6 Osteoporosis in Premenopausal Women

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Case Presentation

A 36-year-old woman was diagnosed with ulcerative colitis at the age of 15. She was treated with different immunosuppressants: azathioprine, mesalazine, infliximab, and intermittently with oral glucocorticoids for many years. At the age of 23, colectomy was performed, and treatment with oral glucocorticoids was almost completely replaced by local treatment until the rectum was removed a year later. Supplementation with calcium and vitamin D was not given during the years with high doses of oral glucocorticoids.

Bone density testing was performed at the age of 27. BMD T-scores of the spine and hip were −2.7 and −3.3. The patient initiated treatment with alendronate, which worsened ulcerative colitis symptoms and alendronate was discontinued. The patient was considering pregnancy and treatment of osteoporosis apart from calcium and vitamin D supplementation was therefore not pursued further.

The patient was referred to our department for treatment of osteoporosis at age 30.

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The patient stated she had regular menstrual periods, had not experienced any fractures with the exception of a forearm fracture as a child, and had no family history of osteoporosis or frequent fractures. She does not smoke and consumes less than 1 unit of alcohol per day. BMI was 22.2 kg/cm^2.

Laboratory evaluation was without signs of secondary osteoporosis. Genetic screening for osteogenesis imperfecta was not performed since the patient had only suffered a single fracture during childhood after a relevant trauma. BMD T-scores were −3.0 at the lumbar spine and −2.9 at the total hip. X-rays of the thoracic and lumbar spine demonstrated multiple vertebral fractures: T6 (40% loss of height), T8 (29%), T9 (28%), T10 (30%), T11 (24%), T12 (43%), L2 (38%), L3 (27%), and L4 (33%).

Assessment and Diagnosis

The fracture rate in premenopausal women is uncertain, but rare. The prevalence of osteoporotic T-scores in premenopausal women varies from 0.5% to 50% depending on the populations studied, the definition of osteoporosis used, and the referral center involved [1–4].

Bone mineral density of premenopausal women depends primarily on bone accrual during childhood and adolescence. Although 40–80% of the variation in BMD and bone microarchitecture is genetically determined [5], other factors including muscle mass, sexual development, and lifestyle factors, including calcium and vitamin D intake and physical activity, are also important [6]. The effect of most contraceptives on bone is neutral; however, the use of depot medroxyprogesterone acetate is associated with an increased risk of fracture [3].

For postmenopausal women, the diagnosis of osteoporosis is based on the World Health Organization operational definition, a BMD T-score ≤−2.5. For women between 20 and 40 years, the International Osteoporosis Foundation (IOF) recommends using the same definition as in post-menopausal women [2], whereas the International Society for Clinical Densitometry (ISCD) pro-

poses using BMD Z-scores ≤−2 to define "bone density below the expected range for age" [7]. Vertebral or other major fragility fractures are considered a hallmark of osteoporosis by both societies. 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 or Z-score ≤−2) after excluding causes of secondary osteoporosis [1, 3].

Osteoporosis in premenopausal women is often secondary to diseases, medical treatments, or lifestyle factors, including endocrine, inflammatory, neuromuscular, oncologic, hematologic, pulmonary, and gastrointestinal disorders and therapies, in addition to tobacco and alcohol use. Obtaining a thorough medical history and performing a biochemical evaluation are needed to exclude causes of secondary osteoporosis [1, 3]. In addition, screening for genetic causes is recommended when there is a strong suspicion of a heritable component based on family history and/or additional clinical features (syndromes) suggestive of underlying monogenetic bone disorders, such as osteogenesis imperfecta, hypophosphatasia, or osteoporosis-pseudoglioma syndrome [2].

There are special cases that need further consideration. Patients with anorexia nervosa, which in addition to low body weight is characterized by significant hormonal changes, including hypogonadism/other causes of amenorrhea, hypercortisolism, low testosterone, and low IGF-1 levels, often have low bone mass and sometimes suffer fractures [8]. Premenopausal women on diets excluding animal meat protein (vegetarianism) or any animal products (veganism) have in some studies been found to have an increased risk of fracture [9]. In premenopausal women with breast cancer, adjuvant therapy including chemotherapy and gonadotropin hormone-releasing hormone (GnRH) analogs can induce secondary amenorrhea and premature menopause. Moreover, treatment with tamoxifen, a selective estrogen receptor modulator which has antiestrogen effects in premenopausal women, has been associated with increased risk of fracture. Treatment with GnRH receptor antagonists for endometriosis is also associated with BMD loss [3]. Glucocorticoid-induced osteoporosis in premenopausal women is usually seen in patients with

autoimmune or inflammatory disorders that may themselves cause osteoporosis. Glucocorticoids exert multiple negative effects on bone, but they also mitigate the negative effects of the underlying disease on bone health, and therefore it is the balance between these effects in combination with the dose and duration of the treatment that determines the outcome [10].

Pregnancy and lactation-associated osteoporosis (PLAO) [11] is a rare condition associated with changes in calcium metabolism occurring during pregnancy and lactation that lead to a transient bone loss, mainly at trabecular sites. Among the factors involved are parathyroid hormone-related protein and the need for additional calcium for mineralization of the fetal skeleton and the production of milk during lactation. In addition, studies have suggested that women developing PLAO may have an underlying osteoblast insufficiency. After lactation, bone mass and strength normally recover.

Hypovitaminosis D may lead to osteomalacia which should be differentiated from osteoporosis as this represents a mineralization deficit that in most cases is reversible. Low bone mass most often improves dramatically upon normalization of vitamin D.

Management

Once a diagnosis of osteoporosis has been made, the next step is to evaluate future fracture risk. Although classical risk factors should be considered, it is important to note that the FRAX® algorithm is not validated for individuals younger than 40 years. Premenopausal women with recent major fragility fractures are generally at high risk for further fractures in the short to medium term, but the risk depends on whether the condition is secondary to another condition that can be treated (e.g., celiac disease) or not.

Management of premenopausal osteoporosis is challenging due to a lack of robust evidence. There is some evidence that increases in calcium and vitamin D intake as well as physical activity may improve or stabilize BMD. In addition, cessation of smoking and excess alcohol consumption is generally recommended [1, 3].

Antiresorptive and bone forming treatments improve BMD in premenopausal women with idiopathic or secondary osteoporosis; however, fracture risk reduction has not been demonstrated (reviewed in [1–3]).

In patients with anorexia nervosa, weight gain and reappearance of regular menstrual periods are important determinants for the recovery of BMD [12].

For premenopausal women treated with glucocorticoids, the current guidelines are not in complete agreement. The joint IOF and ECTS guidelines recommend treatment in premenopausal woman with a previous fragility fracture taking oral glucocorticoid for at least 3 months, while for women without fracture, the treatment decision should be based on clinical judgment [13]. The American College of Rheumatology guidelines recommend treatment with oral bisphosphonates in premenopausal women treated with glucocorticoids at a daily dose $\geq$7.5 mg for $\geq$6 months in the presence of a fragility fracture or BMD Z-score <-3 [14].

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 <-2. In women with a Z score ≤-1 and a 5–10% annual decrease in BMD, bisphosphonates are also suggested [3].

Cessation of lactation in women with PLAO leads to increases in BMD. Women treated with a bisphosphonate or teriparatide experienced larger increases in BMD compared to untreated women; however, none of these studies were powered to investigate the effect on fracture risk [11].

The risk of adverse effects should be considered as part of making treatment decisions for an individual patient. In addition to considering the usual adverse effects, the risk of potential teratogenic effects of the drug during a pregnancy should be considered. The majority of the literature regarding bisphosphonate use in humans does not report severe adverse fetal or maternal events; however, there are reports of spontaneous abortions [3]. As a measure of safety, it has been proposed that bisphosphonate treatment should not be initiated if a woman is planning a pregnancy within the next 12 months. Due to the lack of studies in pregnant women, denosumab and teriparatide are contraindicated in pregnancy.

Outcome

Treatment options including teriparatide and bisphosphonates were discussed with the patient. The patient decided that she wanted to have children and therefore no treatment was initiated. In September 2015, the patient gave birth to a daughter. In November 2015, 2 months after delivery, the patient complained of back pain. The patient was still breastfeeding the baby. DXA showed relatively stable BMD with T-scores at the spine and hip of −2.8 and −2.8, respectively. No X-ray was performed as the back pain was ascribed to the existing vertebral fractures. In March 2017, the patient again had symptoms of intermittent back pain. BMD T-scores of the spine and hip were −2.4 and −2.8, respectively. The patient was planning a second pregnancy, and treatment was therefore not initiated. In August 2018, the patient gave birth to twin sons. In November 2018, the patient came to the outpatient clinic and complained of acute severe low back pain, and X-ray of the spine showed a new compression fracture of L5.

The patient stopped breastfeeding in order to start anti-osteoporosis treatment. Due to the expected catabolic bone status due to pregnancy and lactation, treatment with zoledronic acid was given in December 2018. In March 2019, BMD T-scores were −2.7 and −2.9, respectively, which represented a significant BMD loss at the lumbar spine. Treatment with teriparatide was initiated.

In August 2019, 6 months after initiating teriparatide, the patient was still having severe back pain. Continuing pain many months after a vertebral fracture should always lead to reflection and further investigation as clinically indicated. New fractures, worsening of existing fractures, or other causes of back pain should be considered and investigated. MRI of the spine was performed and showed no new fractures or other pathologies. Edema was seen in L5, suggesting that the L5 fracture was not completely healed, whereas the older fractures were. There is no evidence that vertebroplasty reduces pain due to spine fractures better than medical treatment; however, we had tried medical treatment in combination with physiotherapy for 6 months with only minor improvement in pain. Vertebroplasty of L5 was performed with modest effect on the pain.

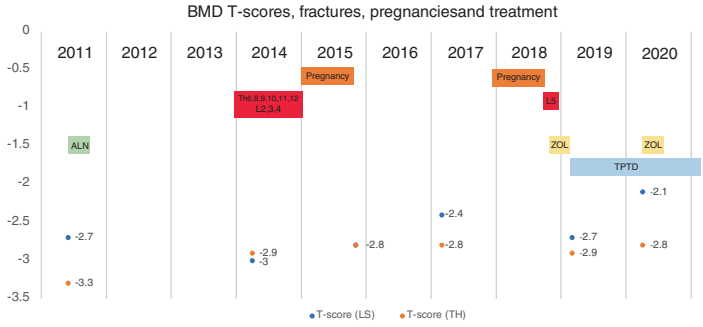

Fig. 6.1 The results of DXA performed over the years in the case are presented. In addition, the two pregnancies (orange boxes), vertebral fractures seen on X-rays (red boxes), and treatments: alendronate (ALN) (green box), zoledronate (ZOL) (yellow boxes), and teriparatide (TPTD) (blue box) are displayed

In April 2020, DXA showed increases in BMD at the spine and hip of 9.1% and 2.2%, respectively. Treatment with teriparatide continues, and the patient had a second infusion of zoledronate in May 2020 because BMD of the hip was still very low and bone loss at the hip should be avoided (see Fig. 6.1 for overview).

Severe osteoporosis with multiple vertebral fractures, back pain, and inability to take care of her three young children due to her disability has been a very difficult situation for the whole family. Despite getting help with household and childcare issues, the patient's husband has been on sick leave due to stress. In addition, the patient had tried working again as a laboratory technician after her maternity leave, but she was not able to work and is now permanently retired. Severe osteoporosis does not only affect the patient, but the entire family, especially when this includes three young children, so we have to include the whole family in the management of the disease.

We have no measurement of BMD before this patient started glucocorticoid treatment as a teenager, but it is a reasonable assumption that the many years of glucocorticoid treatment without calcium and vitamin D supplementation played an important role in the development of severe osteoporosis in this premeno-

pausal woman. It is unlikely that patients now would be treated for many years with glucocorticoids without supplementation with calcium and vitamin and without having DXA performed to monitor bone health. It cannot be determined if the pregnancies and the changes in calcium metabolism associated with pregnancy and lactation were the cause of the new vertebral fracture, but the occurrence of the fracture 3 months after delivery of her twin sons would fit with what is often seen in PLAO and with the notion that PLAO more often occurs in women with preexisting low bone mass or poor bone quality.

This case demonstrates that osteoporosis in premenopausal women is less straightforward than in postmenopausal women. The diagnosis is delayed because osteoporosis is rare in premenopausal women and therefore often not considered even in the presence of conditions or pharmacologic treatments known to be associated with risk of osteoporosis. Although there is increasing evidence of the beneficial effect of antiresorptive and bone-forming treatments on bone turnover and BMD in premenopausal women, there is no evidence for anti-fracture efficacy. The treatment plan has to take family planning into account as therapy should not be used in pregnant women and women planning pregnancy. This in combination with the temporary loss of BMD during pregnancy and lactation makes treatment of osteoporosis in premenopausal women a task for specialists.

Clinical Pearls/Pitfalls

- Osteoporosis in premenopausal women is often secondary to other diseases and pharmacologic treatments, most frequently diseases that involve inflammation and glucocorticoid treatment. Correction or treatment of the secondary cause should be considered if at all possible.
- Once a diagnosis of premenopausal osteoporosis is made using BMD T-score ≤ -2.5 or Z-score ≤ -2 and a major fragility fracture, the patient should be referred to an osteoporosis specialist for treatment.

- The increased risk of osteoporosis associated with a number of diseases and treatments in premenopausal women should be included in relevant guidelines, and physicians should be aware of this complication in order to avoid delay of diagnosis.
- Pregnancy and lactation-associated osteoporosis is a rare condition but gynecologists and obstetricians should keep this in mind in women with severe back pain during the last trimester or in the months following delivery.

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