



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

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Evaluation of bone fragility in endocrine disorders

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Complete List of Authors:	<p>Eller-Vainicher, Cristina; Fondazione Ca'Granda Ospedale Maggiore Policlinico IRCCS, Endocrinology and Diabetology Units, Department of Medical Sciences and Community</p> <p>FALCHETTI, ALBERTO; EndOsMet, Villa Donatello Private Hospital, , Endocrinology; Istituto Auxologico Italiano, IRCCS, Unit for Bone Metabolism Diseases and Diabetes & Lab of Endocrine and Metabolic Research</p> <p>Gennari, Luigi; University of Siena, Department of Medicine, Surgery and Neurosciences</p> <p>Cairoli, Elisa; Istituto Auxologico Italiano, IRCCS, Unit for Bone Metabolism Diseases and Diabetes & Lab of Endocrine and Metabolic Research; Universita degli Studi di Milano, Medical and Surgical Pathophysiology and Transplant</p> <p>Bertoldo, Francesco; Universita degli Studi di Verona, Bone Metabolism and Osteonology Unit, Dept. Medicine</p> <p>Vescini, Fabio; University-Hospital S. Maria della Misericordia Udine, Endocrinology and Metabolism Unit</p> <p>Scillitani, Alfredo; Casa Sollievo della Sofferenza Scientific Institute, Unit of Endocrinology;</p> <p>Chiodini, Iacopo; University of Milan, Department of Clinical Sciences and Community Health; Universita degli Studi di Milano, Dpt of Clinical Sciences & Community Health</p>
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1 **Title:** Evaluation of bone fragility in endocrine disorders

2 **Authors:** ¹Cristina Eller-Vainicher, ²Alberto Falchetti, ³Luigi Gennari, ^{2,4}Elisa Cairoli, ⁵Francesco Bertoldo,
3 ⁶Fabio Vescini, ⁷Alfredo Scillitani, ^{2,8}Iacopo Chiodini

4 **Affiliations:**

5 ¹Unit of Endocrinology Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico Milan, Italy;

6 ²Istituto Auxologico Italiano, IRCCS, Unit for Bone Metabolism Diseases and Diabetes & Lab of Endocrine

7 and Metabolic Research; ³Department of Medicine, Surgery and Neurosciences, University of Siena, Italy;

8 ⁴Department of Pathophysiology and Transplantation and ⁸Department of Clinical Sciences & Community

9 Health, University of Milan, Milan, Italy. ⁵Bone Metabolism and Osteoncology Unit, Dept. Medicine

10 University of Verona; ⁶Endocrinology and Metabolism Unit, University-Hospital S. Maria della

11 Misericordia Udine, Italy; ⁷Unit of Endocrinology and Diabetology, Ospedale “Casa Sollievo della

12 Soffererenza “ IRCCS, San Giovanni Rotondo (FG), Italy;.

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15 **Corresponding author and person to whom reprint requests should be addressed:** Iacopo Chiodini,

16 Unit for Bone Metabolism Diseases and Diabetes & Lab of Endocrine and Metabolic Research, Istituto

17 Auxologico Italiano, IRCCS, Via Magnasco 2, 20149 Milan, Italy; Tel +39 02 61911 2738; email:

18 iacopo.chiodini@unimi.it; i.chiodini@auxologico.it.

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20

21 **Abstract**

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

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

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

37

38 Introduction

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

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

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

66

67 Obesity

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

83 A direct positive correlation between Body Mass Index (BMI) and BMD has been reported in
84 literature (8, 9). Thus, in past years, obesity status was believed to be protective against fragility fractures.
85 Lately, several studies argued that obesity, as defined by WHO criteria by the a BMI equal to or above 30
86 kg/m², could not be longer regarded to as a real protector from bone fragility. In fact, several findings
87 demonstrated that while on the one hand BMI is associated with increased risk of fracture at some skeletal
88 sites, on the other side it may be protective at others skeletal sites, representing the so-called obesity paradox
89 (8). Table 2 reports a summary concerning some of factors, pros and cons, potentially associated in the
90 interrelationship between obesity and bone mass.

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

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

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

122 US (<https://www.medscape.com/viewarticle/896882>), by Watanabe and coauthors. They suggested such a
123 simple measure as an important new tool to potentially and easily assess the risk fracture in obese patients,
124 particularly when the bone strength could be linked to the presence of impaired metabolic health. They
125 investigated a large Caucasian cohort of more than 2,000 overweight or obese patients (82% female, aged
126 45 ± 12 years, mean BMI 36.5 ± 6.2 kg/m²) by assessing body composition, and both DXA LS BMD and
127 TBS. Confirmation of the association between increased BMI, increased BMD, and decreased TBS values
128 has been obtained. The LS BMD/BMI ratio was more strongly correlated with TBS than LS BMD. In obese
129 subjects with metabolic syndrome, the LS BMD was similar to that of metabolically healthy subjects, but
130 both TBS and BMD/BMI ratio were significantly lower. All these preliminary findings suggest that the
131 BMD/BMI ratio offers a simple tool for assessing the risk of fracture in obese subjects
132 (<https://www.medscape.com/viewarticle/896882>). However, it will be necessary to wait for the effective
133 publication of these data, and their possible replication in other studies.

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

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

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

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

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

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

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

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

208

209 **Diabetes**

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

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

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

234 general population, with T-score levels often above the osteoporotic range. Thus, concerning T2D, it has
235 been estimated that a similar increase in hip fracture risk than in non-diabetic subjects occurs at 0.6 SD and
236 0.4 SD higher BMD levels in women and men, respectively (40). In addition to BMD measurement, a spinal
237 x-ray should be mandatory in diabetic patients with a previous fragility fracture or in those with diabetic
238 complications, particularly in the presence of a poorly controlled disease. Indeed, when investigated by a
239 lateral spine radiograph, up to a third of postmenopausal T2D women showed asymptomatic, morphometric,
240 vertebral fractures (42), that *per se* represent a major risk factor for subsequent fractures (43).

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

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

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

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

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

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

276

277 **Acromegaly**

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

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

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

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

298 Another method that is used to measure bone quality is HR-pQCT, which by analysing the distal
299 radius and tibia allows the *in vivo* assessment of both bone microarchitecture and volumetric BMD. Using
300 HR-pQCT in 82 patients with acromegaly, Madeira et al. have found a severe deterioration of trabecular
301 bone microarchitecture that was correlated with patients' gonadal status rather than with the presence of type
302 2 diabetes or the activity of the disease. Therefore a sub-analysis was performed on 45 eugonadal
303 acromegalic patients compared with 45 healthy controls. The patients showed lower trabecular volumetric
304 bone density, bone volume to tissue volume and trabecular number than controls. Moreover they had higher
305 trabecular separation and spacing than healthy subjects (61). All these findings can be associated with greater
306 bone fragility, that, as previously demonstrated, is increased by hypogonadism (62).

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

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

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

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

342

343 **Thyrotoxicosis**

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

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

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

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

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

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

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

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

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

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

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

424

425 **Primary Hyperparathyroidism**

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

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

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

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

466 By using HR-pQCT in PHPT patients, some authors reported decreased volumetric densities, thinner
467 cortices, and more spaced and not omogeneously distributed trabeculae at trabecular and cortical
468 compartments of distal radius and tibia (86). The individual trabecular segmentation (ITS) analysis of radius,
469 derived from HR-pQCT images, showed reductions in both plate and rod trabecular numbers with plate
470 indexes more affected in respect to controls. At the tibia, the ITS analysis showed that the plate trabecular
471 number and plate bone volume were reduced. A reduction in the plate:rod ratio by 22% at the radius and
472 19% at the tibia, respectively, was observed. Data obtained by HR-pQCT showed that post
473 parathyroidectomy, volumetric BMD, microarchitectural indices and estimated bone strengths improve (86).

474

475 **Hypocortisolism**

476 Cushing's syndrome (CS) is a condition characterized by a large group of signs and symptoms that
477 reflect prolonged tissue exposure to glucocorticoid excess of endogenous or exogenous origin. Endogenous
478 cortisol overproduction by the adrenal glands can be due to either adrenocorticotrophic hormone excessive
479 secretion (from a pituitary or other ectopic tumor) or autonomous adrenal hyperfunction. Hypocortisolism
480 is a well-known cause of endocrine-related osteoporosis due to the detrimental effects on bone of cortisol
481 excess, which produces an imbalance between bone resorption (normal or increased, especially in the early
482 phase) and bone formation (impaired, particularly in the chronic phase). This alteration of bone turnover is
483 one of the main mechanisms which leads to bone loss in CS. Many studies investigating bone density in CS
484 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).

513 Indeed, the partial discrepancy between bone mass and fracture risk in CS can be explained by a damage of
514 bone quality other than bone quantity caused by cortisol excess in CS patients. In addition to SDI, TBS has
515 been proposed as another non-invasive technique able to give information on bone microarchitecture.
516 Patients with CS exhibited low TBS values which inversely correlated with the degree of hypercortisolism
517 and which improved more markedly and quickly than BMD after CS remission (94).
518 A recent work of Maurice and collaborators measured BMF content in CS patients by using MRS, which is
519 considered the best available method for BMF quantification. They found that CS patients had increased
520 BMF content compared to cured patients and healthy subjects (95). However further studies are required in
521 order to clarify the precise link between BMF and bone microarchitecture in hypercortisolism.

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

533

534 **Hypogonadism**

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

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

550 There are strong evidences that in the cancer treatment-induced bone loss (CTIBL) as well as young
551 women with endometriosis there is a very compromised bone quality with lower trabecular volume, fewer
552 trabeculae number, higher trabecular interruption and cortical porosity than in controls as evaluated by HR-
553 pQCT (101-103). The fracture incidence in patients with breast cancer treated with aromatase inhibitors was
554 7-26% at 7 years of treatment (104), and about 23-28% in patients with prostate cancer on antiandrogen
555 therapy (105). Overall the fractures occur very precociously after the start of hormonal ablation, when BMD
556 is often not impaired (104, 106). The increased awareness about CTIBL has led to guidelines and expert
557 panel to recommend to monitor for bone loss with BMD by DXA (107). However in a retrospective study on
558 17,110 breast cancer survivor followed about 5 years demonstrated that the increased risk of a fracture was
559 not explained by worse BMD suggesting that BMD does not adequately capture bone strength determinants
560 as shown in other studies (108). When postmenopausal women with breast cancer treated with aromatase
561 inhibitors were randomized to receive placebo or denosumab, the risk of all fracture in placebo group and
562 the risk of fracture reduction in denosumab group were substantially independent of BMD (104).
563 Interestingly, in patients with prostate cancer the fracture risk is better expressed by calculating FRAX
564 without BMD than with BMD (109).

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

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

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

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

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

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

598

599 **Fracture risk assessment in secondary osteoporosis**

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

611 Endogenous hypercortisolism is not formally included but the term “glucocorticoid” is among the ten
612 risk factors and in the place of the term “obesity” the term “BMI” is present. Moreover, FRAX calculation
613 has been included in some International Guidelines as IOF/ECTS, ESCEO and American College of
614 Rheumatology for the management of glucocorticoid osteoporosis and CITBL in breast and prostate cancer
615 (119-121).

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

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

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

635

636 **Conclusions and Perspectives**

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

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

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

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

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

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

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

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

680

681 **Declaration of interest**

682 All Authors declare that there is no conflict of interest that could be perceived as prejudicing the
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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

For Review Only

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.