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Effect of Thyroid Disorders on Bone Function

Bomma Siri Chandana, Syeda Nishat Fathima

Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet, Warangal-506332, Telangana, India

ABSTRACT:

The thyroid gland plays an important role in tissue metabolism and development through the synthesis of thyroid hormones known as thyroxine (T4) and triiodothyronine (T3). Both have systemic effects. Thyroid hormones are necessary to normal development and function of human skeleton. Thyroid hormones are necessary to normal development and function of human skeleton. Abnormal thyroid hormone levels lead to hypothyroid and hyperthyroid states. Thyroid hormones are necessary to normal development and function of human skeleton. Thyroid diseases have widespread systemic manifestations including their effect on bone metabolism. The present review focuses on the effect of thyroid dysfunction on bones.

Keywords: Thyroid hormone; Bones; hypothyroidism; hyperthyroidism

INTRODUCTION:

The thyroid is an endocrine gland. Its location is in the inferior, anterior neck, and it is responsible for the formation and secretion of the thyroid hormones as well as iodine homeostasis within the human body. The thyroid produces approximately 90% inactive thyroid hormone, or thyroxine (T4), and 10% active thyroid hormone, or triiodothyronine (T3). Inactive thyroid hormone is converted peripherally to either activated thyroid hormone or an alternative inactive thyroid hormone. [1]

Thyroid diseases are common worldwide. In India too, there is a significant burden of thyroid diseases. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases. The prevalence of spontaneous hypothyroidism is between 1 and 2%, and it is more common in older women and ten times more common in women than in men. The prevalence of hyperthyroidism in women is between 0.5 and 2% and is ten times more common in women than in men. Epidemiological studies suggest that 1% of men and 5% of women have thyroid nodules detected clinically and that the frequency increases with age and in iodine-deficient populations. In iodine-replete areas, congenital hypothyroidism affects about one newborn in 3500–4000 births, and the value of screening for congenital hypothyroidism in heel-prick blood specimens is unquestioned. [2]

THYROID FUNCTION TEST:

Hypothalamus releases thyrotropin-releasing hormone (TRH) that stimulates the secretion of TSH in the pituitary gland. Increased free T4 and T3 inhibit the release of TRH and TSH through a negative feedback loop. As a result, T3 and T4 secretion and iodine uptake are reduced. Other hormones, such as somatostatin, glucocorticoids, and dopamine, also inhibit TSH production. Cold, stress, and exercise increase TRH release. Thyroid function tests include a battery of blood tests, including the measurement of the thyroid hormones, as well as the measurement of thyroid stimulating hormone (TSH). The normal range of T_4 is suggested to be 77–155 nmol/l, T_3 to be 1.2–2.8 nmol/L and TSH to be 0.3–4 mU/l. They may reveal hyperthyroidism (high T3 and T4), hypothyroidism (low T3, T4), or subclinical hyperthyroidism (normal T3 and T4 with a low TSH).

Other lab tests such as TSH receptor antibodies or antibodies to thyroid peroxidase can help aid in diagnosing Graves disease or Hashimoto thyroiditis, respectively. In pregnant women, thyroid-binding globulin production is increased because of estrogen and beta-human chorionic gonadotropin (beta-HCG). More free T4 will be bound to TGB, leading to increased production of T4. TSH levels and free T4 levels will normalize, and total T4 will increase. Therefore, laboratory values will show normal TSH, normal free T4, and elevated total T4. [3]

PATHOPHYSIOLOGY:

Hypothyroidism is an endocrine disorder with resultant under-production of thyroid hormone. Common symptoms of hypothyroidism include cold intolerance and weight gain due to decreased basal metabolic rate and thermogenesis, depression, fatigue, decreased peripheral reflexes, and constipation, due to decreased stimulation of the central and peripheral nervous system. Many other consequences of hypothyroidism can manifest secondary to the lack of activated thyroid hormone on various tissues and organs of the body.

Hyperthyroidism is an endocrine disorder with excess thyroid hormone production. In contrast to hypothyroidism, hyperthyroidism often causes heat intolerance, weight loss, anxiety, hyperreflexia, and diarrhea, as well as palpitations. Increased stimulation of basal metabolic rate, thermogenesis, resting heart rate, and cardiac output, and central and peripheral nervous systems result in the most common symptoms. However, a multitude of symptoms can present, including brittle hair, dry skin, and pretibial myxedema. In Graves disease, an autoimmune condition where the TSH-receptor becomes activated by an auto-antibody, additional pathophysiology of orbitopathy can be present. The TSH-receptor antibody also activates T cells and causes fibroblast proliferation and accumulation of glycosaminoglycans in the extraocular muscles and retroocular connective tissue leading to proptosis. Hashimoto thyroiditis is a primary cause of hypothyroidism, which is associated with HLA-DR5. The presence of anti-thyroglobulin and thyroid peroxidase antibodies suggest Hashimoto thyroiditis. [4]

FUNCTION:

The thyroid hormones act on nearly every cell in the body. It acts to increase the basal metabolic rate, affect protein synthesis, help regulate long bone growth (synergy with growth hormone) and neural maturation, and increase the body's sensitivity to catecholamines (such as adrenaline) by permissiveness. The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism. Numerous physiological and pathological stimuli influence thyroid hormone synthesis. [5]

MECHANISM OF ACTION OF THYROID HORMONES:

Thyroid hormones are lipophilic and circulate bound to the transport proteins. Only a fraction (approximately 0.2%) of the thyroid hormone (free T4) is unbound and active. Transporter proteins include thyroxine-binding globulin (TBG), transthyretin, and albumin. TBG transports the majority (two-thirds) of the T4, and transthyretin transports thyroxine and retinol. When it reaches its target site, T3 and T4 can dissociate from their binding protein to enter cells either by diffusion or carrier-mediated transport. Receptors for T3 bind are already bound to the DNA in the nucleus before the ligand binding. T3 or T4 then bind to nuclear alpha or beta receptors in the respective tissue and cause activation of transcription factors leading to the activation of certain genes and cell-specific responses. Thyroid hormones are degraded in the liver via sulfation and glucuronidation and excreted in the bile.

Thyroid receptors are transcription factors that can bind to both T3 and T4. However, they have a much higher affinity for T3. As a result, T4 is relatively inactive. Deiodinases convert T4 to active T3 or inactive reverse T3 (rT3). There are three types of deiodinases: type I, II, and III. Type I (DIO1) and II (DIO2) are located in the liver, kidneys, muscles, and thyroid glands. Type III (DIO3) deiodinases are located in the CNS and placenta. DIO1 and DIO2 convert T4 to the active form T3, and DIO3 converts T4 into the inactive form rT3. [6]

THYROID HORMONE AND THE SKELETAL SYSTEM

Bone development occurs in two ways. First by Intramembranous ossification results in the formation of flat bones, like the skull. Osteoblasts differentiate from the mesenchyme and form bone directly. Thyroid receptors (TR) alpha and beta are both expressed in these cells. Followed by endochondral ossification forms bones from a cartilage model with linear bone growth occurring at the growth plate from underlying columns of proliferative chondrocytes. Here too, alpha and beta thyroid receptors are present. For both osteoblasts and chondrocytes, T3 determines the pace of proliferation and the differentiation of these stem cells into bone. 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 receptor activator of NF-kB ligand (RANKL), stimulates RANK, and thus facilitates osteoclast production.

Thyroid hormones mediate their actions through interaction with thyroid receptors (TRs). Majority of the thyroid receptors expressed in the skeletal system (bone marrow, chondrocytes, osteoblasts, and osteoclasts) are TRβ1 and TRα1. Molecular studies have shown that the expression of TRα1 is far greater than that of TRβ1 in the skeletal system, indicating that T3-mediated action on the skeleton system is mostly carried out through TRα1 receptor. T3-mediated bone resorption occurs through TRα1 receptors. Mutation of either both TRα1 and TRβ1 or only TRα1 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 mutation of only TRβ1 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. [7]

HYPERTHYROIDISM AND BONE:

Hyperthyroidism can have various effects on skeletal muscles and their receptors due to the excess production of thyroid hormones, primarily triiodothyronine (T3) and thyroxine (T4). These effects are related to the role of thyroid hormones in regulating metabolism and various physiological processes. The different proposed effect by which hyperthyroidism effects skeletal system are: [8]

1. Thyroid hormones increase the activation of new remodeling cycles and stimulate osteoclastic and osteoblastic activity in trabecular and cortical bone. The mechanisms of thyroid hormone induced bone resorption include cAMP-mediated, increased sensitivity of beta-adrenergic receptors to catecholamines, increased sensitivity of bone cells to PTH, osteoclast activator factor and interleukin-1 (IL-1) mediated increased bone resorption. Thyroid stimulating hormone deficiency, rather than thyroid hormone excess, has been suggested as the underlying cause.
2. Renal calcium excretion is usually increased in hyperthyroidism and correlates positively with excess thyroid hormone levels and cortical osteoclastic activity. It is caused by enhanced mobilization of bone mineral in hyperthyroid state and remains elevated even on calcium deficient diet. In kidney, the filtered calcium load is enhanced due to increase in serum ultrafiltrable calcium and glomerular filtration rate as well as reduced tubular reabsorption because of suppressed PTH levels.
3. Hyperphosphatemia in hyperthyroidism has been explained on the basis of an enhanced tissue catabolism leading to an excess input of phosphorous to the plasma pool from bone and tissues and lower fractional clearance of phosphorous and increased renal tubular reabsorption of phosphorous. The changes in serum phosphorous are due to suppressed PTH levels as well as direct effects of thyroid hormones on tissue phosphate metabolism and renal phosphate handling.
4. Patients with hyperthyroidism have elevated levels of serum alkaline phosphatase in as many as 50% of cases. The raised levels of serum alkaline phosphatase levels could be either of hepatic or of bone origin. Following treatment, serum alkaline phosphatase levels remain elevated for several months suggesting increased bone turnover continues even after restoration of a normal metabolic rate.
5. A decrease in serum PTH concentration was noted in patients with hyperthyroidism. There is inverse relationship between serum calcium and serum PTH levels, indicating that increased serum calcium levels inhibit PTH secretion from parathyroid gland. Suppressed PTH levels also explain the raised serum phosphorous and increased maximal tubular absorption rate for phosphorous.
6. Subnormal Vitamin D levels are seen in hyperthyroidism. In subjects with hyperthyroidism, high serum calcium, low PTH and high phosphorous levels suppress renal 25(OH)D1-α hydroxylase activity leading to decrease in 1,25(OH)2D levels. Serum 24,25(OH)2D levels are increased in patients with hyperthyroidism and they correlate with serum thyroid hormone levels.
7. Hyperthyroidism is an important cause of secondary osteoporosis.

HYPOTHYROIDISM AND BONE:

Untreated hypothyroidism in childhood leads to growth retardation or even growth arrest, disturbances of endochondral ossification, delayed bone age and persistent short stature. Hypothyroidism causes general hypometabolism. Bone formation processes are slowed in 50%, bone resorption processes – in 40%. The calciuria is reduced, serum concentration of osteocalcin and alkaline phosphatase is decreased, but serum concentration of parathyroid hormone and vitamin D can be elevated. Nevertheless, it is considered that hypothyroidism is related with increased risk of fractures. [9]

CONCLUSION:

Thyroid hormones play an important role in bone mineral homeostasis and bone density. Both hyperthyroidism and, to some extent, hypothyroidism are associated with reduced bone mineral density leading to increased fracture risk.

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