Diagnosis of Endocrine Disease: Evaluation of bone fragility in endocrine disorders.

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Abstract

An underlying disease affecting bone health is present in up to 40% and 60% of osteoporotic post-menopausal women and men respectively. Among the disorders leading to a secondary form of osteoporosis, the endocrine diseases are highly represented. A frequent finding in patients affected with an endocrine-related forms of bone disease is that the skeletal fragility is partially independent of the bone density, since the fracture risk in these patients is related more to a reduction of bone quality than to a decrease of bone mass. As a consequence, bone mineral density evaluation by dual-X-ray Absorptiometry may be inadequate for establishing the risk of fracture in the setting of the endocrine-related forms of osteoporosis.

In the recent years several attempts to non-invasively estimating bone quality have been done. Nowadys, some new tools are available in the clinical practice for optimizing the fracture risk estimation in patients with endocrine disorders.

The aim of this review is to summarise the evidences regarding the role of the different imaging tools for evaluating bone density and bone quality in the most frequent forms of endocrine-related osteoporosis, such as obesity, diabetes, acromegaly, thyrotoxicosis, primary hyperparathyroidism, hypercortisolism and hypogonadism. For each of these disorders, data regarding both the current available tools and the future possible new techniques for assessing bone fragility in patients with endocrine diseases are reported.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture (1). Bone strength primarily reflects the material composition and structural design of bone by the integration of bone mineral density (BMD) and bone quality (1). The latter concept mainly include bone geometry (bone size, shape), bono macro- and micro-architecture (eg. connectivity and thickness of trabeculae, thickness and porosity of cortical bone), the balance and rate of bone remodelling, bone mineralization and the type and organisation of collagen or other components of the bone matrix.

Osteoporosis is classified as "primary" when it occurs in the absence of an underlying disease, and as "secondary" when it is due to an underlying disease (2). It is known that up to 40% of post-menopausal women and 60% of men have factors contributing to osteoporosis when evaluated for underlying causes of the disease (2). Among the disorders leading to a secondary form of osteoporosis, the endocrine diseases are largely represented (2) and listed in Table 1. Patients affected with an endocrine-related forms of osteoporosis frequently experience fragility fractures in the presence of a normal or slightly reduced BMD, since the fracture risk in these forms is related more to a reduction of bone quality than to a decrease of BMD (2). As a consequence, the BMD evaluation by, for example, dual-X-ray Absorptiometry (DXA), which is of great importance in evaluating the fracture risk in primary osteoporosis (i.e. a T-score value $\leq$ -2.5), may be inadequate for establishing the risk of fracture in the setting of the endocrine-related forms of osteoporosis.

In the recent years several attempts to non-invasively estimating bone quality have been done. Nowadays, some new tools are available in the clinical practice for optimizing the fracture risk estimation in patients with endocrine disorders affecting bone. The aim of this review is to summarise the evidences regarding the role of the different imaging tools for evaluating bone density and bone quality in the most frequent forms of endocrine-related osteoporosis. Although, in studies examining secondary causes of osteoporosis, low vitamin D levels are consistently highlighted as the most common biochemical abnormality, we will not address this issue, since, hypovitaminosis D is an important contributor to bone fragility but it is not specific of a particular endocrine disorder influencing bone health. Finally, even though the mineralisation disorders may have an endocrine basis, we believed that addressing this issue wass beyond the scope of the present review.

Obesity

Morbid adipose tissue accumulation may be regarded as a quite common disorder in a variety of endocrine diseases, although the factors accounting for the development of obesity in endocrinopathies have not been clearly identified. It is also well-known that adipose tissue is regarded by now as an important endocrine organ since it produces several biologically active substances, e. g. adipokines, with paracrine and endocrine action potentially leading to severe disorders of the endocrine system. Consequently, it is not far from the truth to consider obesity as an endocrine disorder more than a dysmetabolic condition. However, obesity has a complex and still poorly understood relationship to bone health. A fracture-related morbidity seems to be a higher in obese than in non-obese women (3). It is also known that higher fat depots may have negative effects on bone, since both cytokines produced by visceral fat may exert a pro-resorptive and high intramuscular fat accumulation is associated with poorer muscle function, attenuating loading effects and increasing falls risk, partly similar to what observed also in T2DM (4). In a study published in 2000, the waist-hip ratio (WHR) index was been associated with the risk of hip fracture (5), and later visceral adipose tissue (VAT) also was positively associated with nonspine fractures (6). A recent systematic review and meta-analysis of prospective studies reported that abdominal obesity was positively associated with the risk of hip fracture (7).

A direct positive correlation between Body Mass Index (BMI) and BMD has been reported in literature (8, 9). Thus, in past years, obesity status was believed to be protective against fragility fractures. Lately, several studies argued that obesity, as defined by WHO criteria by the a BMI equal to or above 30 kg/m^2, could not be longer regarded to as a real protector from bone fragility. In fact, several findings demonstrated that while on the one hand BMI is associated with increased risk of fracture at some skeletal sites, on the other side it may be protective at others skeletal sites, representing the so-called obesity paradox (8). Table 2 reports a summary concerning some of factors, pros and cons, potentially associated in the interrelationship between obesity and bone mass.

DXA essentially focuses on the mineralized component, and it is still the most widely used tool to assess BMD to estimate the bone fragility fracture risk. In a study on obese patients, more than 50% of subjects, with at least one vertebral fracture, exhibited a normal or only slightly reduced BMD, but not

osteoporosis, and vertebral fractures occurred 4.4 fold more frequently in patients than controls, thus suggesting that in obese population DXA may not represent an accurate instrument to adequately estimate the fracture risk (10). Data on the risk of hip fractures in obese patients are not conclusive even for the influence of diabetes (11). In fact, since obesity and excess fat mass, especially VAT, are increasing risk factors for low BMD and fragility fractures (3), in obese or overweight subjects the BMD measured by DXA may not be a reliable method of assessing fracture risk. Finally, by a practical point of view, in very obese patients, especially in whom the body weight exceeds the limit for the DXA table, the BMD assessment should be not performed only at the "classical" lumbar and femoral sites, but also at the non-dominant forearm. In obese patients undergoing bariatric surgery, or medical (diet) weight loss regimens with anticipated large weight loss, the DXA total body composition with regional analysis can be used in order to assess fat and lean mass changes when weight loss exceeds approximately 10%, but not for fracture risk assessment (12).

Recently, a dedicated algorithm for the assessment of bone microarchitecture at the lumbar spine (LS), the trabecular bone score (TBS), has been introduced. TBS is a textural index based on evaluating pixel gray-level variations in the LS DXA image, providing an indirect index of bone architecture. Thus, TBS can assess bone quality and provide information about fracture risk independent of BMD. Interestingly, BMD has been reported to correlate positively with BMI, whereas TBS has been described to be inversely related to BMI, suggesting that an increase in BMI has a negative impact on bone quality (13). Therefore, TBS seems to be a better measure of bone fragility in individuals who are obese/overweight, and useful in assessing osteoporotic fracture risk, with lower TBS values associated with increased fracture risk. Lately, a prospective study on 38 morbidly obese white women, undergoing Roux-en-Y gastric bypass (RYGB) procedure, followed up to three years, demonstrated that the fracture risk, calculated by FRAX® algorithm (University of Sheffield, Sheffield, UK), with and without adjustment by TBS, was low, and the authors interestingly concluded that women undergoing RYGB in the mid-term have a preserved bone micro-architecture assessed by TBS (14). However, larger randomized prospective clinical trials will be necessary before suggesting TBS as a significant valuable technique for the prediction of fracture risk in obese subjects. A new tool to assess bone health, the BMD/BMI ratio has been recently presented, at the 27th American Association of Clinical Endocrinologists (AACE) meeting, held, on May 2018, in Boston, MA,

US (https://www.medscape.com/viewarticle/896882), by Watanabe and coauthors. They suggested such a simple measure as an important new tool to potentially and easily assess the risk fracture in obese patients, particularly when the bone strength could be linked to the presence of impaired metabolic health. They investigated a large Caucasian cohort of more than 2,000 overweight or obese patients (82% female, aged 45±12 years, mean BMI 36.5 ± 6.2 kg/m^2) by assessing body composition, and both DXA LS BMD and TBS. Confirmation of the association between increased BMI, increased BMD, and decreased TBS values has been obtained. The LS BMD/BMI ratio was more strongly correlated with TBS than LS BMD. In obese subjects with metabolic syndrome, the LS BMD was similar to that of metabolically healthy subjects, but both TBS and BMD/BMI ratio were significantly lower. All these preliminary findings suggest that the BMD/BMI ratio offers a simple tool for assessing the risk of fracture in obese subjects (https://www.medscape.com/viewarticle/896882). However, it will be necessary to wait for the effective publication of these data, and their possible replication in other studies.

As above suggested, obese patients may have normal DXA measured BMD values, despite of a possible deterioration in bone architecture and, consequently, an increased prevalence of vertebral fractures (13). The spinal deformity index (SDI) conjugates and integrates both the number and severity of vertebral fractures as a single parameter and it has been suggested to be an indirect surrogate marker of bone microarchitecture (15). According to this technique, fractures assessed on lateral thoracolumbarspine radiographs were defined as reductions of more than 20% in anterior, middle, or posterior vertebral height. From lateral spine radiographs, each vertebra is visually assessed as intact (semi-quantitative, SQ, grade 0) or as having approximately mild (20–25% compression), moderate (25–40% compression), or severe (>40% compression) deformity (SQ grades 1, 2, and 3, respectively). Subsequently for each subject the SDI was calculated by summing the SQ grade for each of the 13 vertebrae from T4 to L4. In a prospective study on 54 obese subjects (51±16 years, 10 males, 44 females), SDI was found to be an useful index of vertebral fractures risk, as it has been demonstrated in postmenopausal osteoporotic females (10).

Beyond the “classical” thoraco-lumbar projection radiography, DXA scanners can also be utilised for vertebral fracture assessment (VFA) of a lateral image of T4 to L4 spine, with a significantly reduced dose than “classical” X-rays, and a high degree of accuracy in diagnosing fracture (16). This is of importance since the presence of a prevalent asymptomatic vertebral fractures is a strong predictor of future fractures

(17). However, sometimes in large obese subjects, neither DXA nor the VFA can be performed because their weight exceeds the limit for DXA table, or the important thickness of VAT may alter the reliability of the result (12). Further imaging may be required where other underlying pathology is suspected and magnetic resonance imaging (MRI), Computed Tomography (CT), Nuclear Medicine or Positron Emission Tomography CT may be used.

Osteoporosis associates with an increased bone marrow fat (BMF) due to a shift in the differentiation pattern of mesenchymal stem cells that preferentially move more towards the adipocytes phenotype rather than to osteoblastic lineage (18). More recently, several studies have strongly evidenced the role that also non-mineralized bone component potentially play in determining bone health (18, 19). In particular, such studies stand that bone marrow, primarily consisting of adipocytes (yellow marrow areas) or adipocytes and hematopoietic red blood cells (red marrow areas), fills the cavities present at the trabecular bone level, and higher BMF fraction (BMFF) have been associated with lower BMD values (20-26). Moreover, in comparison to white and brown adipose tissue depots or ectopic fat depots in the human body, BMF exerts a distinctly different function, potentially playing an important role in the pathophysiology of metabolic disorders and fragility fracture risk (26). For these reasons, MRI and Magnetic Resonance Spectroscopy (MRS) have been suggested as ideal imaging techniques for a non-invasive investigation of BMF properties. However, MRI-based evaluation of BMF may provide an interesting insight into the pathophysiology of osteoporosis and/or obesity, and it could be useful in the investigations on the association of bone and metabolic disturbances.

BMFF may represent a negative predictor of bone microarchitecture and mechanical properties in obese men and it has been positively associated with ectopic and serum lipid levels in obese men and women and to their increase following a 6-month growth hormone administration in obese women (27). In a study on 47 pre-menopausal women, the vertebral BMFF was positively associated with VAT and inversely associated with insulin-like growth factor 1 (IGF-1), suggesting that VAT might have negative effects on bone health, partially mediated by IGF-1, a regulator of both fat and bone lineage (28). Changes of the BMF and bone mass after RYGB surgery have been investigated on eleven women, six diabetic and five non-diabetic, undergone RYGB, LS MRS, anthropometric measurements, whole body fat, and BMD measurements. A positive correlation between age and BMF content was described, and, interestingly, mean

BMF decreased in the diabetic subjects, versus non-diabetic women who showed only a small change, suggesting that BMF may behave differently than other fat depots in patients without diabetes after RYGB (24). However, further studies with larger number of specimens are needed in order to investigate whether the BMF has an effect on bone strength after correcting for the contribution of BMD. The currently available MRI-based methods, including MRS and water–fat imaging, enable the non-invasive extraction of the BMFF and unsaturation, but the knowledge of the underlying mechanisms is extremely scarce and, above all, no information are available in relation to their effective role in the clinical evaluation of fracture risk in subjects with reduced bone mass; therefore, at the moment, their use is reserved only for research purposes.

Finally, an interesting review on bone health after bariatric surgery in obese patients evaluated also the bone mass technical approaches in this obese population and addressed the use of quantitative computed tomography (QCT)-based modalities to examine volumetric bone mineral density and compartment-specific density and microstructure (29). Promising results come out, indicating that QCT technology can strengthen and advance the knowledge base. In particular, a pronounced reduction of bone mass at appendicular skeleton has been demonstrated by high-resolution (HR) peripheral quantitative computed tomography (pQCT, HR-pQCT), evaluating volume BMD (vBMD), other than in bone mass at the axial skeleton as assessed by DXA and QCT (30-33), even if it has been reported that HR-pQCT underestimates vBMD decrease when performed on important reduction in fat. (32). HR-pQCT studies seem also to adequately provide an individual analysis at both cortical and trabecular compartments, allowing for the identification of distinct pattern of bone loss. In fact, some studies revealed that the decrease in total vBMD, at the radius level, mainly reside in decreasing of trabecular vBMD, whereas the tibial total vBMD mainly reduces either within the cortical compartment or within both trabecular and cortical compartments (31-33). By this approach, information on bone microstructure and estimated strength at the appendicular skeleton can be also extrapolated (30-35). In obese bariatric subjects, undergone different surgical approach, the HR-pQCT analysis provided a quantitative characterization of bone microstructure at compartmental level, documenting deterioration in either trabecular or cortical architecture (30-32): i) a decrease of trabecular number and trabecular separation within the trabecular bone, with consequent increased heterogeneity (31-33); ii) a decrease of the cortical thickness and an increase of the trabecular area, due to endocortical resorption (26-28); iii) a pronounced increase of cortical porosity (31-33). All these findings suggest also

reduction of the bone strength at both the radius and the tibia (31, 32) with the consequent increase in fracture risk.

Diabetes

Emerging evidence suggests that diabetes exacerbates age-related reductions in bone strength and quality leading to increased bone fragility (36). In fact, type 1 diabetes (T1D) is associated with four to six fold increased risk of fractures that begins in childhood and extends across the life span. Likewise, a similar, albeit less marked, increase in the prevalence of fragility fractures has been also described in type 2 diabetes (T2D), particularly affecting the hip and other peripheral skeletal sites (37). While in T1D patients a modest decrease in BMD at trabecular and cortical sites is generally described, in T2D patients normal or even higher than normal BMD levels are frequently observed (37). Collectively, these findings indicate that BMD measurement does not consistently account for the increase in bone fragility in diabetes and suggest that abnormalities in bone microarchitecture and/or material composition (not captured by DXA) are likely responsible for the observed increase in fracture risk in either T1D and T2D diabetic patients.

The mechanisms underlying bone fragility in diabetes have not been clearly established and might differ, at least in part, between T1D and T2D, due to differences in the onset of disease, in insulin concentrations and resistance, as well as in the therapeutic approaches (36, 38). Common mechanisms might include co-morbidities and increased risk of falls associated with diabetes, or direct effects of hyperglicemia on the skeleton such as a suppression of bone turnover and excessive accumulation of advanced glycation end products on collagen fibrils, that impact on bone quality and strength (36).

Based on the above considerations, the stratification of fracture risk in diabetes, particularly in T2D patients, cannot exclusively rely on the DXA measurement of BMD (either alone or in combination with the conventional risk factors for fracture) as it occurs in postmenopausal osteoporosis (39). Likewise, the algorithms such as FRAX, the WHO Fracture Risk Assessment Tool, underestimate fracture risk in T2D patients (40, 31). Obviously, the finding of a low BMD still remains predictive of bone fragility in diabetic patients, as in the general population, and thus has to be considered useful for estimating the fracture risk (39). In fact, for each 1 SD decrease in BMD, the risk of hip fracture is almost equally doubled in individuals with or without T2D (35). However diabetic patients generally have fractures at higher BMD levels than the

general population, with T-score levels often above the osteoporotic range. Thus, concerning T2D, it has been estimated that a similar increase in hip fracture risk than in non-diabetic subjects occurs at 0.6 SD and 0.4 SD higher BMD levels in women and men, respectively (40). In addition to BMD measurement, a spinal x-ray should be mandatory in diabetic patients with a previous fragility fracture or in those with diabetic complications, particularly in the presence of a poorly controlled disease. Indeed, when investigated by a lateral spine radiograph, up to a third of postmenopausal T2D women showed asymptomatic, morphometric, vertebral fractures (42), that *per se* represent a major risk factor for subsequent fractures (43).

As a consequence of the difficulties of relying on BMD to assess fracture risk in diabetes, other imaging techniques have been investigated in the past few years to better understand the mechanisms of skeletal fragility in either T1D or T2D (44), as summarized in Table 3. Different cross-sectional and retrospective reports have suggested that TBS is often reduced in either T1D and T2D (44) and that might predict fracture risk better than BMD (44-46).

The hip structural analysis (HSA) represents an additional tool that can be applied to DXA in order to obtain information on bone geometry and indirectly assess the bone resistance to axial compressive forces (47). However, although a weaker geometry (e.g. a narrower neck width) and compromised estimates of skeletal load response (e.g. a lower buckling ratio) have been described using HSA in some cohorts of T2D patients (47), their additive role on the prediction of fractures remains to be established. Notwithstanding the low cost and the wide availability of quantitative Ultrasound (QUS) devices of the calcaneous and the phalanxes, limited information has been released about their use in diabetic patients. Available information from cross-sectional studies indicate that QUS parameters may be reduced in patients with either T1D and T2D (48), but conflicting data exist concerning their predictive role in discriminating patients with fragility fractures (48, 49). Moreover, a correlation between reduced QUS parameters and poor glico-metabolic control or peripheral nerve dysfunction was also described (50).

Recently, QCT and HR-pQCT of the distal radius and tibia have been employed to obtain a 3-D assessment of bone size, vBMD, bone macro- and microarchitecture (e.g., cortical porosity and trabecular connectivity). The use of these techniques indicated that T1D patients are at risk for smaller sizes of the appendicular bones at the end of pubertal growth and generally shows thinner cortices as well as thinner and more widely spaced trabeculae (44, 51). These structural bone deficit appears more pronounced in the

presence of microvascular complications (52). Similar studies in T2D patients have demonstrated preserved indices of trabecular microarchitecture but increased cortical porosity, particularly in T2D females with fragility fractures (53-56).

Very limited information is available concerning the use of MRI to assess trabecular and cortical bone parameters at both axial and peripheral skeleton and their role in the stratification of fracture risk in diabetic patients (25). Notably MRS of the vertebral bodies evidenced an altered BMF composition (with lower unsaturation of bone marrow lipids) in postmenopausal women with fragility fractures and T2D (21). This approach might represent a promising tool for fracture risk assessment in diabetes, given the negative role of BMF on the commitment of mesenchymal stem cells towards the osteoblast lineage and its detrimental implications one BMD and structural bone integrity (18, 25, 26).

However, despite the promising results from retrospective and cross-sectional observations and the positive indications from experimental studies, the clinical relevance of imaging techniques other than DXA and vertebral morphometry for the prediction of fracture risk in patients with diabetes needs to be confirmed on a prospective basis and their scarce availability and high cost do not consent their routine use.

Acromegaly

Bone cells represent a target for the growth hormone (GH) and for its mediator, the insulin-like growth factor 1 (IGF-1). These hormones mainly act on osteoblasts by inducing their differentiation and by enhancing their function. To a lesser extent IGF-1 may also activate osteoclasts through an increase of RANKL production. Pituitary adenomas overproducing GH cause acromegaly, a disease that induces bone enlargement, particularly in extremities (57). Until recent years, acromegalic patients have been considered as having high bone mass, but in the last decade a large body of evidence have emerged as to the presence of fragility fractures in people with acromegaly (57).

The attempt to measure BMD by means of a traditional method like DXA has given inadequate results in acromegaly. Importantly, spine BMD is usually normal in this disease, while hip BMD may even be higher than normal (57).

Notwithstanding the high bone mass acromegalic patients show a up to 8 fold increased rate of vertebral fragility fractures that may be explained by a reduction of bone quality rather than bone quantity.

An increased cortical thickness and porosity and a reduced trabecular thickness with increased trabecular separation have been demonstrated in acromegalic patients (58); therefore it is reasonable that other methods possibly measuring bone quality have been studied. Recently, two recent papers focused on the role of TBS in acromegaly. Hong and co-authors found lower values of TBS in acromegalic men and women than in matched controls, while no difference in BMD has been observed between the two groups (59). The second study demonstrated that acromegaly treatment increases BMD but contemporarily reduces TBS by 3% in both genders, with males tending to a more pronounced, but not significantly different, TBS decrease than females (60).

Another method that is used to measure bone quality is HR-pQCT, which by analysing the distal radius and tibia allows the *in vivo* assessment of both bone microarchitecture and volumetric BMD. Using HR-pQCT in 82 patients with acromegaly, Madeira et al. have found a severe deterioration of trabecular bone microarchitecture that was correlated with patients' gonadal status rather than with the presence of type 2 diabetes or the activity of the disease. Therefore a sub-analysis was performed on 45 eugonadal acromegalic patients compared with 45 healthy controls. The patients showed lower trabecular volumetric bone density, bone volume to tissue volume and trabecular number than controls. Moreover they had higher trabecular separation and spacing than healthy subjects (61). All these findings can be associated with greater bone fragility, that, as previously demonstrated, is increased by hypogonadism (62).

Although eugonadal acromegalic patients show better bone quality that hypogonadal ones, a deterioration in trabecular microstructure of the radius has been demonstrated also in males with normal testosterone suggesting that acromegaly may overwhelm the protective role of sex steroids (63).

Also cortical bone is altered in acromegaly as both increased cortical porosity and reduced cortical strength have been demonstrated by several papers (58, 63, 60). A recent paper evaluated trabecular and cortical parameters at distal radius level, by means of a HR-pQCT system, in 40 acromegalic patients and 21 healthy subjects (65). Patients with acromegaly showed lower bone-volume/trabecular-volume (BV/TV) ratio and mean trabecular thickness as well as a greater trabecular separation than controls, but no difference between the two groups were observed with regard to cortical thickness and porosity. As compared to acromegalic patients without vertebral fractures, acromegalic patients with vertebral fractures showed lower BV/TV ratio and both greater trabecular separation and higher cortical porosity, but they did not differ in terms of cortical

thickness and porosity (65). These results are very interesting as they show an increase of both cortical area and thickness together with a higher cortical porosity, reflecting a normal response to the enhanced bone turnover induced by GH and IGF-1 excess. Generally the increase of cortical pores reduces the resistance to mechanic loads, but in this very case the simultaneous cortical bone enlargement seems to counteract the reduction of bone stiffness. The authors hypothesize that the difference in trabecular and cortical bone response to enhanced turnover may account for the described difference in fracture occurrence in acromegaly (i.e. increased risk for vertebral, but not appendicular fractures) (66). In contrast with these results a recent paper by Malgo et al. has investigated cortical strength by means of microndentation, a novel technique that allows the in vivo measuring of the so called "Bone Material Strength index (BMSi)" (64). Patients with well-controlled acromegaly showed significantly lower BMSi values than healthy controls These result seem to suggest a reduced cortical bone strength in acromegaly that may be a reflection of persistent alterations in the material properties of cortical bone even after cessation of the disease (64).

In conclusion, a growing body of evidence in the last 10-15 years have shown an increased rate of fractures in acromegaly, particularly at the vertebral level, that are strictly correlated with a deterioration of bone microstructure caused by GH and IGF-1 overproduction. DXA is the most efficient way to measure bone mineral density in the general population and it show a very good correlation with fracture risk; nevertheless its efficacy in acromegaly is poor as BMD is generally normal in this disease, particularly at the hip level. Therefore as we have learned with other diseases, like glucocorticoid-induced or T2D osteoporosis, DXA does not represent a valid tool for fracture risk estimation in acromegaly. Promising results are coming from the few studies on TBS, on HR-pQCT or on microindentation as all these methods seem to be able to estimate bone quality. In particular, pQCT may represent a new method for discriminating acromegalic patients with vertebral fractures and it is a good prospect for predicting fracture occurrence in acromegaly. Further studies are necessary in order both to confirm these data and to test new methods for the assessment of bone quality in acromegaly.

Thyrotoxicosis

Thyroid hormones have important effects on skeletal development, linear growth and the maintenance of adult bone mass and strength. Thyroid gland mainly secrets thyroxine (T4) that is

consequently metabolized in the active hormone 3,4,3'-L-triiodothyronine that enters the cellular nucleus where activates thyroid hormone receptor α or β (TRα, TRβ). TRβ is the main receptor expressed in the hypothalamus and pituitary where it mediates negative feedback control, regulating thyroid stimulating hormone (TSH) secretion, while TRα is the main receptor expressed in the skeleton. During childhood thyroid hormones accelerates skeletal development and bone maturation. Indeed, almost all pre-pubertal children with thyroid hormone excess have tall stature at diagnosis, with a height SD score significantly greater than that of their parents. However, this accelerated bone maturation, with a premature fusion of the growth plate, may lead to an adult short stature. In the adults, thyroid hormone stimulate bone turnover via increased osteoclastic bone reabsorption (67). The thyroid hormones excess causes a reversible bone loss due to an expansion of the re-modeling space and an irreversible loss due to a negative net bone balance and eventually an increased risk of trabecular perforations (68, 69).

Overt hyperthyroidism is a well-established cause of high bone turnover osteoporosis, resulting in an increased susceptibility to fracture. However, even subclinical hyperthyroidism, both endogenous and exogenous (i.e. TSH suppressive therapy), which is characterized by normal thyroid hormones level and suppressed TSH, seems to be associated with an increased risk of fracture. TSH receptor is expressed also in chondrocytes, osteoblasts and osteoclasts and TSH is thought to exert a positive direct effect in bone metabolism (68).

The effects of overt hyperthyroidism on bone mineralization have widely been documented by dual X-rays absorptiometry (DXA). A decrease in BMD is present at all skeletal sites, including spine, femur, radius, and total body and it is greater in postmenopausal women. The close relationship between observed and BMD-estimated fracture risk could indicate that most of the changes in fracture risk are related to changes in BMD, and that other factors, such as an increased risk of falls, play a minor role (69). However, importantly, in the meta-analysis of a Vestergaard and coauthors the increased risk of hip fracture was independent of hip BMD (69). Thus, in the condition of thyroid hormone excess, components of bone fragility that are entirely independent of conventional BMD may be present.

After a diagnosis of hyperthyroidism is made and after at least 1 year of treatment with anti-thyroid drugs BMD increases and returns in the normal range for age and sex within 5 years; in parallel, the fracture risk, which is 2-3 fold increased at both femur and spine in patients with overt hyperthyroidism, returns to

normal after 1 year of treatment, even without specific anti-osteoporotic therapy (69). Interestingly, BMD increases above the expected from 1 to 4 years after diagnosis of hyperthyroidism. This may be explained by the idea that the normalization of thyroid hormone levels induces a decrease in remodelling activity to subnormal levels and, consequently a reduction in the remodelling space in this period. Following a lag time of 5 years or more, normal bone turnover will resume again, expanding the remodelling space to normal size and resulting in normal BMD levels (69).

As observed in overt hyperthyroidism, postmenopausal women with subclinical hyperthyroidism show reduced BMD evaluated by DXA, while data in men and pre-menopausal women are more controversial. A recent paper shows that the annualized rate of bone loss at hip is 2-3 folds increased in individuals with subclinical hyperthyroidism, especially in those with TSH below 0.10 mIU/L and high-normal free thyroxine levels (70). In keeping, recent data show that subclinical hyperthyroidism is associated with an increased risk for hip and other fractures, with the highest risks in individuals with suppressed TSH (below 0.10 mIU/L), in those with endogenous subclinical hyperthyroidism, and in patients above 60 years of age (71).

Nevertheless, in subclinical hyperthyroidism DXA may not represent the best tool to detect bone damages and fracture risk, as in subclinical hyperthyroidism a reduction of bone quality may play an important role in determining the increased fracture risk. Indeed, in postmenopausal women treated with suppressive L-thyroxine doses, duration of TSH suppression was negatively correlated with TBS levels, but not with BMD (72). In keeping, vBMD obtained by central QCT showed a more significant correlation with TBS than areal BMD measured by DXA in these patients (73). Similarly, in postmenopausal women treated with TSH suppressive therapy pQCT showed a significant trabecular bone loss, mainly at non weight-bearing sites such as the radius (74). Moreover, pQCT did not show differences in terms of vBMD between patients and controls, in premenopausal women, but significant differences were observed in postmenopausal ones. Interestingly, in premenopausal women treated with TSH-suppressive L-thyroxine doses cortical thickness was higher at the radius compared with controls. At variance, in postmenopausal women at radius trabecular bone mineral content, area and vBMD and cortical thickness were reduced (74). Therefore, thyroid hormones excess seems to be associated with a reduction of both cortical and trabecular bone, but only in postmenopausal females.

In addition, the analysis of geometric bone structure properties using HSA showed that in postmenopausal women subclinical hyperthyroidism was associated with a decreased bone strength due to an alteration of bone geometry rather than BMD in the hip area, especially at the femoral neck (75).

In terms of fractures, several studies and meta-analyses have reported an association between subclinical thyroid hormone excess and risk of clinical fractures, mainly in postmenopausal women (71, 76). A recent paper showed that about one third of women treated with TSH suppressive therapy present at least one vertebral fracture, evaluated by morphometric analysis (77). The presence of vertebral fractures correlated with duration of TSH suppressive therapy, degree of TSH suppression and age. Interestingly, vertebral fractures were found even in patients with normal BMD, mainly when the TSH level was below 0.5 mU/L.

In conclusion, overt hyperthyroidism is associated with an increased fracture risk in both sexes, that is related to changes in BMD and at least partially reversible using treatment with anti-thyroid drugs. Subclinical hyperthyroidism, both endogenous and exogenous is associated with an higher fracture risk in postmenopausal women, while in premenopausal women and men its possible negative effects remains unclear. In patients with overt hyperthyroidism, DXA may represent a suitable tool to estimate fracture risk. Differently, in subclinical hyperthyroidism BMD changes are not well related with fracture risk, likely due to an impairment of bone quality. In subclinical hyperthyroidism, TBS evaluation may represent a useful and almost easy reachable tool to improve detection of higher risk patients. However, the clinical usefulness of TBS, QCT, pQCT and HAS for the prediction of fractures risk in patients with subclinical hyperthyroidism has still to be demonstrated. Anyway, a vertebral morphometry should be performed in postmenopausal women with subclinical hyperthyroidism, in addition, in patients treated with long term TSH suppressive therapy a vertebral morphometry should be repeated during follow up

Primary Hyperparathyroidism

In western countries the clinical picture of primary hyperparathyroidism (PHPT) with the devastating effect of very high levels of PTH on bone (i.e. osteitis fibrosa cystica) has become uncommon in the last decades, while the reduction of bone mass and the increased risk of fractures is part of the picture of the commonest mild PHPT. The effects due to the high rate of bone remodelling, are well evident at cortical

sites. Indeed, the cortical bone is more affected than the trabecular one. In the early seventies, by using old methods, such as metacarpal index, a cortical thinning has been showed in PHPT patients. Since the amount of cortical and trabecular bone varies among different skeletal sites, the common techniques for evaluating bone mass are influenced by the site of measurement. Indeed, bone mass measurement by DXA shows the greatest reduction in BMD at mid- radius, the site of predominantly cortical bone, while at lumbar spine, a site of predominantly cancellous bone, bone mass can be relatively preserved. At femoral neck a site of mixed composition, BMD is of intermediate value (78). These data have been confirmed by histomorphometric and microcomputed tomography (microCT) studies focused on cohorts of mild PHPT that showed cortical thinning, increased cortical porosity and endocortical trabeculation, but preservation of cancellous bone volume, bone surface and connectivity density of trabecular plates as compared to controls, independent of advancing age (79). These findings suggest that three-dimensional, cancellous bone microarchitecture is preserved in patients with mild PHPT (79). The conservatively follow-up of mild PHPT patients has shown over time a reduction of BMD as evaluated by DXA more evident at sites with prevalent cortical bone, while the surgical treatment, also in mild PHPT, results in increase of BMD by DXA at the distal third radius, femoral neck as well as lumbar spine (80). Consequently, BMD evaluation by DXA is mandatory at diagnosis of PHPT and in the follow-up. The risk of fractures (both at spine and femur) is about 2 fold increased in PHPT and it is reduced by parathyroidectomy (81). Furthermore, in mild PHPT, due to the preservation of trabecular bone, one should not observe any increase of vertebral fractures. In fact, in mild PHPT a higher risk of vertebral fractures was observed, although spine BMD was higher than in controls, thus suggesting that BMD does not seem to be the only factor determining fracture risk in mild PHPT (73), while the impairment of bone microarchitecture and quality (partially evaluated by TBS, HR-pQCT, QUS) could also explain the high risk of fractures. The same results were reported by a subsequent study (82), in which VFA by DXA was utilized for identifying fractures. In this study the accuracy of VFA compared with X-ray was 92% and sensitivity and specificity of VFA were 82.4% and 97.0%, respectively. According to the lower mineralization in PHPT, some phalangeal ultrasound parameters are lower in PHPT than in controls. Phalangeal QUS, seems to evaluate structural characteristics of bone, rather than the mineral content and some QUS parameters would distinguish male and female postmenopausal patients with PHPT

from normal controls, but not premenopausal patients (83). However, QUS is not commonly utilized for the characterization of PHPT patients.

Recent studies showed that TBS appears to be more accurate than spinal BMD for identifying PHPT patients at risk for vertebral fractures (84). Other authors showed that TBS was associated with vertebral fractures regardless of BMD measured at spine, and had a better compromise between sensitivity (75%) and specificity (61.5%) for detecting fractured patients than spinal BMD. In surgically treated patients, TBS and spinal BMD increased over time, while in conservatively followed patients, TBS decreased significantly in those with incident vertebral fractures compared with those without, while spinal BMD did not significantly change (85).

By using HR-pQCT in PHPT patients, some authors reported decreased volumetric densities, thinner cortices, and more spaced and not omogeneously distributed trabeculae at trabecular and cortical compartments of distal radius and tibia (86). The individual trabecular segmentation (ITS) analysis of radius, derived from HR-pQCT images, showed reductions in both plate and rod trabecular numbers with plate indexes more affected in respect to controls. At the tibia, the ITS analysis showed that the plate trabecular number and plate bone volume were reduced. A reduction in the plate:rod ratio by 22% at the radius and 19% at the tibia, respectively, was observed. Data obtained by HR-pQCT showed that post parathyroidectomy, volumetric BMD, microarchitectural indices and estimated bone strengths improve (86).

Hypercortisolism

Cushing's syndrome (CS) is a condition characterized by a large group of signs and symptoms that reflect prolonged tissue exposure to glucocorticoid excess of endogenous or exogenous origin. Endogenous cortisol overproduction by the adrenal glands can be due to either adrenocorticotropic hormone excessive secretion (from a pituitary or other ectopic tumor) or autonomous adrenal hyperfunction. Hypercortisolism is a well-known cause of endocrine-related osteoporosis due to the detrimental effects on bone of cortisol excess, which produces an imbalance between bone resorption (normal or increased, especially in the early phase) and bone formation (impaired, particularly in the chronic phase). This alteration of bone turnover is one of the main mechanisms which leads to bone loss in CS. Many studies investigating bone density in CS patients demonstrated a reduced BMD in these patients (87). Areal BMD, as measured by dual x-ray

485 absorptiometry (DXA), was found to be significantly lower in patients with CS than in healthy controls at
486 both the spine and the hip (88) and this reduction was confirmed even after the exclusion of hypogonadal
487 subjects (88, 89), thus suggesting that the deleterious effects of hypercortisolism on bone overcome the
488 protective effect of eugonadism in CS. The prevalence of osteoporosis in CS patients varies across studies
489 and can be estimated between 30 and 70% (88, 89).

490 The assessment of volumetric BMD, as measured by HR-QCT suggests that the cortisol excess
491 affects more severely trabecular than cortical bone (87), even though some studies were not able to find this
492 difference between these compartments. However, also the microarchitecture of cortical bone is probably
493 injured in CS with lower cortical area and cortical thickness at both the radius and the tibia (88). In a study
494 performed by QCT and pQCT, trabecular, but not cortical and integrated BMD, was significantly reduced in
495 CS patients, suggesting different sensitivities of the two bone tissues to glucocorticoid excess at the forearm
496 (89). In contrast to what observed at the forearm, both trabecular and cortical bone were similarly reduced in
497 CS patients, indicating, therefore, that the different sensitivities to glucocorticoid excess of the two different
498 bone tissues are site specific (i.e. present at the forearm but not at the femur). In addition, by comparing the
499 BMD values for all affected sites in CS patients, spinal trabecular bone, as studied by QCT, was the most
500 severely affected (89).

501 Data on bone density in CS as assessed by QUS are scarce and quite discordant. Few studies found a
502 reduction of QUS parameters at the phalanges of the non-dominant hand (90) and at the heel (91) in CS
503 patients, whereas others were not able to find any significant bone loss as measured by QUS (92).
504 However, the bone loss, independent of the technique used for the BMD measurement, does not fully explain
505 the high fracture risk observed in CS. Indeed, approximately 30-67% of CS patients experienced a clinical
506 fragility fracture in the course of the disease, more commonly at the vertebral level (87) and, as demonstrated
507 by Tauchmanovà and colleagues, this remarkable prevalence of fragility fractures appears to be
508 underestimated, since in about a half of cases vertebral fractures are absolutely asymptomatic. Moreover, in
509 about 10% of CS patients vertebral fractures occur in the presence of normal BMD (86), thus underlying the
510 crucial role of the radiologic evaluation of the thoracic and lumbar spine, regardless of BMD, for the
511 detection of vertebral morphometric fractures. As a consequence SDI has been proposed as a surrogate
512 marker of bone microarchitecture even in CS (15, 93).

Indeed, the partial discrepancy between bone mass and fracture risk in CS can be explained by a damage of bone quality other than bone quantity caused by cortisol excess in CS patients. In addition to SDI, TBS has been proposed as another non-invasive technique able to give information on bone microarchitecture. Patients with CS exhibited low TBS values which inversely correlated with the degree of hypercortisolism and which improved more markedly and quickly than BMD after CS remission (94).

A recent work of Maurice and collaborators measured BMF content in CS patients by using MRS, which is considered the best available method for BMF quantification. They found that CS patients had increased BMF content compared to cured patients and healthy subjects (95). However further studies are required in order to clarify the precise link between BMF and bone microarchitecture in hypercortisolism.

It is worthy of attention how imaging evaluation can define skeletal fragility in patients with subclinical hypercortisolism (SH), which is a condition of cortisol excess in the absence of its classical signs and symptoms (96). As CS, even SH was demonstrated to be detrimental for the bone health, and most studies found a reduction in spinal BMD, as measured by DXA or QCT, in SH patients. At variance, data on femoral BMD in SH are more discordant (96). However, as compared with CS patients, in SH patients the degree of BMD loss is even less predictive of the risk of fracture, which is surprisingly comparable with that of CS patients, especially at the vertebral level. This is probably due to a longer exposition to cortisol excess in SH than in CS due to the absence of clinical signs and symptoms (96). As in patients with overt cortisol excess, in SH an alteration of the bone quality, rather than of bone quantity, is suspected to be the main responsible of the skeletal fragility (92) and TBS was found to be reduced in SH patients and correlated with the number and severity of vertebral fractures and with the degree of cortisol excess (97).

Hypogonadism

Bone health is a major concern in patients with hypogonadism . Estrogens levels lower than 20 pg/ml are associated with significant bone loss and levels below 5 pg/ml are associated with a 2.5 fold increase in hip and vertebral fractures independently of sex, age and body weight (98). In male hypogonadism, the BMD values associated to fracture risk are not so well defined as in postmenopausal women or glucocorticoid induced osteoporosis. In hypogonadism the rate of bone loss is increased due to a very high bone turnover. This, in turn, decreases bone quality and increases the fracture risk partially

independently of BMD reduction (99). Indeed, a high bone turnover impairs bone strength in excess that expected from the change in bone mass. All acquired hypogonadisms, in particular in young age or if occur quickly (i.e surgical or pharmacological castration) are associated with a very high bone turnover. The hormonal ablation for cancer adjuvant therapy or for endometriosis are the best studied secondary osteoporosis due to hypogonadism. Gonadotrophin releasing hormone agonists or analogues are used in prostate cancer, premenopausal breast cancer women and endometriosis. Furthermore aromatase inhibitors nowadays are the standard of adjuvant therapy in estrogen receptor positive postmenopausal breast cancer (100). Bone loss in these patients, begin early after the beginning of hormonal therapy and progresses with high rate (100).

There are strong evidences that in the cancer treatment-induced bone loss (CTIBL) as well as young women with endometriosis there is a very compromised bone quality with lower trabecular volume, fewer trabeculae number, higher trabecular interruption and cortical porosity than in controls as evaluated by HR-pQCT (101-103). The fracture incidence in patients with breast cancer treated with aromatase inhibitors was 7-26% at 7 years of treatment (104), and about 23-28% in patients with prostate cancer on antiandrogen therapy (105). Overall the fractures occur very precociously after the start of hormonal ablation, when BMD is often not impaired (104, 106). The increased awareness about CTIBL has led to guidelines and expert panel to recommend to monitor for bone loss with BMD by DXA (107). However in a retrospective study on 17,110 breast cancer survivor followed about 5 years demonstrated that the increased risk of a fracture was not explained by worse BMD suggesting that BMD does not adequately capture bone strength determinants as shown in other studies (108). When postmenopausal women with breast cancer treated with aromatase inhibitors were randomized to receive placebo or denosumab, the risk of all fracture in placebo group and the risk of fracture reduction in denosumab group were substantially independent of BMD (104). Interestingly, in patients with prostate cancer the fracture risk is better expressed by calculating FRAX without BMD than with BMD (109).

In keeping with the idea that that skeletal fragility is prominently dependent on the poor quality of bone microarchitecture, in In patients with breast cancer treated with exemestane, TBS significantly decreases of 2.3% and BMD of 5% in 24 months of treatment and in particular the changes were independent from each other (110). In a retrospective longitudinal study in breast cancer patients treated

with aromatase inhibitors for more than 3 years, along with an impairment of bone quality parameters, TBS also significantly decreased from baseline to 5 years (2.1%) and this change remained significant after adjusting for lumbar spine BMD (111). In B-ABLE study TBS and BMD significantly decreased in not treated patients with breast cancer, while in bisphosphonates treated subjects BMD increased and TBS remained stable at the end of the treatment with aromatase inhibitors. In both groups the changes in spine BMD and TBS were weakly correlated (112). Similar results were found in premenopausal breast cancer women treated with zoledronic acid (113). Therefore, TBS could be suitable to improve the fracture risk definition in CTIBL patients and could be usefully combined with FRAX and BMD to maximize the identification of patients with elevated risk (114).

In the future, other technologies that capture a combination of bone mass and bone quality and the possibility to assess the separate role of trabecular and cortical bone could potentially be useful for fracture risk definition in CTIBL besides DXA. Indeed, MRI of trabecular microarchitecture actually refers to imaging of the marrow contents of the trabecular bone tissue compartment. These studies were performed with 1.5T, 3T and 7T MRI. Cortical bone is an important contributor to bone strength as evidenced byrecent data using MRI. Cortical bone has a very short T2 relaxation times (<1 ms) and, using a very short or ultrashort echo, cortical bone porosity and collagen-bound water could be captured. The available in vivo clinical studies are so far very few (115).

In patients with prostate cancer on androgens deprivation therapy, with vertebral fracture MRI demonstrated bone quality deterioration at distal radius compared to controls and the addition of these parameters to BMD significantly improves the ability to individuate fractured patients (115). Even pQCT is available method to quantify separately cortical and trabecular bone at peripheral skeletal site. In breast cancer patients on hormonal adjuvant therapy pQCT surprisingly demonstrated a prominent negative impact of anastrozole on cortical bone as compared with healthy control women (104).

Recently also ancillary analyses of PET-CT examinations were compared against values obtained using routine multidetector-row computed tomography (MDCT) with promising performances (116). However, to date, there are not strong evidences that microarchitecture definition by MRI, MDCT or QCT could become the standard methods to assess the risk of fractures in hypogonadal subjects. It is likely that a

combination of different technologies should offer the best definition of bone strength but also the cost-effectiveness of this approach should be determined.

Fracture risk assessment in secondary osteoporosis

In many conditions other than postmenopausal osteoporosis the fracture risk is neglected or underestimated and the use of an algorithm represents the solution to ensure a homogeneous evaluation among specialists and an appropriate approach to therapy. The most commonly used is FRAX® that calculates absolute fracture probability from 10 easily obtained risk factors in optional conjunction with BMD T-score values (117). Among the risk factors "secondary osteoporosis" is included, which encompasses namely: type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (before 45 years), chronic malnutrition and chronic liver disease. Many other well known conditions associated to bone fragility, such as hyperparathyroidism, T2DM , obesity, cancer and ormonal adiuvant therapy, HIV, chronic inflammatory bowel disease and obstructive respiratory disease are not included (https://www.sheffield.ac.uk/FRAX, last access 02.12.2019), although they are been very recently re-evaluated (118).

Endogenous hypercortisolism is not formally included but the term "glucocorticoid" is among the ten risk factors and in the place of the term "obesity" the term "BMI" is present. Moreover, FRAX calculation has been included in some International Guidelines as IOF/ECTS, ESCEO and American College of Rheumatology for the management of glucocorticoid osteoporosis and CITBL in breast and prostate cancer (119-121).

However, FRAX has been designed to assess fracture risk in postmenopausal osteoporosis which substantially differs as compared with the condition of bone fragility due to endocrine disorders. Indeed, in these latter conditions, bone microarchitecture alterations and/or other factors (as for example the risk of fall) are crucial determinant of the fracture risk. Therefore, in these condition the DXA values may substantially underestimate the risk of fracture (4, 43, 84, 85, 122, 123). This explains why in these condition the "secondary osteoporosis" option in the FRAX tool has a much smaller effect on fracture risk than would be expected, and it has been suggested to use the bypass of rheumatoid arthritis in the FRAX tool to correct the estimation of fracture risk (122). Moreover, since BMD in many conditions is not impaired or it is even

higher than expected (4, 43, 84, 85, 122, 123), the fracture risk prediction by FRAX may be improved by excluding BMD in the algorithm computation (4, 124-126) or by downward adjusting BMD by 0.5 standard deviation (39). Finally the TBS-adjusted FRAX , being TBS an independent fracture risk capturing "quality" aspects of bone structure, has suggested to possibly improve the absolute fracture risk definition in secondary osteoporosis (114, 127, 128).

In conclusion for the absolute fracture risk assessment in the majority of secondary osteoporosis FRAX is currently not performing as in postmenopausal osteoporosis and the "secondary osteoporosis" option does not adequately correct the understimation of the fracture risk. Excluding BMD ,or including "Arthritis Rheumatism" or TBS could currently be options to improve the fracture risk predictability using FRAX in secondary osteoporosis. As suggest in the update of the European Guidelines for osteoporosis imminent new FRAX version could be take in account these needs for the management of secondary osteoporosis (118)

Conclusions and Perspectives

In the present review we have summarized the available data about the imaging tools that can be used in evaluating the fracture risk in patients with the most common endocrine forms of osteoporosis and bone fragility. A summary of the main characteristics of the different non-invasive imaging methods for the assessment of bone health is reported in table 4.

It is possible, however, that even in healthy subjects, the endocrine mileau (in term of degree of secretion, peripheral activation and sensitivity) could play a role in predisposing to fracture risk. Indeed, cortisol levels seems to be associated with BMD in women with postmenopausal osteoporosis (129, 130), the activity of the 11βhydroxysteroid dehydrogenase shuttle, which regulates the glucocorticoid peripheral activity, seems to influence the risk of vertebral fractures (131, 132), and the different GC receptor polymorphisms, have been suggested to be associated with the fracture risk in patients with no evidence of cortisol excess (133, 134). Furthermore, recent data show that even in primary aldosteronism femur and spine BMD and TBS are reduced (135-136) and that the fracture risk is increased (137-138). This clinical picture as well as fracture risk recedes after treatment, particularly after surgery (139). Since aldosterone secretion is increased in a large part of hypertensive patients (139), altogether these data may suggest that

cortisol and aldosterone secretion may represent two so far ignored contributors to osteoporosis in the general population.

The issue of hypovitaminosis D and of secondary hyperparathyroidism as possible endocrine causes of bone fragility was beyond the scope of the present review. However, it is important to underline that hypovitaminosis may be a potential contributor to bone fragility in all forms of secondary osteoporosis and may influence their diagnostic work-up. Indeed in up to 30% of cases, the diagnosis of PHPT may be missed if the biochemical workup is performed in the presence of low vitamin D levels (2). Besides hypovitaminosis D, a concomitant mineralisation disorder, impacting on bone density and quality could influence the effect of an endocrine disease on bone fragility (140, 141). Therefore, in all endocrine related forms of bone fragility the vitamin D status has to be assessed and the presence of a mineralization disorder has to be excluded.

Finally, a limit of many studies assessing bone fragility in the endocrine disorders is related to the clinical significance of morphometric vertebral fractures. Indeed, in all studies cited in the presence review the morphometric vertebral fractures were defined as at least a 20% deformity (i.e. at least I grade). However, the significance and predictive ability of grade I vertebral fractures for future fractures is still questioned (142).

In conclusion, the endocrine-related forms of osteoporosis are characterized by an increased risk of fracture which is often hardly predictable by DXA. Even though TBS seems to be useful for assessing the fracture risk in patients affect with an endocrine disease, further studies are needed. In particular, TBS is incapable of directly assessing osseous microarchitecture and the overall effect of the joint use of TBS with FRAX is modest, with most of its clinical impact limited to patients already close to an intervention threshold. Moreover, in some studies TBS did not improve ROC curves on fracture risk over femur BMD alone. Finally, to date, we have not sufficient evidence suggesting that TBS can be used to assess the effect of pharmacologic anti-fracture treatment (143).

Hopefully, in the future new imaging methods for evaluating both bone density and quality could be introduced in the clinical practice. This would help to better identify patients with endocrine diseases at high risk of fracture, therefore consenting their early treatment. These methods could even consent to evaluate the

effect of the drug therapy and medical rehabilitation on the skeletal health in patents affected with an endocrine-related form of bone fragility.

Declaration of interest

All Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. Main endocrine disorders associated with an increased risk of fractures

ENDOCRINE DISORDER
Cushing syndrome
Acromegaly
Thyrotoxicosis
Primary Hyperparathyroidism
Primary Hyperaldosteronism
Diabetes
Male Hypogonadism
Obesity

Table 2. PROs and CONs factors in obesity and bone mass (BMD) interrelationship

PROs
Mechanical load
Increased androgen levels (women)
Conversion from androgen into oestrogen
Increased levels of free sex hormones
Secretion of insulin and amylin by Beta cells
Increased glucagon-like peptide 2
Adipokines
CONs
Reduced insulin-related signalling (insulin-resistance)
Adipokines
Hyperglycaemia in obese-T2DM subjects
Inflammation and pro-inflammatory cytokines
Dyslipidaemia
Reduced vitamin D levels/secondary hyperparathyroidism/calcium malabsorption
Hypogonadism
Abnormal muscular metabolism/function

Table 3. Fragility fracture risk and most frequent findings in the evaluation of bone mineral density and bone quality in the endocrine-related forms of osteoporosis

Disorder	VFx risk	Hip Fx risk	DXA	TBS	Available data from other imaging tools
Obesity	↑	N.A.	N/High	reduced	MRS for BMF estimates
Type 2 Diabetes	↑	↑	N/High	reduced	QUS, HSA, QUS, QCT, HR-pQCT, MRI, MRS for BMF estimates
Type 1 Diabetes	↑↑	↑↑↑	↓↓	reduced	QUS, QCT, HR-pQCT
Acromegaly	↑↑	N.A.	N	reduced	HR-pQCT
Overt hyperthyroidism	↑	↑	↓↓	NA	NA
Subclinical Hyperthyroidism	↑*	↑	↓↓	reduced	QCT, HR-pQCT, HAS
Primary Hyperparathyroidism	↑	↑	↓	reduced	QUS
Overt Hypercortisolism	↑↑↑	↑	↓↓	reduced	QUS, QCT
Subclinical hypercortisolism	↑↑	N.A.	↓/N	reduced	QUS, QCT
Hypogonadism in CTIBL	↑↑	↑↑	↓/N	reduced	MRI, QCT, MDCT

*in post-menopausal women

↑ up to 2 fold increased; ↑↑ 2-5 fold increased; ↑↑↑ more than 5 fold increased; ↓↓ severely reduced (i.e. T-score ≤ -2.5); ↓ reduced (i.e. T-score between -1.0 and -2.5); N: normal (T-score > -1.0); N.A.: data not available; MRS: Magnetic Resonance Spectroscopy; BMF: bone marrow fat; HAS: Hip Structural Analysis; QUS: quantitative ultrasound; QCT: Quantitative Computed Tomography, HR-pQCT: high resolution peripheral QCT; MRI: Magnetic Resonance Imaging; MDCT: multidetector-row computed tomography; CTIBL: Cancer Treatment Induced Bone Loss

Table 4. Summary and main characteristics of the different non-invasive imaging methods for the assessment of bone health

Imaging method	Parameters assessed	Skeletal site	Clinical and research applications	Disadvantages
DXA	Areal BMD	Lumbar spine, hip, radius, total body	WHO diagnosis of osteoporosis, input for FRAX, body composition evaluation	2D nature, lack of compartment-specific BMD measurement
TBS	Pixel gray-level texture	Lumbar spine	Index of trabecular bone quality, improvement of FRAX prediction	Not useful for monitoring treatment response
VFA	Vertebral fractures	Thoracolumbar spine	Detection of vertebral fractures by using DXA image (sensitivity and specificity >90 % for moderate and severe fractures)	Low sensitivity for detecting mild vertebral fractures
HSA	Hip bone geometry	Hip	Evaluation of hip bone strength	For research purposes only
Conventional radiography (X-ray)	Morphometric vertebral fractures	Thoracolumbar spine	Detection of morphometric vertebral fractures, SDI calculation	Low sensitivity for diagnosing low BMD
QUS	SOS, BUA and other derived parameters	Heel, phalanges of the non-dominant hand	Indirect quantification of bone tissue properties and BMD without ionizing radiation exposure	High rate of change of QUS parameters, not to be used for diagnosing osteoporosis, for monitoring treatment response and with FRAX
QCT-based methods	Volumetric BMD	Distal radius, tibia (HR-pQCT) Spine (central QCT)	Assessment of cortical and trabecular bone compartments, QCT-derived FEA modeling for bone strength estimation	High costs, low availability, ionizing radiation exposure. For research purposes only
MRI-based methods	Bone microstructure	Peripheral skeletal sites (HR-MRI) Spine (MRS)	Assessment of bone microarchitecture, MRI-derived FEA modeling for bone strength estimation (HR-MRI). BMF evaluation (MRS)	High costs, low availability. For research purposes only

DXA: dual-X-ray absorptiometry. BMD: bone mineral density. TBS: trabecular bone score (DXA-based measurement). VFA: vertebral fracture assessment (DXA-based method). HSA: hip structural analysis (DXA-based method). SDI: spinal deformity index. QUS: quantitative ultrasound. SOS: ultrasound speed of sound. BUA: broadband ultrasound attenuation. QCT: quantitative computed tomography. HR-pQCT: high-resolution peripheral quantitative computed tomography. FEA: finite element analysis. MRI: magnetic resonance imaging. HR-MRI: high-resolution magnetic resonance imaging. MRS: magnetic resonance spectroscopy. BMF: bone marrow fat.