD and GH excess cause alterations in bone structure with high risk of fragility fractures [110].

Growth hormone deficiency

GHD is the main determinant of skeletal fragility in subjects with hypopituitarism [111]. Moreover, a deregulation of GH-IGF1 axis with functional defect in GH and/or IGF1 can contribute to bone loss in several clinical conditions as ageing, anorexia nervosa, diabetes mellitus and chronic exposure to glucocorticoid excess [110, 112, 113]. Individuals with deficiency in GH and IGF1 have suppressed bone turnover due to impaired osteoblastogenesis [114]. Consequently, bone quality is altered in GHD and risk of fractures is 2–5 higher as compared to general population, regardless of the existence of other pituitary hormone deficiencies [73]. Importantly, symptomatic vertebral fractures occur in more than 30% of adult men and women with acquired untreated

GHD, even in the context of a normal BMD [115]. Data on bone structure in GHD are scanty and no studies evaluated the value of bone quality assessment in predicting the risk of fractures in this clinical setting [73]. Bone biopsies from male adult patients with GHD reveal decreased osteoid and mineralizing surfaces and decreased bone formation rate [116]. Studies of 34 individuals with either childhood-onset or long-standing GHD that used a 3D DXA algorithm at the hip site and HR-pQCT of the distal radius and tibia demonstrated decreased cortical area and cortical thickness, as well as decreased trabecular thickness in cancellous bone [117, 118]. However, bone microarchitecture might not be altered in adults with GHD with onset after the achievement of peak bone mass [119]. Indeed, some of these patients had previously received GH replacement more than 12 months before the study and this may have counteracted any abnormalities in bone structure and strength at the time of evaluation, consistently with the concept that beneficial effects of replacement therapy may be persistent after recombinant human GH withdrawal [120].

Acromegaly

In the context of GH and IGF1 excess, bone resorption is increased to a greater extent than bone formation and as a result bone loss ensues [121]. Consistently, a large number of individuals with acromegaly have abnormalities in bone structure characterized by decreased cancellous bone volume and increased cortical porosity [119, 122, 123]. The first evidence of impaired bone quality in acromegaly was provided by Ueland et al. who described loss of trabecular connections and low trabecular bone biochemical competence in iliac crest biopsies of 13 acromegalic patients with active disease [124]. Following this evidence, many other studies confirmed that trabecular bone structure is profoundly deteriorated in acromegaly regardless of gonadal status of subjects [119, 122, 125]. Indeed, TBS results to be frequently degraded in subjects with acromegaly [126–129]. In a recent meta-analysis including 336 acromegalic patients and 490 non-acromegalic subjects, TBS resulted to be significantly lower in acromegaly as compared to controls irrespective of disease activity and gonadal status [129]. Besides the abnormalities in trabecular microstructure, acromegaly was shown to affect also cortical bone in terms of increased porosity [119, 123, 130] and impaired cortical properties [131]. As a direct consequence of alterations in bone microstructure and quality, vertebral fractures develop in a large number of subjects with acromegaly [121]. Indeed, more than one-third of individuals exposed to GH hypersecretion develop vertebral fractures, with a fracture risk which is 3- to 8-fold greater compared to that in control subjects [121]. Vertebral fractures occur even in subjects with normal BMD [132]. In this setting, vertebral fractures were associated with deterioration

in bone microstructure as assessed by histomorphometry, tri-dimensional DXA of the proximal femur, and peripheral CT of distal radius [123, 126, 130]. Moreover, in a meta-analysis of two studies including 132 subjects with acromegaly who were evaluated for vertebral fractures [126, 133], TBS values were found to be significantly lower in fractured patients as compared to those who did not fracture, with a pooled mean difference of -0.099 [129]. Biochemical control of acromegaly induces a rapid decrease in bone turnover, however, bone microstructure remains deteriorated in a number of individuals following disease control [73]. Indeed, treatment of acromegaly can cause a worsening in TBS values, an increase in cortical porosity and a reduction in cortical bone thickness and structural properties [73, 123, 133, 134]. The mechanisms responsible of deteriorated bone quality in individuals with controlled acromegaly are still largely unknown, but a persistent impairment of osteoblastogenesis and bone formation could be hypothesized [123, 125]. Co-existent hypopituitarism, as well as medications used for the treatment of acromegaly, might contribute to the persistent alterations in bone remodeling and structure in subjects with treated disease [135–137]. As a direct consequence of persistent alterations in bone structure, a high number of individuals with acromegaly are at substantial risk of vertebral fractures after biochemical control of the disease [136, 138].

Only one study including 33 acromegalic subjects has so far evaluated performance of REMS in acromegaly [139]. This technique did not seem to provide any significant advantage in evaluating bone quality as compared to DXA.

Bone quality in male hypogonadism

Hypogonadism is a well-known risk factor for secondary osteoporosis in males [140–143]. Animal and clinical evidence have clarified that testosterone (T) plays a crucial role in regulating bone homeostasis during all ages. Androgen, along with estrogen receptors, are widely expressed on osteoblasts, osteoclasts, osteocytes and marrow stromal cells [143]. Both T and estradiol are involved in periosteal apposition and trabecular bone growth, during pubertal period, contributing to pubertal growth spurts and peak bone mass [142, 144]. However, due to the higher circulating levels observed in males, T contributes to develop higher peak bone mass characterized by wider bones with a thicker cortex when compared to what observed in women [142, 143, 145]. After puberty, androgens still contribute to bone homeostasis by reducing the bone remodeling rate and by regulating a balance between bone resorption and formation [143, 145].

In line to what observed in the pre-clinical models, data derived from the general population have confirmed an inverse association between aBMD and circulating T levels

[146–148]. However, the European Male Aging Study, including more than 3400 subjects aged 40–80 years old, documented a reduced aBMD only when severe hypogonadism (total T < 8 nmol/L) was observed [146]. Similar data were derived from a randomized controlled trial including 198 healthy men, receiving goserelin acetate to suppresses endogenous gonadal steroid production [149]. In line with these observations, available guidelines indicate to routinely assess BMD, through DXA, in patients with organic hypogonadism, which is usually associated with more severe reduction of T levels when compared to what observed in late onset hypogonadism (LOH) [140, 150–153]. However, several male subjects with hypogonadism can have skeletal fragility with high risk of fractures even in the context of a normal BMD [154, 155]. In this setting, evaluation of bone quality is mandatory. Using HR-MRI technique at distal tibia, two studies including 20 hypogonadal men provided evidence that bone loss and skeletal fragility in male hypogonadism are caused by a conversion of plate-like to rod-like trabeculae characterized by low surface-to-curve ratio, high erosion index and low bone properties and mechanical competence, as defined by FEA [156, 157]. The alterations in trabecular bone architecture associated with hypogonadism were also captured by CT techniques [158–160] and DXA-measurement of TBS [161, 162] in 146 subjects with congenital hypogonadism. Noteworthy, alterations in bone microstructure were detected even in subjects with central hypogonadism in whom serum follicle-stimulating hormone (FSH) are very low [160, 163], questioning the relevance in humans of experimental data suggesting a role of high FSH in pathogenesis of hypogonadal bone loss [73]. HR-pQCT technique revealed also reduced cortical area and thickness that could contribute to compromised bone strength in males with hypogonadism [158, 159, 163]. Interestingly, deterioration in bone quality has been associated with increase in visceral fat induced by hypogonadism [162], consistently with the concept that visceral-fat derived proinflammatory cytokines can influence bone remodeling and structure [164]. Moreover, alterations in cortical and trabecular bone microstructure resulted to be more severe in hypogonadal subjects with lower appendicular lean mass index [159].

The positive effects of T replacement therapy (TRT) in males with hypogonadism are well-documented [141, 165, 166]. Data derived from the largest meta-analysis published so far, including all available placebo-controlled Randomized Control Trials and observational studies, showed that TRT resulted in more evident effects on aBMD, at lumbar level, only when studies including hypogonadal subjects (total T < 12 nmol/L) at enrolment were considered. The results were inversely related to baseline T levels and confirmed when subjects without LOH were excluded from the analysis [141]. The magnitude of the effects of TRT on aBMD at lumbar site in LOH, as derived from Corona et al.

[141] study, was similar to that observed by the same group analyzing the results derived from subjects with Klinefelter's Syndrome [165]. Furthermore, the same meta-analysis [141] showed better outcomes in subjects with diabetes mellitus (DM), which is frequently co-morbid in patients with LOH [167].

The effects of TRT on bone quality have been investigated in several clinical contexts. In 211 older hypogonadal subjects, 1-year TRT increased vBMD as determined by QCT, especially in trabecular bone than cortical-rich peripheral bone, and increased estimated bone strength, as determined by FEA [168], whereas TBS did not change significantly [169]. The reasons of such a methodological variability are unknown but one could argue that TBS might not be clinically useful in monitoring the short-term effects of TRT on bone quality. Interestingly, the favorable effects of TRT on bone structure resulted to be more evident in hypogonadal subjects with type 2 diabetes (T2D) than those without T2D [170]. Based on the changes of biochemical markers of bone turnover, it is reasonable to hypothesize a predominant anabolic effect of T on the skeleton of men with T2D, while the antiresorptive effect seems to prevail among those without T2D. In 51 subjects with congenital hypogonadism, the effects of TRT on trabecular bone resulted to be larger when treatment was started early during adolescence, whereas when diagnosis was late and treatment was started after closure of epiphysis only cortical bone can improve as effect of replacement therapy [163].

Bone quality in diabetes mellitus

DM is a common disease, linked to several complications, including osteoporosis and fractures. Fracture risk is highly increased in type 1 diabetes (T1D), mostly in patients with longer duration of the disease, worse glucose control or family history for fractures [171]. In T2D, fracture risk is mostly related to cortical rich bone sites like proximal and distal femur and it is strongly associated to insulin or sulphonylureas use, falls, prolonged poor glycemic control [172, 173]. Contrary to what commonly believed, fracture risk is increased also in subjects with insulin resistance without DM, suggesting that pathophysiology of bone fragility in subjects with DM may begin even before the onset or diagnosis of the disease [174]. Underlying mechanisms of bone fragility in DM are still poorly understood with several factors like gluco-toxicity, inflammation, WNT impairment, oxidative stress, micro-angiopathy playing a main role [175]. Advanced glycation end products (AGEs), linking collagen, reduce bone flexibility and energy dissipation, impair strength and biomechanical properties of cortical and trabecular bone. In the meantime, AGE may interfere with immune cells, increasing cytokines and reactive

oxygen species (ROS), impacting on bone resorption [176]. AGEs are also responsible of microvascular damage that independently affects bone health as well [177]. Low T frequently observed in T2D can represent another risk factor [178]. Serum sclerostin levels are consistently reported as increased in both T2D and Latent Autoimmune Diabetes in Adults (LADA) subjects, underlying the impairment of WNT signaling in DM [179, 180]. Subjects with T2D present also increased *SOST* and lower *RUNX2* gene expression at the bone level, compared to healthy controls, further confirming that impaired WNT signaling plays a key role in determining lower bone formation in DM [181]. These data are in agreement with histological findings that have shown lower tetracycline labeling in bone biopsies in T2D subjects and with reports of lower serum bone formation markers. As a matter of fact, it is now clear that DM is a low bone turnover condition, characterized by both lower bone formation and resorption. This unique feature may cause accumulation of micro-damage, more homogeneous bone structure and, in turn, more propagation of microcracks.

Although fracture risk is increased, BMD in T2D is often normal or even higher than healthy subjects, indicating that bone quality rather than density is likely impaired [182]. On the contrary, T1D patients show low BMD although fracture risk is usually higher than that suggested for a given T or Z-score. On the attempt to investigate this apparent discrepancy between BMD and fracture risk, several studies have investigated bone micro-architecture, used TBS or have combined different available fracture algorithms. Using HRpQCT, cortical porosity has been shown to be increased in T2D in most studies, mostly in subjects with fractures, or cardio-vascular complications [183, 184]. Moreover, creep indentation distance and indentation distance increase were greater (by 18% and 20%, respectively) in cortical bone from T2D than in subjects without DM [185]. However, trabecular bone indices are either comparable or show even increased density compared to controls [186, 187]. Altogether, this evidence proves that subjects with DM may present a unique micro-architecture feature with normal trabecular bone and high cortical porosity that may impair failure load and bone strength. Two large studies including 3051 subjects with DM provided convincing evidence that TBS is more reliable than BMD in capturing the DM-associated fracture risk [188, 189]. Similar results were reported more recently using REMS in 90 post-menopausal women with T2D [190]. In this setting, the percentage of T2D women classified as "osteoporotic", on the basis of BMD by REMS was markedly higher with respect to those classified by DXA and T2D women with fragility fractures presented significantly lower values of BMD-LS by REMS with respect to those without fractures [190].

Treatment of diabetes can influence skeletal health and fracture risk. Fracture risk in DM is increased also because

of higher risk of hypoglycemic events, falls, use of some medications like insulin or sulphonylureas [173]. Therefore, metformin and new medications with a safe bone profile like glucagon like peptide 1-receptor agonist (GLP1-RA) analogues or sodium-glucose co-transporters 2 (SGLT2) inhibitors should be preferred. Optimization of glucose control will not only prevent cardio-vascular complications but will determine also lower oxidative stress, glucose toxicity, bone microangiopathy, AGEs accumulation and inflammation, which will result in better bone quality. All subjects with DM with poor glycemic control or on insulin treatment should be screened for osteoporosis and should start anti-osteoporosis treatment when needed. According to the IOF algorithm, occurrence of fragility fractures (vertebral or proximal femur) or a *T* score of -2 SD should be considered as a threshold for treatment [191]. According to a recent meta-analysis [192], all anti-resorptive medications have a positive effect on both BMD and fracture risk in subjects without DM. In this context of low-bone turnover osteoporosis, teriparatide is expected to expand the “anabolic window” with secondary improvement of bone quality. As a matter of fact, teriparatide has been shown to significantly prevent fracture risk in subjects with DM [193].

Conclusions

Osteoporosis is a frequent complication of several endocrine diseases, including primary hyperparathyroidism, hyperthyroidism, Cushing’s syndrome, GHD, acromegaly, male hypogonadism and DM. Prediction of fragility fractures in these clinical conditions, such as in other forms of secondary osteoporosis, is a challenge since BMD allows to identify only a minority of subjects at risk of fractures. Since bone quality is predominantly altered in endocrine-related osteoporosis, assessment of skeletal fragility in endocrine diseases may take advantage from the use of non-invasive techniques to detect perturbation in the trabecular and cortical bone architecture with the aim of best identify high risk patients (Table 1). In this context, HRpQCT represents the gold standard technology for the non-invasive evaluation of bone quality in several skeletal disorders. Notwithstanding, owing to the unavailability of HRpQCT in clinical practice,

Table 1 Summary of available studies employing techniques for the assessment of bone quality in major endocrinopathies with increased bone fragility

| | TBS | REMS | vQCT | HR-pQCT |
|---------------------|-----|------|------|---------|
| Hyperparathyroidism | X | – | X | X |
| Hypoparathyroidism | X | – | X | X |
| Hyperthyroidism | X | – | X | X |
| Hypothyroidism | X | – | X | X |
| Cushing syndrome | X | – | X | X |
| GH deficiency | X | – | X | X |
| Acromegaly | X | X | X | X |
| Male hypogonadism | X | – | X | X |
| Diabetes | X | X | X | X |

TBS, REMS and vQCT can be routinely performed in clinical settings; HR-pQCT is still limited to research settings

TBS trabecular bone score; *REMS* radiofrequency echographic multispectrometry; *vQCT* volumetric quantitative computed tomography (including both pQCT, i.e. peripheral QCT, and cQCT, i.e. central QCT performed at the lumbar spine or at the hip); *HR-pQCT* peripheral quantitative computed tomography

clinicians may be supported by the use of modern DXA machines and related DXA-derived parameters in the diagnostic work-up of endocrine disease-related osteoporosis. These technologies provide several additional information on bone structure, properties and geometry not captured by the isolated measurement of BMD and essential to identify subjects with skeletal fragility. For instance, evaluation of bone quality by using DXA measurement of TBS might be proposed for all individuals with endocrine disorders potentially causing skeletal fragility, which do not have BMD values in the range of osteoporosis. The finding of degraded TBS in these cases might help the clinicians to perform a careful monitoring of skeletal fragility and to put in place the prevention of fractures. In Fig. 4, a screening procedure for bone fragility assessment in endocrinopathies is proposed. Indeed, in this context, more data from longitudinal studies assessing changes in these parameters over time associated with the cure of the underlying endocrine disorder, as well as the effectiveness of bone active agents, will significantly impact the clinical management of these patients.

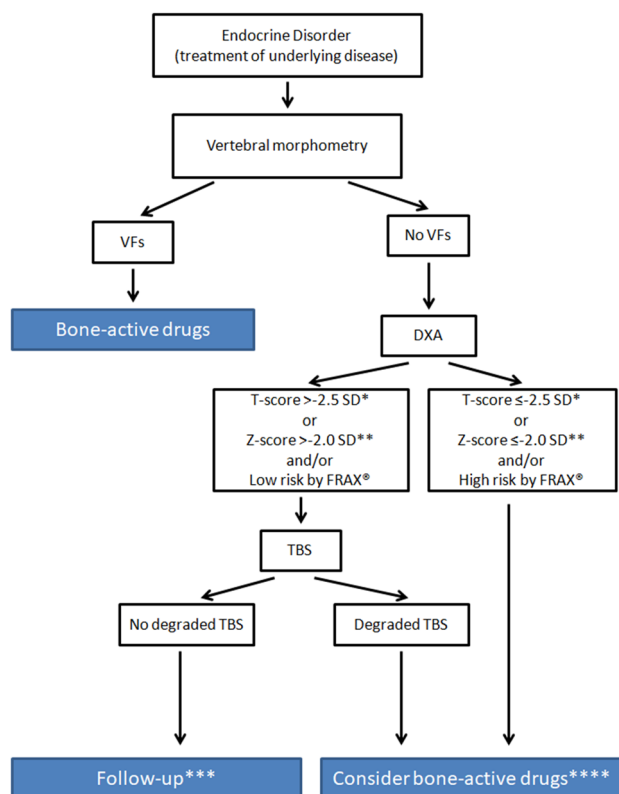


Fig. 4 Proposed clinical assessment of bone fragility in secondary endocrine osteoporosis (treatment of underlying endocrine disease is taken for granted and mandatory); *VF* vertebral fracture; *DXA* dual-energy X-ray absorptiometry; *FRAX*[®] international algorithm to estimate the risk of major osteoporotic fractures and hip fractures in a 10-year time; *, *T*-score is used in post-menopausal women and in men older than 50 years; **, *Z*-score is used in pre-menopausal women and in men younger than 50 years; ***, follow-up is advised if there are coexistent risk factors of fractures or the endocrine disorder is not resolved; ****, consider treatment with bone-active drugs if there are coexistent risk factors of fractures or the endocrine disorder is not or cannot be resolved. The proposed therapeutic flow-chart doesn't consider the country-specific criteria of drug reimbursement for osteoporosis

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Declarations

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Informed consent For this type of study, formal consent is not required.

Research involving human participants and/or animals The authors received the permission by two patients followed-up in the outpatient bone clinic for using anonymously for research purposes the images of their DXA and CT exams.

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