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Thyroid Disorders and Osteoporosis

Ayotunde Oladunni Ale

Abstract

Adequate amount of thyroid hormone is an essential requirement for normal development and maturity of bones in the early life as well as for the maintenance of the skeletal system (bone remodeling). Osteoporosis, one of the most common metabolic bone disorders, is strongly associated with hyperthyroidism (endogenous and exogenous), whereas association of the same disease with hypothyroidism is not quite established. Most of the data describing the association between osteoporosis and hyperthyroidism are collected among elderly population (especially postmenopausal women), and only a few studies in literature researched into osteoporosis and hyperthyroidism in <50 years of age; hence further studies are required in the younger population (including premenopausal women and younger males).

Keywords: bone remodeling, hyperthyroidism, hypothyroidism, postmenopausal women

1. Introduction

The skeletal system maintains a dynamic characteristic throughout its life by continuously undergoing bone modeling and bone remodeling processes [1–7]. Both bone modeling and remodeling processes include bone resorption mediated by osteoclasts and bone formation mediated by osteoblasts. Bone modeling is the predominant event during childhood, whereas in adults bone remodeling is the principal event [8]. In the case of bone modeling, both bone resorption and bone formation lead to major cur independently of one another at different sites of the skeletal system and lead to major change in the skeletal framework, whereas in the case of bone remodeling, both the processes of bone resorption and formation are closely related both in terms of time and site so that bone volume and density both remain more or less unchanged. The continuous process of bone remodeling repairs micro fractures, prevents formation of brittle bones, and balances calcium and phosphate homeostasis [6–8].

A number of systemic and local factors regulate the process of bone remodeling. Whenever the tightly coupled processes of bone resorption and bone formation in bone remodeling are disturbed, bone mineral diseases occur, excessive bone resorption leads to osteoporosis, and excessive bone formation leads to osteopetrosis [9].

Osteoblasts and osteoclasts are the two key players of bone remodeling; other cells involved in the process are osteocytes (derived from osteoblasts and acting as mechanosensor) and the bone lining cells [9]. The process of bone remodeling increases with aging; in both perimenopausal and menopausal women, the remodeling is faster than premenopausal women [9].

There are a number of factors which are responsible for the development, maturation, and normal functioning of the skeletal system; these are genetic factors, maintenance of hormonal and metabolic harmony, adhering to balanced diet, exercise, etc. Any change in the abovementioned factors might lead to skeletal abnormality including restricted stature, deformity, osteoporosis, etc. [8, 10].

Osteoporosis leads to poor bone mass along with increased risk of fracture. Osteoporosis has emerged as a global healthcare problem with an estimated huge economic burden. Around 40% of women and 13–22% of men above 50 years will experience at least one episode of fracture (usually of spine, femur, or forearm) due to underlying osteoporosis in his or her lifetime [11]. Besides postmenopausal women and men above 50 years of age, the risk of secondary osteoporosis has increased in younger people as well [11].

Due to the increase in the number of patients with osteoporosis, all the secondary risk factors attributed to osteoporosis should be thoroughly investigated.

A number of factors are responsible for maintenance and development of the skeletal system; these are genetic factors, adequate hormonal and metabolic functions, intake of balanced diet, and exercise (mechanical load) [11]. Any type of imbalance among the abovementioned factors might lead to severe consequences like short stature, bony deformities, and fractures. The final outcome depends upon age, type, severity, and duration of the underlying imbalance. Although not all of the abovementioned factors can be modified (like genetic factors), some of them can be modified [11, 12].

A rising number of new osteoporosis cases both in elderly and in young patients warrant the need for thorough investigations to identify all other secondary conditions that might affect the disease negatively. Of all the secondary conditions, hormonal conditions are the most important ones that can lead to or aggravate osteoporosis [12]. Most commonly implicated endocrinological conditions are Cushing's syndrome, hyperthyroidism, hypogonadism, acromegaly, diabetes mellitus, etc. Fortunately, majority of the negative effects of these hormonal disorders on the skeletal system can be modified [10–12].

1.1 Osteoblasts

Osteoblasts, the bone-forming cells in bone remodeling process, are derived from the pluripotent mesenchymal stem cells. Osteoblasts are also responsible for the secretion of Type I collagen which in turn is the major bone matrix protein. Besides the abovementioned functions, osteoblasts are also responsible for adequate mineralization of the new bone (osteoid). Bone mineralization occurs due to the locally released phosphates from the osteoblast-derived vesicles located within the osteoid. Extracellular calcium also contributes to the process of bone formation by the production of hydroxyapatite crystals. Maintenance of correct balance between bone matrix and minerals is the key factor for ensuring the right amount of rigidity and flexibility of the skeletal structure. Adult human cortical bones consist of 60% mineral, 20% organic material, and 20% water [8, 9].

1.2 Osteoclasts

These are micronucleated cells that are derived from the mononuclear monocyte-macrophage cells. Osteoclasts, the only bone-resorbing cells, depend on two cytokines, colony-stimulating factor-1 or the macrophage colony-stimulating factor (CSF-1) and receptor activator of NF- κ B ligand (RANKL), for production, expansion, and survival. Osteoprotegerin (OPG) acts as a decoy receptor for RANKL and

inhibits the action of RANKL; hence the ration of RANKL to OPG determines the extent of osteoclast maturation and expansion [8, 9].

2. Physiology of thyroid hormones

The level of thyroid hormones in the circulation is controlled by the hypothalamic-pituitary-thyroid axis (HPT axis) [13]. Thyrotropin-releasing hormone (TRH) is produced and secreted from the medial neurons of the paraventricular nucleus (PVN) of the hypothalamus. TRH in turn regulates both production and secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary cells. Next, TSH through action on its receptor (TSHR) located on the follicular cells of the thyroid gland stimulates synthesis and secretion of the thyroid hormones. There are two types of thyroid hormones, 3,5,30,50-L-tetraiodothyronine (T4), the pro-hormone, and 3,5,30-L-triiodothyronine (T3), the active hormone [14].

Thyroid hormones exert negative feedback effect on TRH and TSH and thus inhibit own synthesis and secretion.

Thus the HPT axis maintains a balanced relationship between the circulating thyroid hormones and their regulators like TSH and TRH. The set point for adequate functioning of the HPT axis is partly determined by genetic factors; there is an estimated genetic variation of 45–65% [13, 14].

2.1 Intracellular T3 supply

Circulating concentrations of both T4 and T3 along with target tissue uptake of the same and local activation or inactivation determine the intracellular supply of T3 (the active hormone). The thyroid gland secretes the pro-hormone T4 in larger proportions which is converted to the active form T3 in the liver and kidney through deiodination of T4 by type 1 iodothyronine deiodinase enzyme (DIO1). A major part (around 90%) of the circulating thyroid hormone remains bound to plasma proteins, and the concentration of free T3 (fT3) exceeds that of free T4 (fT4) by three to four times [13, 14].

There are specific membrane transporters associated with target tissue uptake of thyroid hormones; considered as monocarboxylate transporters (MCT8, MCT10), and organic acid transporter protein-1c1 (OATP1C1) [15]. Activity of T3 inside the cell is regulated by DIO2 and DIO3, as DIO2 converts T4 to T3 and DIO3 blocks the activation of T3 by producing reverse T3 [16].

Thyroid hormones mediate their actions through interaction with thyroid receptors (TRs). Unbound TRs bind with corepressor proteins and bind with thyroid response elements located at the promoter regions of the target genes and suppress transcription. Once thyroid hormone binds with its receptor, the receptor undergoes a conformational change with the unbinding of the corepressor proteins and facilitation of gene transcription following binding with the thyroid response elements at the target genes [14–16].

3. Thyroid hormone and the skeletal system

Action of T3 hormone on the skeletal system is rather complex and not completely understood. T3 mediates its action on the bones via direct and indirect pathways and affects the different phases of bone remodeling. T3 facilitates both osteoblastic (bone formation) and osteoclastic actions (bone resorption). T3 facilitates osteoblastic

activity by promoting production and differentiation of osteoblasts and also increases the expression of osteocalcin, collagen (Type 1), metalloproteins, alkaline phosphatase, etc. Similarly, T3 also facilitates differentiation of osteoclasts through increased expression of interleukin-6 and prostaglandins. It also exhibits synergistic action with hormones facilitating osteoclastic activity (like parathyroid hormone and vitamin D). Moreover, T3 promotes the expression of mRNA of RANKL, stimulates RANK, and thus facilitates osteoclast production [14–16].

Majority of the TRs expressed in the skeletal system (bone marrow, chondrocytes, osteoblasts, and osteoclasts) are TR β 1 and TR α 1. Molecular studies have shown that the expression of TR α 1 is far greater than that of TR β 1 in the skeletal system, indicating that T3-mediated action on the skeleton system is mostly carried out through TR α 1 receptor [17]. There were no changes in the bone mass following the treatment of adult female rats with TR β -selective agonist 3,5-dimethyl-4-(4-hydroxy-3-isopropylbenzyl)phenoxy acetic acid (GC-1); however, the administration of supraphysiological dose of T3 led to significant loss of bone mass in the adult female rats [18]. These findings suggest that T3-mediated bone resorption occurs through TR α 1 receptors [18]. Animal models with genetic modifications (for TRs) have led to better understanding of the actions of T3 on the skeletal systems. All these studies showed that mice with mutation of either both TR α 1 and TR β 1 or only TR α 1 had delayed bone growth due to delayed ossification and decreased bone mineralization in early life, whereas increased bone mineralization in later years of life is similar to the effects of hypothyroidism in humans. However, mice with mutation of only TR β 1 receptors had skeletal phenotype similar to thyrotoxic patients characterized by increased mineralization and faster ossification during early life and decreased bone mineralization and poor bone mass in adult life [18].

3.1 Hyperthyroidism and osteoporosis

Thyroid hormones are known to play a key role in the linear growth of the skeletal system, and these hormones are essential to achieve the expected bone mass [19]. However, hyperthyroidism or thyrotoxicosis, a rather rare occurrence in children, if present, leads to accelerated ossification (both intramembranous and endochondral) and rapid linear growth [17]. This accelerated increase in bone age often results in early epiphyseal closure and short stature. In younger children severe degree of thyrotoxicosis might lead to premature closure of cranial sutures and craniosynostosis (impaired growth of brain and skull) with neurological complications [17, 20]. Sometimes severe untreated thyrotoxicosis in mother might lead to craniosynostosis in the growing fetus [20].

In adults hyperthyroidism shortens the bone turnover and poor bone mineralization [11, 17]. Finally there is loss of bone mineral density by around 10–20% especially in the cortical bones [11]. The increased concentration of circulating thyroid hormones causes significant shortening of bone remodeling cycle by about 50%. Normally the average bone remodeling cycle lasts for 200 days; however, with hyperthyroidism it is shortened to an average of 113 days [11, 21, 22]. Hence the balance between bone resorption and bone formation is disturbed; the bone formation phase is severely compromised (the duration is decreased by 2/3) and is ultimately responsible for poor mineralization (loss of about 10% of mineralization of bone per cycle) [11]. All these effects lead to increased risk of osteoporosis and increased chance of fracture.

Another contributory factor for increased risk of osteoporosis in patients of hyperthyroidism is that there is increased circulatory concentration of IL-6 in these patients; IL-6 is known to be an activator for osteoclast production and facilitates action of parathyroid hormone in bones [11, 23]. Hyperparathyroidism is also

known to cause negative calcium balance due to hypercalcemia and hypercalciuria. Negative calcium balance further increases the risk of osteoporosis in these already vulnerable patients.

Many researchers since Von Recklinghausen have been conducting researches on the effects of thyroid dysfunction on bones. Svare A and his colleagues conducted a cross-sectional study to assess the relationship between BMD of forearm and TSH level in Norwegian female population (HUNT2 Study) [24]. They found that women with lower TSH (<0.5 mU/L) had lower forearm BMD than the reference category. Similarly, the prevalence of osteoporosis was found to be higher in women with osteoporosis than those without any history of thyroid disorder.

Again, the occurrence of osteoporosis secondary to hyperthyroidism (thyrotoxicosis) is more common in postmenopausal women than premenopausal women. Ercolano MA and his colleagues conducted a non-interventional and cross-sectional study on euthyroid (who had euthyroid for the past 6 months) pre- and postmenopausal women with past history of hyperthyroidism due to Graves' disease [25]. It was found that BMD was significantly affected only in the postmenopausal group of women who remained euthyroid for the past 6 months and have a past history of Graves' disease. Again, Tuchendler and Bolanowski conducted a study on premenopausal women with hyper- and hypothyroidism to assess the effects of thyroid dysfunction on osteoporosis [26]. They found that only hyperthyroidism and not hypothyroidism can significantly affect BMD (measured at the femoral neck), and following the treatment for 12 months, a statistically significant increase in BMD in femoral neck was observed in premenopausal women with hyperthyroidism and not hypothyroidism.

Similar study was conducted in men by El Hadidy and his colleagues [27]. The study included males between 23 and 65 years with hyperthyroidism (Graves' disease or toxic nodular goiter). The researchers found that the men with hyperthyroidism had a significant fall in BMD compared to age-matched healthy men without any thyroid dysfunction. Besides this, the severity and the duration of hyperthyroidism were directly related to the increase in bone turnover markers and the degree of bone loss.

Similar study was conducted by Ale and her colleagues [28]. This cross-sectional study included females and males between 22 and 50 years. It was found that BMD measured in hyperthyroidism was significantly reduced compared to age- and sex-matched healthy controls. Osteoporosis was documented in hyperthyroidism but not in the controls.

Again a systematic review and meta-analysis of cohort studies by Yang and his fellow researchers documented that although both subclinical hypo- and hyperthyroidism are associated with increased risk of fracture, only subclinical hyperthyroidism and not subclinical hypothyroidism showed significant association with low BMD (osteoporosis) [29].

3.1.1 Subclinical hyperthyroidism and osteoporosis

Although medical data describing the relation between subclinical hyperthyroidism and osteoporosis is not much, still there are studies which have explored the relationship between the two. Segna and his colleagues published a study exploring the association between subclinical hyperthyroidism and osteoporosis [30]. They included all the prospective cohort studies (published between 1946 and 2016) in the electronic database (MEDLINE/EMBASE) which provided baseline thyroid hormone status and repeated measurements of BMD. The study found that in adult patients subclinical hyperthyroidism is significantly associated with bone loss in the femoral neck region leading to increased risk of osteoporosis and fracture.

However, some earlier studies as the one conducted by Földes and his colleagues have described that although in premenopausal women with subclinical hyperthyroidism BMD in femoral neck, lumbar spine, and in the midshaft of radius did not decrease significantly, the same condition might contribute to osteoporosis in postmenopausal women especially in the cortical bones [31]. Another study published by Lee and his fellow researchers revealed that both subclinical hypo- and hyperthyroidism are associated with increased risk of hip fracture in elderly men; however, no such association was found with women [32].

Vadiveloo and his colleagues published a retrospective study exploring the long-term consequences of subclinical hyperthyroidism (TEARS study) [33]. The researchers identified suitable patients using population record linkage technology retrospectively between January 1, 1993 and December 31, 2009. They found that patients with endogenous subclinical hyperthyroidism showed an increased risk of osteoporosis-related fracture (hazard ratio being 1.25) when compared with reference population; however, once these patients developed overt hyperthyroidism or euthyroidism and are excluded from the study, this association is lost.

Again, Saler and his colleagues described in their study that in contrast to exogenous subclinical hyperthyroidism, endogenous subclinical hyperthyroidism does not compromise BMD in premenopausal women and therefore do not pose a risk for either osteoporosis or osteopenia [34]. However, Tauchmanová and her colleagues found that BMD of the femoral neck was significantly decreased in both pre- and postmenopausal women with endogenous subclinical hyperthyroidism (greater in postmenopausal women). Study of lumbar spine BMD revealed bone loss only in postmenopausal women. Similar findings were documented by Rosario and his colleagues [35].

Thus it can be suggested that the threat of osteoporotic fracture is greater with exogenous subclinical hyperthyroidism especially in postmenopausal women.

3.2 Overt hypothyroidism and osteoporosis

Hypothyroidism is a rather common condition in children and is characterized by delay in the development of the skeletal system, poor growth, and impaired and early endochondral ossification leading to short stature and defective bone maturation. Patients often present with patent skull sutures (delay in closure of skull fontanelles) and typical facial characteristics like flattened nasal bridge and broad face due to defective ossification.

In severe cases postnatal growth can be completely arrested, impaired with skeletal growth characterized by epiphyseal dysgenesis, dislocation of hip joints, scoliosis, persistent patency of the fontanelles, and delay in eruption of tooth. Thyroid hormone replacement therapy in these children leads to “catch-up” growth with achievement of skeletal maturity and improved bone mineralization. Finally in most of the children, normal adult height and bone mineral density are achieved. However, in severely affected children and those with significant delay in receiving thyroid hormone replacement therapy, expected adult stature might not be achieved.

Several studies were conducted in adults to understand the effect of thyroid hormone disorder on adult skeletal system [11]. But several factors like heterogeneity of the study population, the presence of different confounding factors, and different end points for different studies have led to the uniform interpretation of the results obtained from these studies.

Earlier histomorphometric studies have shown that hypothyroidism in adults led to slow bone turnover with both poor bone formation by osteoblasts and decreased

bone resorption by osteoclasts. Also increase in the bone remodeling time led to prolonged secondary mineralization of the bone without any change in the existing bone volume. However, all the abovementioned changes are very slow to occur, and there are hardly any clinical data to suggest these findings in adult patients [11].

Although the exact mechanism is not known, hypothyroidism is considered to increase the risk of fracture. Vestergaard and his fellow researchers documented in their study that following diagnosis of primary idiopathic hypothyroidism, the risk of fracture (in forearm) was significantly increased in patients above 50 years [36].

However, González-Rodríguez and his colleagues while assessing the prevalence of thyroid dysfunction in adult female population, from the data collected in the Latin American Vertebral Osteoporosis Study (LAVOS), documented that although there was a high prevalence of hypothyroidism in these females, no association between loss of bone mineral density and hypothyroidism was found [37]. They also found that there was no association between fractures (vertebral or nonvertebral) and hypothyroidism.

3.3 Prolonged treatment with TSH suppressive therapy with supraphysiological dose of levothyroxine (synthetic form of T4) and osteoporosis

Supraphysiological doses of levothyroxine are prescribed in patients of thyroid cancer following surgery and radioactive iodine therapy. Prolonged exposure to levothyroxine therapy might increase the risk of secondary osteoporosis [11].

Heemstra and his colleagues described that, although long-term thyroxine therapy increased the risk of poor BMD and thus osteoporosis, it was not seen in men and in premenopausal women [38].

In the year 2018, Mazziotti and his colleagues published a cross-sectional study conducted mainly on postmenopausal women (178 women were postmenopausal out of 179 of the study participants) [39]. These women underwent thyroidectomy for differentiated thyroid carcinoma and were receiving levothyroxine therapy. Radiological vertebral fractures (VF) are considered as an early indicator of bone fragility. The researchers found that the prevalence of VF was significantly greater in patients with TSH level <1.0 mU/L, duration of levothyroxine therapy, and densitometric diagnosis of osteoporosis.

Thus it can be suggested that the risk of osteoporosis increases with suppression of TSH therapy.

4. Conclusion

Osteoporosis is considered to be one of the most common skeletal disorders affecting both elderly and young patients. Besides the few primary causes (aging and menopause), in most of the cases, osteoporosis occurs due to underlying secondary causes. Common secondary risk factors for osteoporosis include hormonal disorders like Cushing's disease, hyperthyroidism, diabetes mellitus, hypogonadism, etc. Several studies have established that hyperthyroidism both endogenous (due to Graves' disease or toxic nodular goiter) and exogenous (due to prolonged levothyroxine therapy especially in patients with differentiated thyroid cancer) increases the risk of osteoporosis profoundly in postmenopausal women. Even subclinical hyperthyroidism especially the exogenous ones might lower BMD and increases the risk of osteoporosis, more commonly in postmenopausal women. Hypothyroidism, on the other hand, although responsible for an array of bone disorders, does not usually contribute to osteoporosis.

Most of the studies, exploring the association between hyperthyroidism (exogenous or endogenous) and osteoporosis, are usually conducted among elderly population (postmenopausal women and elderly men). Hence further studies are to be conducted to explore the association of hyperthyroidism and osteoporosis in younger population (premenopausal women and younger males).

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