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Chapter 6

Skeletal Manifestations of Hyperparathyroidism

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Abstract

The presentation of hyperparathyroidism changed over the last decades which gave rise to more variable presentations than before. Hyperparathyroidism has a catabolic effect on the skeleton whether the disease is symptomatic or asymptomatic or normocalcemic. It is now understood that the effect of parathyroid hormone (PTH) on the bone is mediated by complex interaction between different bone cells and cells of the immune system especially T lymphocytes. Protecting the skeletal system against bone loss and pathological fractures is among the important treatment goals of hyperparathyroidism. To achieve this goal, more complex laboratory tests to monitor the bone turnover and imaging techniques and modalities as high-resolution peripheral quantitative computed tomography (HR-pQCT) and trabecular bone score (TBS) are employed. These imaging techniques showed the affection of microarchitecture of the cortical and the trabecular bone. For the time being, surgery and alendronate treatment are believed to reverse the catabolic effect of hyperparathyroidism on the bone. Vitamin D supplementation in case of vitamin D deficiency may also has a protective effect on the skeleton.

Keywords: osteitis fibrosa cystica (OFC), bisphosphonates, brown tumor, RANKL, parathyroid hormone, bone metabolism

1. Introduction

Over the last hundred years, the effect of parathyroid hormone (PTH) on bone metabolism was extensively discussed. PTH acts on the bone cells through several mediators, and its action involves a variety of cells. It is now understood that parathyroid hormone has both catabolic and anabolic effects on bone metabolism [1]. Mandl in Austria was the first to prove that the enlarged parathyroid was responsible for the skeletal manifestations of hyperparathyroidism after the first successful removal of parathyroid adenoma [2]. The clinical picture of the disease also changed dramatically over the years from a disease of "stones, bones,

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abdominal groans, thrones and psychiatric overtone" to a disease which can be only detected by elevated calcium and the PTH level on laboratory tests or even the elevated PTH level with no hypercalcemia [2, 3]. This change in clinical presentation was accompanied by the introduction of newer lab tests to assess bone turnover and newer imaging techniques to assess the bone quality [2]. The treatment modalities also evolved, allowing more individualized approach for treating each patient [4].

2. Action of parathyroid hormone on the bone in hyperparathyroidism

The main function of PTH is to maintain calcium levels within the normal range thorough its action on the bone, kidneys, and intestine. It also decreases serum phosphorous through inhibiting renal reabsorption [5, 6]. PTH can produce catabolic or anabolic effect on bone metabolism depending on the level of the hormone, periodicity, and duration of exposure [6, 7]. Primary hyperparathyroidism (PHPT), continuous PTH infusion (cPTH), and intermittent PTH treatment (iPTH) increase bone turnover in trabecular and cortical bone and elevate the markers for bone resorption and formation [2, 8–10]. PHPT and cPTH enhance cortical bone loss by increasing osteoclastic activity but produce cancellous bone that is relatively preserved or modestly increased [2, 9, 11]. iPTH treatment stimulates trabecular bone formation by osteoblast stimulation and can cause small cortical bone loss [12, 13]. The pattern of bone loss in PHPT is different from the pattern of bone loss in osteoporosis. In osteoporosis, the trabecular bone loss predominates, while in PHPT the cortical bone loss predominates [14].

2.1. Action of parathyroid hormone on bone cells

Normally, bone structural integrity is maintained by the process or remodeling where the bone is removed by osteoclasts and new bone is synthesized by osteoblasts [15]. The osteoclasts and osteoblasts are arranged in a structure called the basic multicellular unit (BMU). A BMU consists of osteoclasts in front with osteoblasts, some blood vessels, and connective tissue behind [16, 17]. Osteoclasts are formed by fusion of mononuclear precursors, while osteoblasts originate from undifferentiated mesenchymal cells [16, 18]. Parathyroid hormone produces its effects by binding to its receptor PPR (also known as PTH-1R). While osteoblasts, osteocytes, and lymphocytes, mesenchymal stromal cells express PPR, osteoclasts respond indirectly to PTH through various mediators and cytokines produced by cells which carry PPR [6, 19–23]. It is now believed that osteocytes are the primary cellular target of PTH in the bone. Osteocytes are the main cells that express PPR in the musculoskeletal system [14]. Saini et al. designed a study where they generated mice with PPR deletion in osteocytes. These mice showed significant increase in bone mineral density (BMD), reduced osteoblast activity, and decreased skeletal response to anabolic or catabolic PTH regimen [24]. Other studies also supported the fact that osteocytes rather than osteoblasts are the main source of the receptor activator of nuclear factor kappa-B ligand (RANKL) in the process of osteoclastogenesis [25, 26]. Where mice lacking RANKL in osteocytes had less bone loss compared to control mice when they are exposed to dietary calcium deficiency for 30 days causing secondary hyperparathyroidism.

There was less RANKL expression and less osteoclast number in the group of mice lacking RANKL [25]. Another study was designed with a co-culture of osteoclast precursors and osteocytes. The study showed that RANKL is provided through dendritic processes of osteocytes to osteoclast precursor and that soluble RANKL had less contribution to osteoclastogenesis [27]. In humans, the RANKL/osteoprotegerin (OPG) ratio is higher in patients with PHPT than controls. This ratio is decreased with parathyroidectomy (PTx) or medical treatment by alendronate [28]. Another study on patients with PHPT showed that RANKL correlated with bone resorption markers in these patients and suggested that it can be used to determine patients of PHPT with greater risk of bone loss [13]. Another study was conducted on patients with PHPT where transiliac bone biopsy was done before PTx and 12 months after surgery and mRNA for RANKL and OPG were measured. The study showed that the mRNA ratio of RANKL/OPG decreased significantly after surgery [13].

PTH increases RANKL/OPG ratio with continuous exposure to high dose which produces catabolic effect as in hyperparathyroidism. This results in increased bone turnover, osteopenia, and bone loss in hyperparathyroidism. In addition, several extraskeletal manifestations of hyperparathyroidism are due to increased bone catabolism and hypercalcemia as nephrolithiasis, renal failure, peptic ulcer, and mental changes [2]. On the other hand, intermittent low-dose exposure to PTH has an anabolic effect through the SOST/sclerostin pathway [6].

The OPG-RANK-RANKL pathway is the mechanism by which hyperparathyroidism induces bone catabolism. PTH regulates the production of RANKL and its soluble decoy receptor OPG by osteoblasts and osteocytes [29–31]. RANKL binds to the receptor activator of nuclear factor kappa-B (RANK) on the osteoclast precursor stimulating their differentiation to osteoclasts and on the surface of the osteoclasts increasing their bone-resorbing activity. OPG inhibits the action of RANKL by binding to RANKL, thus preventing its access to the receptor RANK. In this way, the process of bone resorption is controlled by the balance between the concentration of RANKL and OPG [32–36]. In rats, continuous infusion of human PTH increased RANKL and RANKL mRNA expression and decreased OPG and OPG mRNA [37]. In vitro studies also showed that PTH activates of cAMP/PKA–CREB pathway increase the Tnfsf11 gene encoding RANKL, whereas a PTH inhibits the mRNA encoding for OPG expression through a PKA-CREB-AP-1 pathway [38–40].

2.2. Effect of parathyroid hormone on cells of the bone marrow and cells of the immune system

Cells of bone marrow also play a role in the effect of PTH on bone metabolism. Lymphocytes are believed to play a role on bone metabolism. T lymphocytes express PPR [23]. T cells express RANKL and CD40L on their surface that binds with RANK and CD40 in osteoclast precursors and osteoclasts to stimulate them [13, 41, 42]. Th17 cells form a subset of T lymphocytes that contribute to bone resorption. TH17 cells secrete IL-17, RANKL, TNF-α, IL-1, and IL-6, along with low levels of IFN-γ which contribute to osteoclastogenesis [43–46]. IL-17 stimulates the secretion of RANKL by osteoblasts and osteocytes and upregulates RANK [46, 47]. This is consistent with a human study that showed statistically significant elevation of IL-17 in postmenopausal women who had osteoporosis when compared with postmenopausal women who had osteopenia [47]. It is also noted that cPTH stimulates the production of TGF-β, IL-6, and TNF-α by bone cells and

stromal cells [7, 48, 49]. TGF-β and IL-6 direct the differentiation of naive CD4+ cells into TH17 cells [50–52]. TNF-α plays also an important role as a mediator of PTH catabolic action. PTH stimulates T cells to produce TNF-α. In mice lacking T-cell TNF-α, PTH failed to produce bone resorption but did not affect bone formation. Thus, in these mice there was no cortical bone loss, and there was increased trabecular bone formation [19]. TNF-α stimulates osteoclast formation and activity by multiple mechanisms. TNF-α increases the production of RANKL by osteoblasts and osteocytes. It also increases the expression of CD40 by stromal cells and osteoblasts increasing their responsiveness to CD40L expressed by T cells. Activation of CD40 on stromal cells and osteoblasts decreases the OPG secretion, thus increasing the RANKL/OPG ratio [7].

Bone marrow macrophages also play a role in the action of PTH on the bone. Macrophages express PPR. Depletion of the precursors of macrophages decreases the anabolic effect of iPTH [19]. The monocyte chemoattractant protein-1 (MCP-1) which is a chemotactic factor for monocyte and macrophages is a mediator for PHT-induced bone resorption [6]. MCP-1 was proven to attract pre-osteoclast in in vitro studies, thus increasing bone resorption [53]. It was found that the expression for MCP-1 increased by cPTH and iPTH in rat osteoblastic cells. With cPTH the MCP-1 expression was sustained, while with the anabolic protocol, the expression of MCP-1 was transient yet more pronounced. This suggests that the transient increase of bone resorption may be necessary before the anabolic effect of PTH on the bone [53, 54]. In human studies, MCP-1 levels correlate with PTH levels in patients with PHPT. After PTx, the levels of MCP-1 decreased significantly starting from 15 minutes following parathyroid adenoma removal [55].

3. Skeletal abnormalities in symptomatic hyperparathyroidism

3.1. Incidence

Hyperparathyroidism was first described in 1891 by von Recklinghausen. Despite of the fact that primary hyperparathyroidism was classically described as disease of "stones, bones, abdominal groans, thrones, and psychiatric overtone," the presentation of the disease changed dramatically over the past decades. Nowadays, the classical presentation with osteitis fibrosa cystica and pathological fractures is rarely seen in developed countries. Currently, larger numbers of patients are being identified with neuropsychiatric or cardiac manifestation and laboratory studies in the USA and Europe [2, 56]. In developing countries, the symptomatic form of PHPT was prevalent for a long time, but some countries as Brazil and China are having a shift toward the asymptomatic disease. However, other countries as India, Iran, Saudi Arabia, and Thailand still have high prevalence of the symptomatic form of the disease with pronounced skeletal manifestations [56–58].

3.2. Clinical manifestations

The signs and symptoms of severe bone disease include bone pain and pathologic fractures. Skeletal muscles are also affected by hyperparathyroidism where the patients have proximal muscle weakness and hyperreflexia [2, 59].

One of the features of skeletal involvement in hyperparathyroidism is hungry bone syndrome. It is characterized by hypocalcemia and hypophosphatemia following PTx. It is thought to be

due to withdrawal of osteoclast stimulation by high levels of PTH. This condition is treated by high doses of calcium and vitamin D [60, 61].

3.3. Investigations

3.3.1. Imaging

3.3.1.1. Radiography

Plain X-rays can show the classical findings of osteitis fibrosa cystica. This is characterized by marked thinning of the cortex (demineralization). Salt and pepper appearance for skull X-rays is also seen. Bone resorption of distal third of the clavicle is also seen. Hand X-rays show subperiosteal bone erosions in the distal phalanges and the lateral aspects of middle phalanges. Lytic lesions can also be seen in the pelvis and long bones with pathological fractures. Lytic lesions are referred to as brown tumors; these are a mixture of hemosiderin (hence, the brown color on pathological examination), woven bone, fibrous tissue, and osteoclasts. However, the lesions are nonneoplastic [2].

3.3.1.2. Bone mineral density

Bone mineral density can be measured by dual energy X-ray absorptiometry (DEXA) scan in all patients where measurements should be taken for lumbar spine, hip regions (total hip and femoral neck), and distal 1/3 of the radius. It is important to measure the bone mineral density in distal radius as it is a cortical site, and hyperparathyroidism is known to have catabolic effect on cortical bone [2, 56].

3.3.1.3. High-resolution peripheral quantitative computed tomography (HR-pQCT)

This is a noninvasive technique that allows assessment of the cortical and trabecular bone quality in PHPT [56]. HR-pQCT measures volumetric bone density, bone geometry, skeletal microarchitecture, and bone strength in the cortical and trabecular compartments. HR-pQCT showed that microarchitectural deterioration in both cortical and cancellous sites has decreased volumetric densities, more widely spaced, and heterogeneously distributed trabeculae and thinner cortices [62–64].

3.3.1.4. Trabecular bone score (TBS)

TBS is obtained from DEXA scan by applying special software. It is a textural analysis that provides an indirect index of trabecular microarchitecture. It can differentiate between DEXA scans showing similar bone densities. A high TBS is associated with a dense trabecular network and greater bone strength, and a low TBS indicates poor microarchitecture and poor strength [65–67].

3.3.2. Histomorphometry

Histomorphometry of transiliac biopsy will show reduced width of the cortex with increased porosity, while the trabecular bone is preserved [14].

3.3.3. Laboratory tests

In severe PHPT, serum calcium and parathormone are elevated. There are special markers for bone elevation as osteocalcin, type I procollagen peptide, and alkaline phosphatase. Alkaline phosphatase is much above the normal in all cases of hyperparathyroidism with increased bone turnover. Markers of bone resorption are also typically elevated PHPT. These include deoxypyridinoline, N-telopeptide, and C-telopeptide. These markers are products of breakdown of type 1 collagen [2]. Renal functions and urinary calcium should be evaluated. 25OH vitamin D levels should be as lower as the levels of 25OH vitamin D correlate with higher bone turnover and lower BMD, and both improve with repletion of 25OH vitamin D [68, 69].

4. Skeletal abnormalities in asymptomatic primary hyperparathyroidism

4.1. Manifestations

In 1970s, the wide availability of measurement of serum calcium changed the clinical presentation of hyperparathyroidism giving rise to the entity of asymptomatic primary hyperparathyroidism [14]. These are patients with hypercalcemia and elevated PTH but who are discovered accidentally while doing laboratory studies [58]. These patients have no X-ray finding of symptomatic hyperparathyroidism previously described [58]. These patients show decreased bone mass in cortical sites when measured by DEXA scan. Thus, DEXA scan shows reduction of bone mineral density at distal 1/3 of forearm (which is composed primarily of cortical bone), while bone density of lumbar spine (which is formed mainly of trabecular bone) is preserved. However, bone scan may remain stable for years in patients with asymptomatic hyperparathyroidism. Rubin et al. noted that the BMD of the lumbar spine remained stable for 15 years while it started to fall in cortical sites before 10 years [70, 71]. Micro-CT and histomorphometric studies show reduction of cortical bone with preservation of cancellous bone in PHPT [70, 71]. However, clinical studies showed that patients with hyperparathyroidism have higher risk of fractures both at cortical and cancellous sites [72, 73]. HR-pQCT helped to resolve this controversy. HR-pQCT showed that microarchitectural deterioration in both cortical and cancellous sites has decreased volumetric densities, more widely spaced, and heterogeneously distributed trabeculae and thinner cortices [62–64]. These studies also highlighted that weight bearing is a factor that can prevent the microarchitectural deterioration where they showed that the radius is more negatively affected than the tibias [63, 64]. Stein et al. performed individual trabecula segmentation that gave an insight into the trabecular microstructure. They found that the number of plate-like trabeculae is reduced relative to the rod-like trabeculae (decrease P-R ratio); there is reduced connectivity and less axially aligned trabecular network [64]. Another imaging modality which can show skeletal affection in asymptomatic cases is the trabecular bone score (TBS). Romagnoli et al. showed that TBS was significantly lower in patients with PHPT compared to controls. Among patients with PHPT, TBS was significantly lower in patients with vertebral fractures when compared to patients without vertebral fractures [74]. Eller-Vainicher et al. showed that TBS was associated with vertebral fractures regardless of age, gender, BMD, and BMI [75].

4.2. Natural history of bone disease in asymptomatic hyperparathyroidism

Age and female genders are associated with higher fracture risk in PHPT [73]. Currently, it is still unclear whether fracture risk assessment tools as FRAX can help to predict risk of fractures in patients with PHPT or not [14]. Concerning changes in BMD over time, Rao et al. monitored 80 patients with asymptomatic PHPT for a mean of 46 month. They did not observe deterioration of biochemical markers nor BMD measurements [74]. Silverberg et al. followed up 121 patients with PHPT of whom 101 were asymptomatic for up to 10 years. Twenty-five percent of patients showed disease progression. They also noted that patients younger than 50 years old had more likelihood of disease progression [71]. Rao et al. conducted randomized controlled trial on patients with PHPT and concluded that BMD at the hip and spine improves after PTx [76]. Rubin et al. studied 116 patients with PHPT of whom 99 were asymptomatic, PTX improved the biochemical markers and BMD, and without surgery PHPT progressed in one third of the cases [76]. Eller-Vainicher et al. studied 92 patients with PHPT and 98 controls for 24 months. DEXA scan and TBS in patients treated surgically and conservatively. In the surgical group, BMD and TBS increased significantly although it remained lower than controls. In the conservative group, BMD showed a decrease which was not statistically significant, and TBS showed a decrease which was not statistically significant; except in three patients who had vertebral fractures, the TBS showed a statistically significant decrease [75]. Hansen et al. measured BMD and HR-pQCT in women with PHPT before and 1 year after PTx. BMD improved after PTx, and HR-pQCT showed improvement of the cortical and trabecular parameters of the radius and tibia [77].

5. Skeletal abnormalities in normocalcemic primary hyperparathyroidism

5.1. Manifestations

This is a cohort of patients which includes patients with normal total and ionized calcium but elevated PTH in the absence of causes of secondary hyperparathyroidism. This may be due to target organ resistance of the bone and kidney, or these patients are in early stages of the disease [78, 79]. Lowe et al. described a cohort of patients in whom 57% had osteoporosis, 11% had fragility fractures, and 14% had renal stones [80]. Amaral et al. compared normocalcemic to hypercalcemic PHPT patients. They found that 15% of normocalcemic patients had previous fractures compared to 10.8% of normocalcemic patients and the incidence of renal stones was 18.2 in normocalcemic vs. 18.9% of hypercalcemic patients [80]. Charopoulos et al. used peripheral quantitative CT to compare the effect of normocalcemic PHPT to the effect of hypercalcemic PHPT on volumetric BMD and bone geometry. They noted the catabolic effect on both groups although it is more severe in the hypercalcemic group. In the normocalcemic group, cortical properties were adversely affected, while the trabecular properties were preserved [80].

5.2. Natural history of bone disease in asymptomatic hyperparathyroidism

The natural history of bone loss in normocalcemic hyperparathyroidism is not fully defined. Lowe et al. showed decrease in BMD by at least 5% in 43% of the patients [80]. Koumakis

et al. measured BMD before and 12 months after PTx for patients with normocalcemic and hypercalcemic PHPT. Both groups showed statistically significant improvement of BMD at the postoperative measurement [14].

6. Treatment

6.1. Effect of surgery on the skeletal manifestations of hyperparathyroidism

Skeletal affection is among the indications of surgery in hyperparathyroidism. Even in asymptomatic cases, surgery is suggested for perimenopausal or postmenopausal women and men 50 years or older who have a T-score of −2.5 or less for any skeletal site. In premenopausal women and men under 50 years old, T-score of less than −2.5 is the cutoff for surgery. The presence of fragility fractures is also among the surgical indication [2, 4, 81].

Surgery improves the bone turnover marker and PTH level. Within the first year following surgery, the BMD improves [70, 71, 82, 83]. This is due to uncoupling of bone resorption where the osteoclast stimulation by PTH stops, while bone formation continues [84]. Rubin et al. showed that the gain in BMD was sustainable up to 15 years following surgery at cortical and cancellous sites despite of expected age-related losses in BMD. The increases in BMD were recorded in the study at years 1, 5, and 10 and showed that the lumbar spine increased to 9, 6, and 12%; the femoral neck 1, 7, and 10%; and the distal radius 4, 8, and 7% [70]. Christiansen et al. studied the BMD and bone turnover markers for the first 6 months after surgery. They reported that the bone turnover markers were normalized and increased bone density in regions rich in cancellous bone but not cortical bone [82]. Similarly, Silverberg et al. noted improvement of BMD in lumbar spine and femoral neck but not the radius [71]. This may be explained by the fact that remodeling in cortical sites is slower than in trabecular bone. Thus, it takes a longer time for changes to be more pronounced [70]. Surgery also decreases the risk of fractures in hyperparathyroidism [72, 85, 86]. Vestergaard et al. demonstrated that the risk of fractures started to increase 10 years prior to surgery and reached its maximum 5–6 years following surgery. This risk falls back to normal after surgery [72]. Rudser et al. compared patients on dialysis who receive PTx to patients on dialysis without PTx. Fracture risks were lower among hemodialysis patients who underwent PTx compared to the dialysis patients who did not undergo PTx [84].

6.2. Effect of pharmacological treatment on skeletal manifestations of hyperparathyroidism

6.2.1. Bisphosphonates

Bisphosphonates (BP) are used in treatment of hyperparathyroidism as they act by inhibiting osteoclastic activity which is the cause of hypercalcemia and bone loss [2]. Several studies assessed the use of alendronate in hyperparathyroidism. Studies reported a reduction in the level of bone turnover markers and an increase in BMD. The increase in BMD was more for the trabecular than the cortical sites [87–92]. Although alendronate can lower the serum calcium initially, serum calcium tends to rise over 6 months, and the level of PTH may increase more than the pretreatment level [2, 90–93]. Pamidronate in several studies showed lowering of the serum calcium. However, due to limited time frame, no changes in BMD nor complications

were reported [94–100]. Clodronate use was associated with lowering of the serum calcium [101–103]. Several studies using clodronate reported lowering of urinary hydroxyproline and hence decreased bone turnover [101–103]. The use of risedronate in treatment of hyperparathyroidism was assessed in few studies [104, 105]. Tournis et al. reported that surgery is superior to risedronate as it improved the BMD and trabecular mineralization. Risedronate treatment in their study did not result in significant change in volumetric BMD or peripheral quantitative computed tomography [104]. A small number of studies reported the use of several BPs. Lee et al. reported the can prevent hungry bone syndrome among a very small number of patients [104]. Two other studies reported increase in BMD in the lumbar spine and hip [85, 106].

In conclusion, alendronate is the most studied BP in hyperparathyroidism. It decreases bone turnover and increased BMD. The effect of alendronate on serum calcium appears to be short lived.

6.2.2. Cinacalcet

This is a calcimimetic agent which increases the sensitivity of calcium-sensing receptors of the parathyroid gland to calcium, thus decreasing PTH secretion [107]. The effect of cinacalcet on bone turnover markers and BMD appears to be controversial. Several studies measured bone turnover markers with either decrease in the markers [108], no change [109, 110], or increase in the level of the markers [111, 112]. Similarly, the reported effects on BMD were an increase in BMD [113], a decrease [114], and no change [108, 111, 112]. Faggiano et al. compared cinacalcet monotherapy with cinacalcet with alendronate. The patients who received the combined therapy had better improvement of BMD in lumbar spine and hip compared to the monotherapy group. There was no significant difference between biochemical changes in both groups [108]. Moe et al. studied the effect of cinacalcet in reducing the fracture risk in patients receiving hemodialysis. There was no significant effect of cinacalcet on fracture reduction in the intention-to-treat analysis. However, a lag-sensoring analysis which took into consideration the crossover effect showed significant reduction of fracture risk in patients who received cinacalcet [84].

6.2.3. Vitamin D and calcium

Dietary calcium deficiency can induce elevation of PTH levels. Low vitamin D levels are associated with increased bone turnover, deteriorated hip geometry, and lower BMD [68, 84, 115]. Patients with low calcium intake and PHPT who received calcium supplementation had lower levels of PTH and improved BMD of femoral neck [116]. For patients with vitamin D deficiency, vitamin D repletion may decrease PTH levels and improved bone mineral density [116–118]. However, vitamin D supplementation may slightly increase serum calcium levels and urinary calcium excretion; thus, monitoring of calcium levels is valuable [81, 119, 120].

6.2.4. Other treatments of hyperparathyroidism which affect bone metabolism

Estrogen was found to improve BMD in women with hyperparathyroidism. The BMD of the lumbar spine and femoral neck increases, and bone turnover markers decrease with estrogen administration which has no or minimal effect on serum calcium [121, 122]. Raloxifene was also associated with improved BMD in PHPT [123, 124]. However, there is no data on the effect of estrogen or raloxifene on reducing the risk of fracture [120].

Denosumab is a monoclonal antibody against RANKL that inhibits the binding of RANKL to RANK [125]. A study was conducted on patients with secondary hyperparathyroidism on dialysis in whom denosumab was administered. The BMD improved in the femoral neck and lumbar spine. However, a transient increase in PTH levels occurred in the patients.

7. Conclusion

Despite of the fact that many patients with hyperparathyroidism do not show symptoms of skeletal affection, clinicians always need to keep an eye on the catabolic effect of hyperparathyroidism on the skeletal system. Better understanding of the mechanism of action of PTH of bone showed that many cells and mediators can influence the RANK/RANKL/OPG system, namely, T lymphocytes. Newer imaging modalities as TBS and HR-pQCT can be useful for detecting subtle bony changes. While parathyroidectomy is proven to reverse the skeletal effects of hyperparathyroidism, many patients may not be indicated for surgery, yet they should receive medical treatment that will protect them from the catabolic effect on the bone. Alendronate was extensively studied and showed to decrease bone turnover and increase BMD. Vitamin D supplementation for patients with vitamin D deficiency has a protective effect on the bone. Denosumab also has a protective effect, but clinical data about its use for patients with hyperparathyroidism is still limited.

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Conflict of interest

The author has no conflict of interests to declare.

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