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Osteoporosis in premenopausal women: a clinical narrative review by the ECTS and the IOF

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Abstract

Context: Consensus regarding diagnosis and management of osteoporosis in premenopausal women (PW) is still lacking, due to few studies carried out in this population.

Design: ECTS and IOF convened a working group to produce an updated review of literature published after 2017 on this topic.

Results: Fragility fractures in PW are rare and mostly due to secondary osteoporosis, i.e. in presence of an underlying disease such as hormonal, inflammatory or digestive disorders. In absence of another disorder, low bone density (BMD) together with fragility fractures qualifies as "idiopathic osteoporosis". In contrast, low BMD alone does not necessarily represent osteoporosis in absence of bone microarchitectural abnormalities.

BMD increases in PW with osteoporosis when the underlying disease is treated. For example, in celiac disease, an increase of 9% in radius trabecular volumetric density was achieved after 1 year of gluten-free diet, while anti-TNF alfa improved BMD in PW with inflammatory bowel diseases. In amenorrhea, including anorexia nervosa, appropriately delivered estrogen replacement therapy can also improve BMD. Alternatively, antiresorptive or anabolic therapy has been shown to improve BMD in a variety of conditions, the range of improvement (3-16%) depending on skeletal site and the nature of the secondary cause. No studies were powered to demonstrate fracture reduction. The effects of bisphosphonates in childbearing women have been scantly studied and caution is needed.

Conclusion: The majority of PW with osteoporosis have an underlying disease. Specific therapy of these diseases, as well as antiresorptive and anabolic drugs, improve BMD, but without evidence of fracture reduction.

Key words: premenopausal women, osteoporosis, fracture, secondary osteoporosis, pregnancy, antiresorptive therapy

Introduction

The epidemiology of osteoporosis and fracture rate in premenopausal women is uncertain. The prevalence of "osteoporosis" in premenopausal women varies from 0.5 to 50% depending on the population studied, the definition of osteoporosis used, and the referral center involved (1, 2). A European study in premenopausal women (mean age 34.8± 0.5) from the general population found no subjects with osteoporosis (defined as a T score ≤ -2.5) and 10.6% with osteopenia (T-score >-2.5 and ≤-1.0) (3). However such data can be misleading since a low areal bone mineral density (aBMD) alone at a young age may reflect a relatively thinner skeleton, for instance in a constitutionally lean person, but with normal volumetric BMD and no alterations of microstructure, i.e. not necessarily more fragile bones. In contrast, in premenopausal women with known causes of secondary osteoporosis, the prevalence of low bone mass (defined as Z-score ≤ -2) was recently reported as 17.3% in patients affected by systemic lupus erythematosus (4), 7.3% in rheumatoid arthritis (5), 44.5% in Cushing diseases (6), 35% in HIV (7), and 45% in cystic fibrosis (8), and these disorders are associated with an increased risk of fragilty fractures.

A premenopausal woman with a prior fracture has a 35 to 75% higher risk of having a fracture in her postmenopausal years than a premenopausal woman without fracture (9). Therefore, early diagnosis and management may be beneficial, although currently no studies have investigated this strategy with respect to reducing fractures later in life (10,11). Few reviews on osteoporosis in premenopausal women have been published (1,2,10,12-15), with the latest narrative review and guidance paper dating from 2017 (16, 17). The purpose of the present review is to provide an update on literature published after 2017 regarding diagnosis and management of osteoporosis in premenopausal women, excluding children and adolescents.

Search strategy

The European Calcified Tissue Society (ECTS) and the International Osteoporosis Foundation (IOF) formed a working group to carry out a comprehensive review of existing literature by means of a search in PubMed for english language literature published from January 2017 to July 2019 using the following search terms in the title, without exclusion criteria: “premenopausal”, “osteoporosis”, “fracture”, “pregnancy and lactation induced osteoporosis”, “secondary osteoporosis”, “anorexia/eating disorders”, “vitamin D”, “bisphosphonates”, “teriparatide”, “denosumab” and “calcium”.

Among the 248 papers identified, we considered as high quality papers those reporting on randomized controlled trials (RCTs), but we also included observational studies, case series, meta-analysis and reviews, if it was clearly stated that premenopausal women were enrolled. At the end, a total of 139 papers were included in this review.

Factors affecting peak bone mass and early fracture risk

The bone mineral density (BMD) of premenopausal women depends primarly on their bone accrual during childhood and adolescence as the final peak bone mass is reached around the age of 20 years, depending on the skeletal site.

Although 40-80% of the variation in BMD and bone microarchitecture is genetically determined (18-19), a myriad of diseases and lifestyle factors, even from very early life (20), may influence physiological bone accrual resulting in a lower bone mass in adulthood, as recently reviewed (21).

Lean body mass is a significant predictor of aBMD at all skeletal sites, accounting for 7–26 % of the variance ($p = 0.043–0.001$) (22), after adjusting for age, and bone specific physical

activity. The association between lean mass and bone accrual might also be due to other factors, such as nutrition, hormones and genetic factors that have independent effects on muscle and bone.

Moreover, muscle power has been shown to be a positive determinant of femoral neck (FN) and total hip BMD, FN cross sectional area, FN cross-sectional moment of inertia (CSMI) and FN Z-score in 148 women between 18-35 years (23). Thus, it can be speculated that exercise, which improves lean mass and muscle power, has a positive effect on peak bone mass accrual, as it has been shown in previous studies (24-27).

Sexual development and function is crucial for bone mass accrual. A recent Canadian cross-sectional, population-based study of 499 menstruating women with a BMD measurement after attaining peak bone mass, showed that 18% of lumbar spine (LS) BMD was attributed to positive contributions of current body mass index (BMI) and height, with negative influences from previous history of amenorrhea and androgen excess. Approximately 20% of the variation in FN BMD was explained by current BMI and height (positive effect) and age at menarche (negative effect) (28), as also reported previously (29). A specific group of women, that may experience menstrual dysfunction, are those actively involved in sports at the competitive level. When this is accompanied by a low caloric intake and a low bone density, it constitutes the so called "female athlete triad". Components of the "triad" are interrelated if one is identified, the others should be activelly evaluated as suggested by the 2017 update consensus on issues in female atheletes (30).

Oral contraceptives

Although, hormonal contraception during adolescence was considered a controversial issue regarding bone health in the past, the latest meta-analysis, including 1535 adolescents, showed that combined hormonal contraceptives resulted in a weighted mean LS BMD difference of -0.02 g/cm^2 (95% CI: -0.05-0.00, p = 0.04) compared to non-users over a 12 month period (31). The same difference in BMD was seen over 24 months. However a recent retrospective case control study including 12.970 premenopausal women reported a significant decrease of fracture risk with the use of combined oral contraceptives (COC). The magnitude of the risk reduction was larger with increased duration of COC use (32). Depot medroxyprogesterone acetate (DMPA) is a safe injectable contraceptive but most users become amenorrheic within 1 year due to suppression of gonadotropin secretion and consecutive inhibition of ovarian estradiol production. In young women (less than 30 years old) with long-term exposure to DMPA (≥10 prescriptions), a higher fracture risk was identified (OR 3.04, 95 % CI 1.36-6.81). Similar findings were reported for women in their late reproductive years with past use of DMPA (OR 1.72, 95 % CI 1.13-2.63) (33).

Lifestyle habits

In 2016, the National Osteoporosis Foundation (NOF) published a position statement on peak bone mass and lifestyle, as lifestyle habits may contribute to 20–40% of the mean variance of adult peak bone mass. The best available evidence (grade A) exists on the positive effects of calcium intake and physical activity (34). In addition, protein intake has been shown to enhance the effect of physical activity in the young, in particular at weight bearing sites (35). It should be noted that there are gene-environment interactions in the skeletal response to nutrition and exercise during growth (36). In particular, a model, which takes into account the early influence of vitamin D receptor (VDR-3) polymorphisms, calcium intake and puberty on areal BMD gain, has been proposed to explain the relation between these genotypes and

peak bone mass (37, 38), but further longitudinal studies are needed to substantiate this hypothesis. Vitamin D sufficiency promotes normal bone mineralisation necessary to obtain an optimal peak bone mass. At the age of 16 years, 25-hydroxyvitamin D (25(OH)D) ≥ 50 nmol/L has been associated with a higher total body aBMD, with a lower porosity at the radius and with a higher trabecular number at the tibia as shown by high-resolution peripheral quantitative computed tomography (HR-pQCT) (39). However, data from the United Kingdom National Diet and Nutrition Survey showed that 22 % of adolescents aged 11–18 years had 25(OH)D <25 nmol/L (40). Measuring 25(OH) D in this population, during winter season, increased this percentage up to 40 % (40).

The corollary to the major influence of hormonal and life style habits on peak bone mass acquisition is that childhood disorder affecting pubertal maturation, BMI, nutritional intake or exercise capacity, among others, will likely have long-lasting repercussions on BMD and fracture risk. A good example is type 1 diabetes mellitus, which is usually diagnosed at a young age, whereby several alterations detrimental to bone health, such as glucose toxicity and deficit in the insulin/IGF1 axis, lead to a lifelong fracture risk approximately six-fold higher than in the non-diabetic population (41).

Diagnosis

For post-menopausal women the diagnosis of osteoporosis is based on the WHO operational definition of a dual x-ray absorptiometry of bone (DXA) with a T score below or equal to -2.5 SD. For subjects younger than 40 years old, the International Society for Clinical Densitometry (ISCD) proposed us BMD Z-scores below or equal to -2 (comparison to age and sex matched value) to define “low bone mass”, which is a value “below the expected range for age” (42).

The International Osteoporosis Foundation (IOF) also defines low bone mass in the young as Z-scores below-2, however only before 20 yrs of age. Thereafter, they kept the same definition as in post-menopausal women, namely a T score ≤ −2.5 for individuals older than 20 years and in the absence of delayed puberty (1).

Such BMD threshold differences in the definition of premenopausal osteoporosis may result in confounding epidemiological data in the literature. Nevertheless, vertebral and/or multiple fragility fractures with low BMD are a hallmark of osteoporosis for both societies. Hence, for premenopausal women with low BMD (i.e. Z-score ≤ -2 or T-score ≤ -2.5) but without fractures, a diagnosis of low peak bone mass vs. osteoporosis may be difficult to ascertain. It is important to remember that the pathophysiology of osteoporosis involves not only a deficit in bone quantity, i.e. BMD, but also microarchitectural alterations, which in postmenopausal osteoporosis result from increased bone resorption and imbalanced bone remodeling, whereas in premenopausal women they may also result from disturbances in peak bone mass acquisition (above). Indeed deficits in bone mass, structure, and strength (stiffness) have ben reported using QCT in younger patients with low bone mass and without fracture, as well as in patients with idiopathic osteoporosis with fractures (43). Further studies are therefore needed to define the utility of specific radiological and/or biochemical tools that may help to differentiate true osteoporosis from physiologically low bone mass in the young.

In practice, several steps are necessary for a correct diagnosis of premenopausal osteoporosis, also taking into consideration that current guidelines are based on postmenopausal osteoporosis and do not generally recommend DXA screening in premenopausal women (44). After a detailed medical history and a DXA measurement, including if possible a vertebral fracture assessment (VFA), an adapted biochemical evaluation is needed to ascertain causes of secondary osteoporosis, as proposed by IOF in 2012 (1). A genetic evaluation is suggested when there is a strong suspicion of a heritable component based on both family history and/or

additional clinical features (syndromes) suggestive of an underlying monogenetic bone disorder (1). In absence of the above, a diagnosis of idiopathic osteoporosis can me made.

Identifying patients at high fracture risk

Once a diagnosis of osteoporosis has been made, the next step is to evaluate fracture risk. Although classical risk factors should be taken into account, it is important to note that the FRAX® algorithm is validated for individuals older than 40 years only. Premenopausal women with recent major fragility fractures (hip, vertebral, proximal humerus and distal forearm fractures) should be considered at high risk for further fractures in the short to medium term, and further assessment is recommended. For example, in a 6-year follow-up study, approximately 25% of a cohort of 107 patients affected by pregnancy- and lactation-associated osteoporosis had a new fracture, and among individuals who had a new pregnancy, 20% sustained a new fracture (45).

Premenopausal women without a fracture often undergo a DXA because of existing risk factors for bone fragility. For example, in the case of celiac disease, a Canadian position statement suggests performing DXA measurement at the time of first diagnosis of the underlying disease, which is often at premenopausal ages (46). In this case, as in most cases of secondary osteoporosis, the fracture risk is not only related to BMD and the classical risk factors, but also to the specific characteristics of the underlying disease and its treatment , as also recently illustrated for diabetes (47).

In a small prospective study investigating the performance of bone turnover markers in relation to distal radius fractures in premenopausal women, osteocalcin, pro-peptide of type I procollagen (PINP), bone alkaline phosphatase, and C-terminal telopeptide of type 1 collagen (CTX-I) all showed only moderate prediction (48). To note that bone turnover markers were evaluated three months after the fracture, which may still be influenced by the late phase of

fracture healing. On another side, in healthy premenopausal women in the transition to menopause (age 44-57) followed for 5 years, higher PINP and CTX concentrations predicted lower BMD, suggesting that bone turnover markers could have potential use in identifying women at higher risk of rapid bone loss (49). Yet another recent study suggests that single bone turnover markers may not be able to identify bone loss for an individual patient (50).

As mentioned above regarding their potential utility in the diagnosis of osteoporosis, there are more sophisticated imaging modalities able to assess bone microarchitecture which might also help in the identification of patients at high fracture risk. Although longitudinal studies on the role of HR-pQCT in predicting fracture risk in premenopausal women are not available, new cross-sectional data warrants attention. Premenopausal women with distal radius fracture and mean age 29.8 ± 8.0 years showed no differences in aBMD at the radius, femoral neck and lumbar spine when compared to subjects of the same age, race, BMI, caffeine intake, alcohol consumption and physical activity not having experienced fractures (51). However, HR-pQCT revealed impaired trabecular and cortical parameters in women having sustained fractures. The addition of individual trabecular segmentation (ITS) to HR-pQCT images helped to further identify women with radius fractures. The area under the curve (AUC) for discriminating patients with fracture from women without was 0.74 for the proportion of axially aligned trabeculae (which is an ITS parameter at radius), whereas AUC values for classical parameters such as aBMD and trabecular density were lower (51). The same trend was reported for tibia measurements (51). Thus, although HR-pQCT parameters are able to capture a difference in bone microstructure between women with and without fracture, independently of BMD, more sophisticated analyses may be necessary to better characterize premenopausal women at increased risk of fracture.

Causes of secondary osteoporosis

Osteoporosis in premenopausal women is more frequently caused by underlying diseases, with the more recent publications summarized in table 1 (for a more complete list of diseases associated with secondary osteoporosis see (1)). In case series and observational studies, which included both premenopausal women and young men with osteoporosis, the majority of the subjects were found to have a cause of secondary osteoporosis at a range varying between 50% to 90% depending on the setting and time of diagnosis (52-54). These include well-known conditions with a negative impact on bone health, such as endocrine, inflammatory, neuromuscular, oncological, hematological, pulmonary and gastrointestinal disorders that are not specific for premenopausal age, but are often diagnosed before menopause (4-6,55-63). Other causes are HIV infection (7), hyperthyroidism (64) and TSH suppressive therapy (65). New data from HR-pQCT studies indicate impaired trabecular and cortical compartments in the majority of these diseases, at times detected earlier than the impairment detected by DXA scan (table 1). A recent retrospective study, which compared the characteristics of minimal trauma versus high trauma hip fractures in young patients, showed higher comorbidity rates in the former group. In addition, endocrinological and neurological diseases as well as nicotine intake were the most frequent. In particular, the number of patients with chronic endocrinological diseases was significantly higher in the minimal trauma group compared to the high trauma group (34.9%; vs 0%, p=0.04) (66).

There is a limited number of heritable diseases with a known mutation causing secondary osteoporosis (67). Some of them are solely characterized by bone fragility, while the majority present with additional organ manifestations. Knowing the exact mutation(s) is of pivotal importance when a specific therapy is available. As an example, loss-of-function mutations in the gene encoding the tissue nonspecific alkaline phosphatase cause hypophosphatasia. The diagnosis is based on low alkaline phosphatase activity in serum and

genetic testing that identifies the gene mutations, while bone fragility is present with a clinical heterogeneity due to more than 300 mutations of the gene discovered to date (68). Of interest, enzyme replacement therapy is now available for hypophosphatasia, and gene therapy is currently being investigated (68). However, for some other heritable diseases, the discovery of the exact genetic defect has not led to a specific therapy yet. This applies to osteoporosis-pseudoglioma syndrome, which is a rare autosomal-recessive disorder with significant phenotypic variability caused by loss of function mutations in the gene *LRP5* characterized by bone fragility and blindness (69).

Anorexia nervosa

Anorexia nervosa (AN) is another condition associated with the development of osteoporosis in premenopausal women. The classical picture of an anorexic patient is a combination of psychiatric symptoms and somatic manifestations including low BMD, malnutrition, low body fat and lean mass. Furthermore significant hormonal changes (hypogonadism/amenorrhea, hypercortisolism, low testosterone levels and resistance to growth hormone with low IGF-1 levels) leads to a significantly lower BMD and higher fracture risk (70). A recent study applying new criteria for diagnosis of AN demonstrated low BMD in 78% of patients with the "classic form" of anorexia nervosa, in 82% of patients with low BMI without amenorrhea, and in 69% of patients with atypical AN (normal BMI but psychological symptoms of AN)(71). Thus, the deleterious effects of eating disorders on BMD appear to extend beyond our current knowledge of low BMI and amenorrhea-induced detrimental effects on BMD (71). A recent systematic review and meta-analysis showed that AN is associated with an increased likelihood of osteoporosis (OR = 12.59) and fractures (OR = 1.84) (70).

Importantly, a low BMI together with low BMD but without bone fragility or eating disorders, as seen in constitutionally lean subjects, should should not be mistaken with AN-related osteoporosis (71).

Lifestyle and dietary alterations

Lifestyle habits such as excessive alchol consumption, as well as heavy smoking, play an important role in the pathogenesis of bone fragility in premenopausal women. In a population of 789 premenopausal women aged 20-40 years, the odds ratio for low LS BMD compared to non-smokers was 1.59 (95% CI 0.65, 3.91) and 2.55 (95% CI 1.12, 5.82) for subjects with tobacco use of less or more than 3 pack-years, respectively (72).

Exclusion of animal meat protein intake (vegetarianism) and even more so strict exclusion of any animal products (veganism) also carry an increased risk of osteoporosis. In a Bayesian meta-analysis, which included 9 studies (2749 individuals, 1880 women with an average age ranging from 20 to 79 years), vegetarians showed a significant BMD reduction amount to 4% and an increase of 10% higher in fracture risk compared to non-vegetarians (73). However, in a recent cross-sectional study, which included vegetarians and vegans with a mean age of approximately 30 years, 83 % of whom were female, calcaneus mineral density did not differ between vegetarians and non-vegetarians or between vegans and lacto-ovo vegetarians (74). Of note, the majority of vegetarians followed this diet for less than 5 years, and the authors used heel ultrasound, rather than DXA which is the standard technique to measure bone density. In this study, protein, calcium and vitamin D intakes of vegetarians, were all lower than the respective intake of subjects whose diets included meat ($p<0.05$) (74). Hypovitaminosis D, although more frequent in vegetarians, is also an issue in meat-consuming premenopausal women (75), often in association with intestinal malabsorption. Osteomalacia should be differentiated from osteoporosis when a low BMD is reported. It should be noted, that malnutrion can also have a socio-economical background, in particular

in developing countries, i.e. a cross-sectional study conducted in among 430 women of reproductive age showed malnutrition in 48.6% of the subjects (76).

Cancer-related and Drug-induced osteoporosis

There is new evidence regarding the deleterious skeletal effects of drugs used only in women, in particular in the setting of breast cancer (77-80) (table 2). Hence adjuvant therapy, including chemotherapy and GnRH analogs can induce secondary amenorrhea and premature menopause. Moreover, tamoxifen, a selective estrogen receptor modulator (SERM), which has a protective role on bone in postmenopausal women, acts as an antiestrogen in premenopausal women and has been associated with a 75% increased risk of fracture in premenopausal patients with breast as compared to healthy controls (HR 1.75; 95% CI 1.25–2.48) (77).

In 2018, the FDA approved elagolix, an orally administered non-peptide GnRH receptor antagonist, for endometriosis associated-pain managment. Administered from 6 to a maximum of 12 months, this drug was associated with BMD loss, especially with higher dosage (81,82) (table 2). Recently, elagolix has been successfully used for uterine bleeding caused by fibroids, and also in this instance its use resulted in decreased bone density which was mitigated when estradiol, 1 mg, and norethindrone acetate, 0.5 mg, both taken once daily, were added (83)

Regarding cancer-related osteoporosis, both cancer itself, as well as its treatment, may induce bone loss. For example, autologous or allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for most young patients with malignant hematological diseases, however HSCT-related bone loss and increased fracture rate are among the main complications of this life-saving therapeutic intervention (84).

Glucocorticoid-induced osteoporosis in premenopausal women is usually seen in patients with autoimmune/inflammatory disorders and rheumatological diseases, themselves a cause of osteoporosis. Even if glucocorticoids exert multiple negative effects on bone health (85), they are also able to some extent to control the activity of the underlying disease, which in turn may exert some favorable effects on the preservation of bone mass/strength. These aspects have not been adequately investigated in premenopausal women (86), but current management guidelines are discussed below.

Idiopathic osteoporosis

Idiopathic osteoporosis is defined as the occurrence of a low trauma fracture in the presence of low BMD (lumbar spine and or hip T score ≤-2.5 SD) after excluding causes of secondary osteoporosis (1). The exact mechanisms underlying this disease remain incompletely understood but abnormalities in bone formation have been found on bone biopsies (87). Constitutionally lean subjects with low BMD, which is usually caused by low peak bone mass accrual related to both the genetic constitution, life style and environmental conditions (1), should not be considered affected by idiopathic osteoporosis, at least not in the absence of fragility fractures.

Examination of bone microstructure using HR-pQCT showed numerous similarities between a group of 23 young patients with idiopathic osteoporosis defined as prevalent fragility fractures and low BMD (without mutations in known osteoporosis-causing genes) and a group of 21 age and sex-matched patients affected by mild to moderate osteogenesis imperfecta (OI) (type 1 and type IV). Both groups showed significant reduction in volumetric BMD and alterations in microstructural parameters at the distal radius and tibia compared to healthy controls. The only difference reported between OI patients and patients with

idiopathic osteoporosis was regarding geometry of the radius. No other differences were detected in HR-pQCT parameters at the radius and tibia (88).

In an attempt to better characterize idiopathic osteoporosis in young patients, next-generation sequencing was performed to screen for genes previously associated with fracture or low BMD in a cohort of 123 young adults with idiopathic osteoporosis. Novel variants were found in 11 subjects (regarding the following genes: *COL1A2*, *WNT1*, *PLS3*, and *DKK1*), however there was no control group. In addition, previously reported "osteoporosis-causing " variants in the *LRP5* gene were found in 22 patients (89). In contrast, 45.5% of the patients studied carried no genetic variants in the examined genes. LRP5 variants have previously also been associated with idiopathic osteoporosis in men (90).

Pregnancy and lactation associated osteoporosis (PLAO)

During pregnancy and lactation, the changes in calcium metabolism lead to a transient bone loss, mainly at trabecular sites (91). Among the factors involved, parathyroid hormone related protein (PTHrP) is secreted into the maternal circulation from the breasts tissue and placenta and reaches its highest concentrations during the third trimester. After lactation, recovery of bone mass and strength normally occurs (92). In the long term, some studies showed that pregnancy and lactation have a negative effect on bone health later in life, while other studies did not, as previously reviewed (93,92). Recently, in a study including 16,000 women followed for 16 years, parity and lactation were found to have a neutral effect on the long-term development of osteoporosis or fragility fractures (both clinical and morphometric) (94).

Against this background, PLAO is characterized by fragility fractures occurring during pregnancy or lactation, and has been reported in approximately 210 cases in the literature but is much more common in reality (95,96). The precise cause of this rare disorder remains

unknown, in particular it remains unclear whether it is entirely caused by pregnancy itself in certain individuals and/or whether pregnancy reveals a status of prior bone fragility. A search for causes of secondary osteoporosis should be undertaken in women suffering a fracture during pregnancy and lactation.

The largest case-control study (102 PLAO subjects) identified various risk factors associated with this condition. Performing fewer sports both before and after puberty, having had dental problems in childhood, and having suffered severe diseases and immobilization during pregnancy were all risk factors significantly more frequent in PLAO subjects than in controls (95). The same risk factors were identified in a retrospective case-control study for transient osteoporosis of the hip (TOH) during pregnancy, where immobilization during pregnancy was thrice more frequent in patients with TOH compared to the control group (96). The latest and largest bone biopsy study in PLAO women where bone biopsies were performed 12 months postpartum, aimed to assess the baseline state of bone remodeling. Transiliac bone biopsies in these women, showed a low bone turnover state, which was also confirmed by circulating bone turnover markers compared to patients affected by idiopathic osteoporosis, itself already a state of low bone formation (97). This study showed a dissociation between low PINP in PLAO compared to controls, while the concentration of CTX-I did not significantly differ (97).

These novel findings suggest the possibility of an underlying defect in osteoblast function taking into consideration the lower bone formation reported in PLAO women in the absence of lower osteoblast number (97).

In a small study of 7 PLAO patients, in addition to HR-pQCT which revealed a reduction of the trabecular and cortical thicknesses and DXA assessment which revealed low BMD, a comprehensive genetic analysis was carried out. Using a custom-designed gene panel, a heterozygous missense variant in the *LRP5* gene was reported in one of the patients, and two

women were diagnosed with osteogenesis imperfecta caused by heterozygous mutations in the *COL1A2* and *COL1A1* gene (98).

In summary, PLAO patients appeared to have the same risk factors for osteoporosis as those recognized for the development of postmenopausual osteoporosis and/or a possible osteoblast dysfunction revealed from bone biopsy and genetic analysis. Thus, it might be possible that a pre-existing bone impairment is present before pregnancy and that pregnancy is a trigger for its clinical development. However, further studies are needed to fully understand the exact mechanism beyond PLAO.

Management

Management of premenopausal osteoporosis is challenging due to a lack of robust evidence of how best to predict and decrease future fracture risk. Only few studies have assessed the effect of medical treatment and all were small-scale (table 3).

A flow-chart for the overall management of premenopausal women with osteoporosis and fragility fractures is shown in Figure 1.

Non-pharmacological approaches

A 2-year randomized controlled trial (RCT), which included 470 premenopausal women, aged 25–44 years, showed that educating young women concerning classical osteoporosis risk factors was associated with long-term improvements in osteoporosis preventive behaviour. This change in behavior, followed-up for 10 years, led to an approximate 2.4% attenuation of femoral neck BMD loss in this population (99). This is of particular importance considering that a recent review on the knowledge, beliefs and practices regarding osteoporosis among young adults revealed their lack of awareness about the disease (100).

Recently, new evidence on the effects of physical activity in premenopausal women has been published (101, 102). Forty young women, aged 30 to 45 years and recently diagnosed with osteoporosis, were divided into 4 groups with the following interventions over a period of 10 weeks: training (aerobic-resistance) group plus milk consumption (500 ml daily), only milk consumption, only training and controls. This study showed that there were significant differences in hip and LS BMD in the training plus milk group with higher values compared to training, milk consumers and control groups (101). However, the small sample size and short duration of intervention limits a clinical translation of these findings.

A RCT, including 206 premenopausal women diagnosed with breast cancer before the age of 55 years, showed that an exercise intervention with a combination of resistance training and aerobic exercise within two years of receiving adjuvant chemotherapy, prevented LS bone loss over a 12 month follow-up (LS BMD $+0.001 \pm 0.005$ g/cm^2 treatment group vs. -0.014 ± 0.005 g/cm^2 control group, $p = 0.03$) in women who did not suffer loss of lean mass during the study (102).

Although it is strongly advocated to quit smoking and alcohol consumption, no studies have demonstrated its effects on BMD/fracture risk in premenopausal women.

Pharmacological treatment

Calcium and vitamin D

In the latest NOF report, 93% of premenopausal women (aged 19-30 years) had a dietary calcium intake below that suggested in the guidelines (34). When specifically asked about perceived adequate calcium intake, premenopausal women (aged 18-34 years) answered that they were uncertain of what the benefits would be for their own age group, but understood the importance for older ages (103). Vitamin D deficiency in premenopausal women, was observed in various geographic areas, as recently reported by the latest ECTS position statement on vitamin D (75). Of particular concern, are the specific risk factors of

hypovitaminosis D, such as covering of the body for traditional and/or religious reasons (104) and malabsorption syndromes, where higher rates of severe vitamin D insufficiency have been shown (105). Specific randomized trials with different dosages or schemes of calcium or vitamin D supplementation are lacking in this population in order to draw definite conclusions regarding the best treatment strategy. Thus, in clinical practice, guidelines for the supplementation of calcium and vitamin D, with a target level of at least 50 nmol/L 25(OH) vitamin D in postmenopausal osteoporosis are usually implemented also for premenopausal patients with osteoporosis (44).

Antiresorptive and bone forming therapy

Women at high fracture risk, such as patients with fragility fractures and low BMD, should be treated with bone drugs particularly if the underlying disease is difficult to control; however, fracture risk reduction with both antiresorptive and bone forming treatment has not been demonstrated for premenopausal women with either secondary or idiopathic osteoporosis. Studies carried out so far usually were small-scale with short follow-up periods and assessed BMD changes as the primary outcome. Several studies confirm that treatment of the underlying disease improves BMD in PW with secondary osteoporosis (table 4, 106-110), but may not be sufficient.

Several recent publications, albeit few in the form of randomized trials, have shown improvement in BMD of premenopausal women using these drugs (111-115), as summarized in table 3. This table also includes RCTs published after 2012, the time when the latest table summarizing treatments was published by IOF (1).

Two systematic reviews were recently published concerning treatment of osteoporosis in men and women affected by cystic fibrosis (116) and by ß-thalassemia (117), and although only a few premenopausal women were included, both reviews concluded that bisphosphonates

exerted a positive effect on BMD in these patients, but evidence regarding fracture reduction was lacking.

The latest meta-analysis in patients with inflammatory bowel disease (IBD), which included 13 RCTs and 923 male and female patients (age range 30-47 years) demonstrated an improvement in BMD and a fracture reduction following bisphosphonate treatment, however, only 96 premenopausal women received an active bisphosphonate treatment, representing only 10% of the sample (118).

In patients with AN, weight gain is an important determinant for the recovering of BMD (119) and bisphosphonates are an option for increasing BMD (120). The latest review included 1,119 participants, and 10 of the 19 included studies were double-blind RCTs. However, the majority of the studies had a short follow-up period (ranging from 3 to 34 months) and the participants ages ranged from 11 to 37 years, thus also patients who had not yet reached peak bone mass were included (120). Interestingly, in this review, the authors reported that administration of oral contraceptives did not significantly increase BMD in randomized controlled trials; however, transdermal administration in adolescents was efficient in improving BMD, without data on fracture reduction (120). Another option such as low-dose testosterone did not change BMD but increased lean body mass in a one year follow-up study (121).

Glucocorticoid Induced Osteoporosis (GIOP)

In 2012 IOF and ECTS published a joint paper on the management of GIOP and considered a premenopausal woman taking oral glucocorticoid for at least 3 months at risk for future fractures if she had a previous fracture (122). Clinical risk factors and the dose of prednisolone should also be taken into account for fracture risk assessment (122)

Furthermore, the latest American College of Rheumatology Guidelines, published in 2017, considered women <40 years of age with a fragility fracture at high risk for future fractures. DXA measurement is recommended for patients at high and moderate risk, but also for patients receiving very high dosages of glucocorticoids or with other known risk factors for osteoporosis (123). Subjects with a hip or spine BMD Z score < -3 SD, or with a rapid bone loss (≥10% at the hip or spine over 1 year) and who have been treated with glucocorticoids for ≥6 months at a daily dose ≥7.5 mg are considered at moderate risk. Low risk subjects are those treated with glucocorticoids without the above-mentioned conditions (123). We believe that due to the well-known detrimental effects of glucocorticoids, it may be a too conservative approach to not consider patients who have been receiving glucocorticoids for ≥6 months at a daily dose ≥7.5 mg with a BMD Z score <-3 SD, or with a rapid bone loss, at high risk for fracture. Until now, long term follow-up studies designed to distinguish between high and moderate fracture risk in young premenopausal women, in this setting, are missing.

For low risk patients the American College of Rheumatology recommend the administration of only calcium and vitamin D . For moderate and high-risk patients, oral bisphosphonates, in view of their safety and cost, are the preferred drugs (123). The IOF-ECTS GIO Guidelines Working group suggested to start osteoporosis treatment for premenopausal women with fractures, while for women without fracture treatment decision should be based on clincal judgment, due to limited evidences (122).

Cancer-related osteoporosis

In the absence of guidelines for fractures prevention in premenopausal women with breast cancer and hormone ablation therapy, it has been suggested that bisphosphonates should be initiated in women with a *Z* score less than −2 SD. In women with a *Z* score equal to or less than −1 and a 5–10% annual decrease in BMD, bisphosphonates are also suggested together with calcium and vitamin D supplementation (124).

In patients with early stage breast cancer under adjuvant chemotherapy, zoledronic acid 4 mg every 3 months for 2 years was shown to prevent bone loss in a randomized controlled trial in women who developed ovarian failure after adjuvant chemotherapy (125). Over a period of 5 years, in a study of 34 women (mean age 43 years), who were also treated with 4 mg intravenous zoledronic acid every 3 months during 2 years, bone loss was prevented at the hip and significantly reduced at the spine compared to placebo-treated women, and BMD was maintained up to 3 years after bisphosphonate treatment was discontinued (126). Bone loss induced by ovarian suppression therapy (goserelin) and tamoxifen or anastrozole can also be prevented by zoledronic acid 4 mg every 6 months for 3 years in premenopausal women with endocrine-sensitive early-stage breast cancer. Moreover, in this large study, disease-free survival was prolonged in patients receiving zoledronic acid (127).

Pregnancy-associated osteoporosis

For PLAO treatment, there are new data available from retrospective studies. In particular, a retrospective case-series of 12 patients diagnosed with PLAO at mean age of 31 ± 5 years and treated with alendronate or zoledronic acid (n=6), with a follow-up period of 6 up to 48 months, confirmed a gain in BMD and a decrease of bone turnover markers in each patient (128). The largest retrospective, multicenter study, including 52 patients, with a mean of 3.8 ± 2 vertebral fractures, reported that patients without any treatment had an annual mean gain

of LS BMD of 6.6% and 2.3% at the hip, whereas patients treated with bisphosphonates had an increase in LS BMD of 10.2% and 2.6% at the femoral neck (129). Patients treated with teriparatide had an annual mean BMD gain of 14.9% at the lumbar spine and 5.6% at the femoral neck. Approximately 19% had a new fracture during follow-up (36 months) regardless of treatment administered. Interestingly, the same magnitude of increase in LS BMD was reported in another retrospective study of 32 PLAO women with multiple fractures treated with teriparatide for 12 months, with greater BMD increases in the teriparatide group compared to controls (15.5 ± 6.6% vs 7.5 ± 7.1%, p = 0.02) (130).

Idiopathic osteoporosis

RCTs are missing with regard to the treatment of premenopausal idiopathic osteoporosis. Teriparatide has been used, as previously reviewed, in a small sample of women with this disorder (17). The latest study using teriparatide included analyses of bone biopsies and the expression of the insulin growth factor (IGF)-1 receptor (IGF-1R) on circulating osteoblast progenitor (COP) among peripheral blood mononuclear cells (PBMCs) (131). In 11 premenopausal women treated with teriparatide for 24 months, a BMD increase of 2.9± 5.7% at the spine and a 6.9± 4.6% increase at the femoral neck were reported (131). This study showed that the %COP cells and IGF-1R expression on COP cells reflected tissue level bone formation (131). Thus, the authors proposed that the amount of IGF-1R on COP cells may reflect IGF-1 resistance downstream from the IGF-1R in premenopausal idiopathic osteoporosis. This new study is in line with previous studies that suggested an IGF-1 resistance in premenopausal idiopathic osteoporosis (132).

Possible teratogenic effects of anti-osteoporotic drugs

Treatment of premenopausal women should always take into consideration the potential teratogenic effects of the drug during pregnancy. Although a toxic effect in pregnant rats after exposure to bisphosphonates has been described (133), the majority of the literature regarding bisphosphonate use in humans does not report severe adverse fetal and maternal events (134). Nevertheless, a few reports regarding shortened gestational age, lower neonatal birth weight and transient hypocalcemia in the newborns and very rare cases of spontaneous abortions and congenital anomalies have been published (135-137). These studies, however, do not include controls or the reasons for bisphosphonate treatment.

In 2018, data were published from the "French Reference Centre of Teratogenic Agents" which included women who received bisphosphonates in the 6 weeks before or during pregnancy and had systemic (n=23) or bone diseases (n=13) (138). This paper reported the reasons for bisphosphonate treatment and included control groups. The most frequent cause for bisphosphonate treatment was a rheumatologic disease (for which also concomitant drugs were prescribed) and these patients were compared to women with the same diseases without bisphosphonate exposure. In patients exposed to bisphosphonates due to systemic diseases, therapeutic terminations of pregnancies were higher compared to controls (4/23 [17.4%] vs 1/92 [1.1%], p = 0.006). No difference in the rate of congenital malformations was reported, but the rate of neonatal complications was higher for cases than controls (4/16 [25.0%] vs 4/64 [6.3%] p = 0.027). Neonatal complications included cardiac arrhythmias (n=1), maternal-fetal infection (n=1), acute fetal distress (n=1), polycythemia and thrombocytopenia (n=1). Considering women without any systemic disease, who received bisphosphonates for primary non-malignant bone diseases (bone disease group), the live birth rate was lower compared to healthy controls (8/10 [80%] vs 50/50 [100%], p = 0.025). No congenital malformations were reported in either group; however, fetopathological examinations were

not performed. It might be possible that the complications reported were mainly due to the severity of the underlying diseases and other concomitant medication, however a "severity index" for the diseases was not reported. The authors stated that the expected rate of spontaneous abortion is approximatively 12% in the general population in France, thus using the healthy control group as a comparison for the "bone disease" group without spontaneous abortions might not be appropriate. Further studies are needed to clarify this issue. As a measure of safety, it has been proposed that bisphosphonate treatment should not be initiated if a woman is planning a pregnancy in the next 12 months (16).

There are no human case reports on the fetal effects of teriparatide or denosumab in pregnant women. In cynomolgus monkeys, who were exposed to denosumab in utero, the following persistent congenital defects were reported: dental dysplasia, decreased bone length, reduced cortical thickness, and decreased peak load and ultimate strength at the femur diaphysis, while others bone features which resembled an osteopetrotic phenotype appeared partially reversible (139).

Hence both denosumab and teriparatide are contraindicated in pregnant women, this recommendation is based on the lack of studies in pregnant women.

Conclusions

Underlying diseases are common among premenopausal women with osteoporosis. The diagnosis of osteoporosis in premenopausal women requires not only the presence of low BMD but also evidence of bone fragility, which reflects an abnormal bone microarchitecture . In contrast to post-menopausal women, however, bone turnover is not necessarily elevated in premenopausal osteoporosis, at least not when estrogen deficiency is absent. In the rare cases of idiopathic osteoporosis, new evidence from HR-pQCT and genetic evaluations suggest that the primary deficit is in the osteoblast function, but the exact mechanisms

remains unknown. Identifying premenopausal women at risk of fracture remains challenging and further HR-pQCT studies may contribute to understand the importance of bone microstructural alterations in this population, although the clinical use of this technology remains uncertain. Morover, we need additional research to establish normative databases for premenopausal women, so that in the future, HR-pQCT will be more useful clinically. Meanwhile, DXA with VFA, common clinical risk factors as well disease- and drug-related risk factors (in case of secondary osteoporosis) must all be taken into account to properly assess fracture risk in these women, as recently illustrated in diabetes (47).

The treatment of underlying causes of secondary osteoporosis is beneficial not only with regards to BMD but also to bone microstructure. In case treatment of the underlying cause is not successful and/or in presence of severe osteoporosis, antiresorptive and bone forming drugs can be used as in postmenopausal osteoporosis. Further RCTs with fracture reduction as a primary outcome are needed to better tailor treatment to patients at high risk of fracture. Although some new data on bisphosphonate safety in women at childbearing potential are now available, more robust evidence is needed as well as data on denosumab and bone forming drugs like teriparatide, abaloparatide and romosozumab in humans.

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Figure 1: Flow-chart on management and pharmacological treatment in premenopausal women with osteoporosis and fragility fracture (age > 20 years old).

Table 1: Diseases associated with osteoporosis in premenopausal women, papers published since 2017

DISEASES	PATIENTS	FINDINGS SUMMARY	REF
Rheumatology			
SLE	N = 173, mean age 31±8 years	Prevalence of BMD Z <-2 was 17.3%.	4
	N= 136, mean age 38.8±12.9 years	Multivariate linear regression analysis considering age, duration of disease, BMI, high-dose glucocorticoid use and current dose of glucocorticoids selected as independent variables, showed that disease duration was negatively associated with LS and FN BMD. BMI was positively associated with total hip and FN BMD.	55
	N=34274, 92.6% were female, mean age 41 years,	Multivariable HR for any fracture in SLE age <50 compared to age and sex matched controls was: HR 2.28 (1.90–2.74); HR adjusted for glucocorticoids use 1.74 (1.40–2.15), HR adjusted for comorbidities 1.97 (1.61–2.41). All p<0.01.	56
RA	N= 96, mean age 36.9±5.3 years	Higher rate of osteoporosis in RA patients compared to age matched controls was found. In RA patients, the prevalence of osteoporosis at radius was 9.38%, at hip 6.25% and at LS 7.29%. Stepwise linear regression analysis showed that total lean mass was the best, independent significant predictor of BMD at all different sites, followed by the score of the disease severity (DAS28) at femoral sites.	5
Endocrine			
Cushing's disease	N=37, 28 premenopausal, mean age 30.7±11.7 years	44.5% of patients had osteoporosis, 35.1% had morphometric vertebral fractures.	6
PHPT	N=54, mean age 40.5±6.8 years	18.5% of patients had osteoporosis at any site. T-score BMD: at distal third radius was -1.1 ±1.2, at LS 1.7±1.3, at FN 1.5±1.2.	57
DM type 1	N=35925 (male and female), mean age 18-50 years	This meta-analysis showed a RR for any fracture of 1.85 (95%CI 1.5-2.3, p<0.001) in diabetic females compared to controls.	58
Gastroentrology/Malnutrition			
Celiac disease	N= 563 premenopausal women and men, age NA	In this meta-analysis, the pooled prevalence of osteoporosis was 14.4% (95% CI: 9–20.5%) and osteopenia was 39.6% (31.1–48.8%) respectively.	59
IBD	N=59, mean age 23.1±5.8 years	IBD patients had a nearly 10% lower aBMD at radius, spine and hip and alterations in trabecular and cortical bone microarchitecture. Higher disease activity scores had a negative impact on aBMD and vBMD, as well as microstructure. Prevalent fractures in IBD were not associated with aBMD (adjusted for age, sex and height), but with vBMD and with alterations of trabecular bone microarchitecture.	60
Anorexia nervosa	N=25, mean age 27.5 years (23.8; 29.6)	Lower bone mass and impaired bone microarchitecture in adult AN patients, compared to normal weight controls. The impairment of cortical thickness and estimated failure load were significantly more pronounced in the weight-bearing tibia, compared to the radius.	61

Infectious disease			
PLWH	N=103, median age 35 (25-45 years)	Osteoporosis was documented in 35% of females with HIV as compared to 8% of HIV-negative controls (p<0.001). BMI was an independent predictor of osteoporosis, after adjusting for age and disease duration.	7
Genetic			
Cystic fibrosis	N= 42 patients (24 females, mean age 34.0 ± 8.4 years)	A BMD Z score below −2.0 or lower and at least one prevalent fragility fracture were found in 22 patients (52.4%) and 18 patients (45.2%), respectively.	8
	N= 53, mean age 27.5 (25.7-29.3)	20% of patients had osteoporosis at LS (T score <-2,5), and 35% at femoral sites.	62
Thalassemia major	N =82 patients, N=39 premenopausal women, mean age 32± 6 years	15 patients had vertebral fractures, their mean LS BMD Z score was -2.66 SD and TBS 1.173, both significantly lower than in the patients without fractures.	63

Abbreviations: SLE=systemic lupus erythematosus, RA=rheumatoid arthritis, DM=diabetes mellitus, PHPT=primary hyperparathyroidism, IBD=inflammatory bowel disease, PLWH=people living with HIV, BMD=bone mineral density, HR=hazard ratio, TBS=trabecular bone score, BMI=body mass index, LS =lumbar spine, FN= femoral neck, N=number, REF= references, NA= not available.

Table 2: Drugs specifically used in women and their effects on bone, papers published since 2017

DRUGS	PATIENTS	STUDY DESIGN	FINDINGS SUMMARY	REF
Tamoxifen	N=3634; mean age 44.1±5.1 (18-50 years)	Retrospective study	In patients with breast cancer treated with tamoxifen, a cumulative incidence of fractures was 6.3% compared to a cumulative incidence of 3.6% in the control group (p<0.001). The risk of fracture was 75% higher for patients taking tamoxifen than that for healthy controls (HR 1.75; 95% CI 1.25–2.48).	77
Tamoxifen	N=1761 , mean age 43.3±6.1 years; age 41–50 years (72.8%) age 31–40 years (22.3%) age 18–30 years (4.9%)	Retrospective cohort	A positive association was found between breast cancer and fractures, adjusted HR=2.39, (p< 0.001). HR was 2.58 (p<0.001) for women on tamoxifen versus healthy women, while HR for women without tamoxifen treatment versus healthy women was not statistically significant. After 10 years, women with fractures were 14.7% in the tamoxifen group vs 12.9% in the group without tamoxifen. This difference was not statistically significant.	78
Tamoxifen plus ovarian function suppression (OFS)	N=4690, age 40 years	RCT SOFT and TEXT trial (8 years follow-up)	Percentage of patients with T score of less than −2.5 was 3.9% in the tamoxifen group, 7.2% in the combined tamoxifen–ovarian suppression group, and in 14.8% in the combined exemestane–ovarian suppression group.	79
Aromatase inhibitor (AI) plus OFS	N=27, mean age 43 years (range 30.4 to 53.7)	Cross-sectional	In patients with early breast cancer treated with OFS + AI for a median duration of 17 months, the cortical and trabecular volumetric BMD, assessed by HR-pQCT, was reduced compared to healthy age-matched controls. Also matrix mineral density was 1.56 SD (0.90 to 2.22) lower than controls.	80
Elagolix	N= 872 in Elaris EM-I trial N= 817 in Elaris EM-II trial Mean age 31 years old	Double-blind, placebo-controlled phase 3 trials (6 months)	In Elaris EM-I, after 6 months, a decrease of more than 5% in LS BMD was reported in 3.8% of patients on a low dose of elagolix, compared to 20.9% of patients in the higher-dose elagolix group. In Elaris EM-II, the respective percentages were 2.3% and 16.4%.	81

Elagolix	EXTENSION TRIAL EM-III AND IV N=569 women Mean age 32 years old	Double-blind, placebo controlled phase 3 trials (12 months)	After 12 months, in EM-III, the mean percent change from baseline in LS BMD was -0.63% for the low dose (Elaris EM-IV -1.10%) and -3.60% for the high dose (Elaris EM-IV- 3.91%). None of the patients had a Z-score below -2.0.	82

Abbreviations: N=number, RCT=randomized control trial, BMD=bone mineral density, HR= hazard ratio, HR-pQCT= high-resolution peripheral quantitative computed tomography, REF= references.

Table 3: Randomized control trials (RCT) with antiresorptive or anabolic drugs in premenopausal women, papers published since 2012.

DISEASES	PATIENTS	STUDY DESIGN	INTERVENTION	FINDINGS SUMMARY	REF
Rheumatology					
RA	N=167 women, 6% <40 years, 20%<50 years Premenopausal 27% in the ibandronate group, 20% in the placebo group	A 48-week double-blinded randomized placebo-controlled investigator-initiated trial	Ibandronate 150 mg or placebo every 4 weeks for 48 weeks	After 48 weeks, the % of LS BMD changes was significantly different between the ibandronate and the placebo groups (3.7% vs -1.9%, p<0.0001). The % of BMD changes in FN and total hip also showed similar results (p<0.0073 and p <0.0031, respectively).	111
Gastroenterology/Malnutrition					
Celiac Disease	N=28, mean age 26 years (14 female)	Randomized, open-label clinical trial	Group A = calcium/vitamin D for 1 year (N=13) Group B: 4 mg zoledronic acid + calcium/vitamin D for 1 year (N=15)	Group A had a T-score increase from -3.31±1.46 to -2.12±1.44 SD, (p<0.05) while Group B from -2.82±1.27 to -1.06± 1.84, (p<0.001). The difference in improvement of T-score in the zoledronic acid group as compared to the control group was not statistically significant.	112
Anorexia Nervosa	N= 21, mean age 47 years	Randomized, placebo-controlled trial	Teriparatide for 6 months (N=10) placebo (N=11).	After 6 months, there was a 6.0%±1.4% increase in LS BMD compared to 0.2%± 0.7% increase in the placebo group (all p<0.01). No differences were found with regards to femoral BMD changes after 6 months.	113
Infectious disease					
PLWH	N= 44 (2 women), median age alendronate 43 years placebo 47	Randomized, double-blind, placebo-controlled trial	Alendronate group (N=20) placebo group (N=24) treated for 96 weeks	A mean difference improvement at the site with a T-score < -2.5 was found in the alendronate vs placebo group of	114

	years			6.1% (95% CI 2.8 - 9.3), p=0.0003.	
Genetic					
Cystic Fibrosis	N= 171, female N= 84, mean age 14, years (5-30)	Randomized, placebo-controlled trial	Alendronate group (N=65) and placebo group (N=63) treated for 12 months.	Alendronate significantly increased BMD 16.3% vs 3.1% compared to the placebo group (p=0.001).	115

Abbreviations: RA=rheumatoid arthritis**,** PLWH= people living with HIV, BMD=bone mineral density, LS=lumbar spine, N=number, REF= references.

Table 4. Bone effects of treatment of underlying causes of secondary osteoporosis in premenopausal women, papers published since 2017.

DISEASES	PATIENTS	STUDY DESIGN	INTERVENTION	FINDINGS SUMMARY	REF
Endocrine					
PHPT	N=10, median age 44.5 years (28-55)	Retrospective study	Parathyroidectomy	Approximately 12±6 months after parathyroidectomy a percentage increase of BMD was observed at LS 2.2±4.5, total hip +2.6±2.2, radius -0.8±3.2. The mean percentage difference did not differ between pre- and post-menopausal PHPT patients.	106
Gastroenterology/Malnutrition					
IBD	Group treated with anti TNF-a N=23 (90% premenopausal women) Mean age 33.4±12.1years Group not treated with anti TNF-a N=48 (66.7% premenopausal) Mean age 39.6±11.6 years	Longitudinal prospective cohort	Treatment with anti TNF-a therapy	After 7 years of follow-up, LS and FN BMD increased significantly in patients treated with anti-TNF-a. No difference in the number of incident fractures in the two groups was observed. However, new fractures were more common and more severe in the group not receiving anti-TNF-a therapy, despite this being the group of patients who was treated with a smaller doses of glucocorticoids.	107
IBD	Early treated with anti TNF-a (N=122) Age at	Longitudinal prospective cohort	Treatment with anti TNF-a therapy	Osteoporosis was significantly less frequent among the early treated (11,4% of patients)	108

	diagnosis 27 Late treated with anti TNF-a (N=373) Age at diagnosis 24 Never treated (N=341) Age at diagnosis 29			compared to late treated (28.2%) and never treated (20.8%).	
Celiac disease	N= 26, mean age 31.1±8.7 years (19- 50)	Longitudinal prospective cohort	Gluten free diet for 1 year	HR-pQCT revealed improvement at the distal radius of approximately 9% of trabecular volumetric density, BV/TV and trabecular thickness (all p<0.05). A decrease of cortical thickness was reported (-3.6% [p=0.03]). At the distal tibia, all volumetric parameters, the total, trabecular and the cortical density increased significantly (3.6% [p=0.004], 8.3% [p<0.0001], and 1.54% [p=0.0004], respectively). A BV/TV and trabecular thickness increase of approximately 8.3% (both p<0.05) were reported. A decrease of cortical thickness was observed (–0.8% [p<0.05]).	109
Anorexia nervosa	N=160, mean age 28.3±10	Retrospective	Body weight regain	No significant changes in hip and LS BMD	110

	years			were observed after 3 years. However fat mass gain was a significant factor associated with BMD improvement at follow-up (8.0±9.1 vs 3.0±3.5 kg, p=0.02), as well as weight gain (7.7±8.2 vs 3.2±5.6 kg, p=0.10).	

Abbreviations: RA=rheumatoid arthritis, PHPT=primary hyperparathyroidism, IBD=inflammatory bowel disease, BMD=bone mineral density, LS=lumbar spine, N=number. TNF= tumor necrosis factor, HR-pQCT= high-resolution peripheral quantitative computed tomography REF= references.

Figure 1