



How does Hashimoto's thyroiditis affect bone metabolism?

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Abstract

Bone marrow contains resident cellular components that are not only involved in bone maintenance but also regulate hematopoiesis and immune responses. The immune system and bone interact with each other, coined osteoimmunology. Hashimoto's thyroiditis (HT) is one of the most common chronic autoimmune diseases which is accompanied by lymphocytic infiltration. It shows elevating thyroid autoantibody levels at an early stage and progresses to thyroid dysfunction ultimately. Different effects exert on bone metabolism during different phases of HT. In this review, we summarized the mechanisms of the long-term effects of HT on bone and the relationship between thyroid autoimmunity and osteoimmunology. For patients with HT, the bone is affected not only by thyroid function and the value of TSH, but also by the setting of the autoimmune background. The autoimmune background implies a breakdown of the mechanisms that control self-reactive system, featuring abnormal immune activation and presence of autoantibodies. The etiology of thyroid autoimmunity and osteoimmunology is complex and involves a number of immune cells, cytokines and chemokines, which regulate the pathogenesis of HT and osteoporosis at the same time, and have potential to affect each other. In addition, vitamin D works as a potent immunomodulator to influence both thyroid immunity and osteoimmunology. We conclude that HT affects bone metabolism at least through endocrine and immune pathways.

Keywords Hashimoto's thyroiditis · Bone metabolism · Osteoimmunology · Autoimmune diseases

Abbreviations

HT	Hashimoto's thyroiditis	SLC	solute carriers
RANK	receptor activator of nuclear factor-kappaB	DIO1	type 1 iodothyronine deiodinase
RANKL	receptor activator of nuclear factor-kappaB ligand	DIO2	type 2 iodothyronine deiodinase
AIT	autoimmune thyroiditis	DIO3	type 3 iodothyronine deiodinase
TH	thyroid hormones	GWA	genome-wide association
TSH	thyroid stimulating hormone	HPT	hypothalamic-pituitary-thyroid
T4	thyroxine	TR	thyroid hormone nuclear receptor
T3	triiodothyronine	IGF-1	insulin-like growth factor-1
OATP	organic anion transporting polypeptide	OPG	osteoprotegerin
MCT	monocarboxylate transporter	LT4	levothyroxine
		NK	natural killer
		TgAb	antibodies against thyroglobulin
		TPOAb	antibodies against thyroid peroxidase
		CDC	complement-dependent cytotoxicity
		ADCC	antibody-dependent cell-mediated cytotoxicity
		FRAX	Fracture Risk Assessment Tool
		1,25(OH)2D1,25-dihydroxyvitamin D	
		VDR	vitamin D receptor
		IL	interleukin
		ST2	suppression of tumorigenicity 2 protein
		TNF- α	tumor necrosis factor- alpha
		IFN- γ	interferon-gamma

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L-SAT	lymphocytic- spontaneous autoimmune thyroiditis
TRAF6	tumor necrosis factor receptor associated factor 6
RUNX2	runt-related transcription factor 2
Se	selenium
SeNPs	Se nanoparticles
ALP	alkaline phosphatase

1 Introduction

In the bone homeostasis, osteoclasts act in concert with osteoblasts and osteocytes. Osteoclasts mediate bone resorption and osteoblasts mediate bone formation, playing predominant role in the maintenance of bone homeostasis[1]. Osteocytes, deriving from mature osteoblasts, regulate both osteoblast and osteoclast function. Bone marrow functions as a maturation site for mesenchymal stem cells that give rise to osteoblasts and monocyte/macrophage lineage that give rise to osteoclasts. It also contains resident cellular components that are not only involved in bone maintenance but also regulate hematopoiesis and immune responses[2]. B cells and T cells regulate the coupling activity of osteoblasts and osteoclasts, both of them express strong inhibitors or agonist to influence osteoclastogenesis[3]. With the discovery of receptor activator of nuclear factor-kappaB (RANK) ligand (RANKL), a molecule expressed on immune cells (particularly T cells) and a major differentiation factor for osteoclasts[4], people have gradually realized that osteoporosis is not only a metabolic disease but a disease closely related to immune system. In a sense, the difference between a tolerogenic and an immunogenic encounter with antigen relies on the differential upregulation of co-stimulatory pathways[5]. As a kind of co-stimulatory molecule[5], RANKL-mediated effects on osteoclasts are regulated by a series of immune receptors that are also important in host defenses and aggravation of inflammation[4]. This link helps to clarify why many autoimmune diseases characterized by excessive immunoglobulin production with enhanced bone loss and fracture risk[6]. Because the production of autoimmune immunoglobulin is a manifestation of the aberrant activation of co-stimulatory pathways. Science that studies the influence of the immune system on bone is known as “osteimmunology”, a term coined by Arron and Choi[7].

Chronic inflammation, such as rheumatoid arthritis and Crohn’s disease, has been widely reported to accelerate bone loss and increase fracture risks, suggesting that chronic immune activation is detrimental to bone[6]. And glucocorticoids, widely used as anti-inflammatory treatments, will aggravate the situation. Chronic lymphocytic thyroiditis,

also named Hashimoto’s thyroiditis (HT), is the classic type of autoimmune thyroiditis (AIT) and is one of the most common autoimmune diseases. Euthyroidism is critical for skeletal development and maintenance of bone homeostasis. The role of different thyroid statuses of HT and thyroid autoimmunity itself in the process of bone metabolism have been underestimated.

In this review, we summarized the mechanisms of action of thyroid hormones (THs), the long-term effects of HT on bone, and the relationship between thyroid autoimmunity and osteoimmunology. We speculate that it works in at least two ways: as an endocrine disease, HT influences bone remodeling through thyroid function or thyroid stimulating hormone (TSH) levels; as an immune dysregulated disease, HT affects bone metabolism by affecting osteoimmunology.

2 Materials and methods

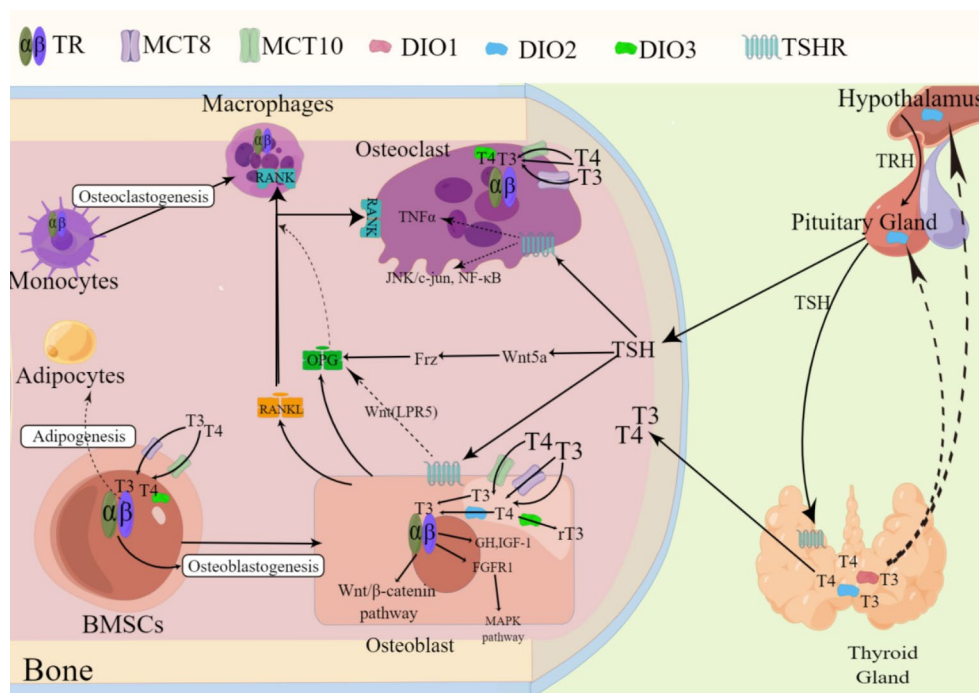
We performed a literature search for articles published until August 2022 in PubMed by using the search terms “bone metabolism”, “osteoporosis”, “bone mineral density”, “osteimmunology”, “fractures”, “Hashimoto’s thyroiditis”, “thyroid autoimmunity”, “thyroiditis”, “TPOAb” and “TgAb”. A total of 1213 articles were initially retrieved. Articles on various topics of the relationship between bone metabolism, osteoimmunology and thyroid function, thyroid autoimmunity were included. Articles that focus on secondary osteoporosis, thyroid dysfunction unrelated to Hashimoto’s thyroiditis, and articles that do not conform to the topic of this review will be excluded. Titles of interest were further reviewed by abstract. Two-hundred fourteen articles were finally included in this review.

3 Literature Review

3.1 The endocrine function of the thyroid and bone metabolism

It is known that with the stimulation of TSH, the thyroid gland synthesizes and secretes THs. THs are important hormones that play their function in bone metabolism. With the help of TH transporters, THs are effectively transported into cells, and thyroxine (T4) is then deiodinated to the biologically active form of TH, triiodothyronine (T3). T3 interacts with thyroid hormone nuclear receptors (TRs) to exert its biological effects mainly through genomic action, thereby activating the downstream signaling pathways. In addition, TSH may have direct effect on bone. Any abnormality in this process may affect bone metabolism (Fig. 1; Table 1).

Fig. 1 The role of thyroid hormone and TSH on bone. By Figdraw



Thyroid dysfunction will also lead to bone metabolism disorders.

3.1.1 Thyroid hormones and bone metabolism

3.1.1.1 Thyroid hormone transporters As a kind of fat-soluble molecule, THs can enter cells directly or via TH transporters, proteins facilitating the cellular importation of THs. They include members of the polyspecific organic anion transporting polypeptide (OATP) family, the monocarboxylate transporter (MCT) family and the solute carriers (SLC) family [8]. The important and efficient thyroid hormone transporters are: MCT8, MCT10, OATP1C1, and SLC17A4 [9]. However, the roles of MCT8 and MCT10 with regards to bone biology have been investigated more deeply. TH transporters affect bone by regulating local TH concentrations and may also have unique effects on bone. In a mouse model, MCT8 mRNA was expressed in chondrocytes, osteoblasts and osteoclasts at all stages of cell differentiation [10]. Global *Mct8*-knockout (*Mct8*-KO) mice were reported to demonstrate lower trabecular bone loss [11]. *In vivo*, conditional *Mct8*-KO in osteoblast and osteoclast progenitors resulted in trabecular bone gain in 12-week mice [11]. In addition, conditional *Mct8*-KO mice of different ages exhibited different skeletal phenotypes. For example, *Mct8* deficiency in osteoclast precursors led to spine trabecular bone gain in 6-week mice but led to femur and vertebra trabecular bone loss in 12-week mice [8]. However, *in vitro* studies of osteoblasts showed no significant changes in osteogenic marker gene expression and mineralization

capacity. Therefore, the role of MCT8 in the process of bone metabolism needs more researches. Besides, there might be compensatory factors that could help to import THs. MCT10, another protein that functions as a TH transporter [12], was shown to be another site- and age-dependent regulator of bone mass and turnover [13]. The exact effects of TH transporters on bone need to be investigated in greater detail in future studies.

3.1.1.2 Deiodinases THs mainly refer to T3 and T4. Genomic actions of TH are mediated in the nucleus by T3, and non-genomic actions are mediated by T4 or T3 at the cell membrane or cytoplasm [14]. Deiodinases, kinds of selenoenzymes, regulate TH concentrations in different tissues. Type 1 iodothyronine deiodinase (DIO1) and type 2 iodothyronine deiodinase (DIO2) both function by converting T4 to T3 and removing iodine from the 5' position or outer ring, while type 3 iodothyronine deiodinase (DIO3) removes iodine from the inner ring of T4 and T3, thus resulting in T3 inactivation [15]. Studies found that *Dio1* mRNA and its enzyme activity were both undetectable in primary chondrocytes, osteoblasts and osteoclasts [10], as well as in cell lines [16], indicating that DIO1 has an insignificant physiological role in bone. A study reported that DIO1 deficiency contributes to excess TH-induced differences in peak bone mass accrual between DIO1-deficient mice and normal C57BL/6J mice, indicating that DIO1 assumes an indirect but relevant role in bone mass when systemic homeostasis is challenged by excess THs [17]. DIO2 activity was only present in mature osteoblasts [10]. Bones from adult *Dio2*-KO mice are brittle and exhibit a 50% reduction

Table 1 Skeletal phenotypes in gene deficient mice

Year/ Researchers	Gene name	Gene function	gene mutations	Outcome
2020–2022/ Lademann, F.et al.[8] and [11]	<i>Mct8</i>	Thyroid hormones cellular import	Global <i>Mct8</i> -KO mice (<i>in vivo</i>) conditional <i>Mct8</i> -KO in OB or OC progenitors (<i>in vivo</i>) conditional <i>Mct8</i> -KO in late OB or osteocytes (<i>In vitro</i>) <i>Mct8</i> -KO OB	T3 ↑1.7-fold; osteoblast ↑45%, osteoclast ↑41% ; trabecular bone loss ↓28%; cortical BMD ↑. OB progenitors: (6w) osteoblast↑, spine trabecular bone mass↑; 24w and 6w mice skeletal differences -; OC progenitors:(6w) spine trabecular bone mass↑; 24w mice: femur and vertebra trabecular bone mass↓. 6w mice: spine and femur trabecular bone volume↓; 24w mice: -. Osteogenic marker-, mineralization capacity -.
2019/ Zaitune, C. R.et al.[17]	<i>Dio1</i>	Thyroid hormone activity conversion	C3H/HeJ mice ^a (deficient of DIO1)	A gross euthyroid TH deficiency: BMD accrual↓, bone strength↓ TH excess: less deleterious to BMD accrual, bone strength↓.
2010/ Bassett, J. H.et al.[18]	<i>Dio2</i>	Thyroid hormone activity conversion	Global <i>Dio2</i> -KO mice	Bone formation ↓50%; skeletal mineralization↑
2011/ Monfoulet, L. E.et al.[30]	<i>Thra</i> <i>Thrb</i>	subunit of thyroid hormone receptor subunit of thyroid hormone receptor	TRα-deficient mice TRβ-deficient mice	In hyperthyroxinemic than in hypothyroxinemic status, (3w) trabecular bone volume ↓35% In hyperthyroxinemic than in hypothyroxinemic status, (3w) trabecular bone volume -; (5w) trabecular bone volume ↓33%
2007/ Bassett, J. H.et al.[29]	<i>Thra</i> <i>Thrb</i>		TRα(0/0) mice TRβ -/- mice	Adults: Osteosclerosis, osteoclastic bone resorption↓; Juveniles: Delayed endochondral ossification, bone mineral deposition↓ Adults: Osteoporotic, bone resorption↑; Juveniles: Ossification, bone mineral deposition↑
2012/ O'Shea, P. J.et al.[33]	<i>Thrb</i>		(<i>in vivo</i>) <i>Thrb</i> ^{PV/PV} mice (<i>in vitro</i>) in <i>Thrb</i> ^{PV/PV} OB	Wnt pathway↑ Canonical Wnt signaling↑; T3 ↓Wnt signaling
2008/ Bassett, J. H.et al.[61]	<i>Tshr</i>	Thyroid stimulating hormone receptor	Pax8 -/- mice ^b Hyt/hyt mice ^c	TSH ↑1900-fold, normal TSHR, undetectable T4 and T3; Delayed growth and ossification; chondrocyte differentiation↓, cortical bone↓, trabecular remodeling↓, bone mineralization↓ TSH ↑2300-fold, a nonfunctional TSHR, T4 ↓95%
2012/ Baliram, R.et al.[49]	<i>Tshr</i>		<i>Tshr</i> -/- mice	Hyperthyroid <i>Tshr</i> -/- mice, areal BMD↓, degeneration of bone microstructure
2017/ Lindsey, R. C.et al.[34]	<i>Tshr</i> <i>Thrb</i>		<i>Tshr</i> -/- mice TH receptor β-specific agonist GC-1	Marrow adiposity ↑>20%, T3/T4 rescued this phenotype; T3/T4 ↑browning-specific markers in white fat Bone marrow-derived adipocytes↓ in <i>Tshr</i> -/- mice; expression of several brown/beige fat markers↑.

a: C3H/HeJ mice are deficient of DIO1. b: Pax8 -/- mice lack a transcription factor essential for thyroid development. c: Hyt/hyt mice harbor a TSHR loss-of-function mutation. ↑: Increase. ↓:Decrease. -: No significant differences were observed

in bone formation and a generalized increase in mineralization, uncovering an essential role for DIO2 in osteoblasts in the optimization of bone strength and mineralization[18]. In addition, DIO2 also played a role in the perichondrium during early skeletal development, and the degradation of DIO2 promoted growth plate chondrocyte differentiation[19]. Adult mice lacking the *Dio2* have increased subchondral bone but normal articular cartilage[20]. A cohort study enrolling 6,022 participants found that the *DIO2* Thr92Ala polymorphism was associated with decreased bone mineral density in tibial in female subjects[21]. However, a

genome-wide association (GWA) meta-analysis including 27,061 subjects found no association between *DIO2* and bone mineral density or fractures[22]. One study sequenced the critical exons of *DIO2* in subjects with relevant high BMD, indicating that *DIO2* mutations are unlikely to be a common cause of increased BMD in euthyroid postmenopausal women[23]. DIO3 activity was detectable throughout chondrocyte, osteoblast and osteoclast differentiation in primary cell cultures[10], suggesting that DIO3-mediated regulation of TH activity plays an important role during

skeletal development. In fact, the effect of deiodinase on bone still acquires further study.

3.1.1.3 Thyroid hormone nuclear receptors It is known that the hypothalamic-pituitary-thyroid (HPT) axis is involved in bone remodeling[24]. T3 action is mediated by TRs, which activate T3 target gene transcription. TRs are composed of two subunits, TR α and TR β , encoded by *Thra* and *Thrb* respectively, and each subunit has subtypes. TR α and TR β are expressed to varying degrees in almost all tissues. TR α 1, TR α 2, and TR β 1 are expressed in osteoblasts, osteoclasts, and chondrocytes [25, 26]. TRs are also expressed in skeletal mast cells, and their localizations are not affected by changes in thyroid status, suggesting that disrupted endochondral ossification in hypothyroidism may be mediated in part by skeletal mast cells[27] for their ability to synthesize and store matrix-degrading enzymes. Previous studies have suggested that TR β is mainly expressed in the pituitary and hypothalamus to negatively regulate the HPT axis. In the skeleton, TR α is expressed at higher levels than TR β and mediates T3 action on bone and cartilage[28]. Analysis of T3 target gene expression revealed skeletal hypothyroidism in TR α (0/0) mice but skeletal thyrotoxicosis in TR β -/- mice[29], demonstrating that bone loss in thyrotoxicosis was mediated mainly by TR α . Further research confirmed that TR β mediated the effects of transient TH concentration changes on bone remodeling, whereas TR α mediated the long-term effects of chronic changes in TH metabolism[30]. When a point mutation of the *Thra* allele was introduced to weaken its function, severely delayed skeletal development and high adult bone mass were shown, whereas point mutations in the *Thrb* gene showed accelerated bone formation and mineralization followed by rapid bone loss[31]. The PV mutation is an insertion mutation of the *Thrb* gene resulting in TR β dysfunction. Homozygous *Thrb*^{PV/PV} mutant mice had elevated circulating TH levels and accelerated skeletal development[32]. A microarray study found elevated activity of the canonical Wnt/ β -catenin pathway in the skeleton of *Thrb*^{PV/PV} mice *in vivo* and in *Thrb*^{PV/PV} osteoblasts *in vitro*, while T3 inhibited the Wnt pathway by facilitating proteasomal degradation of β -catenin and preventing its accumulation in the nucleus[33]. This finding demonstrated that Wnt signaling pathways were involved in the T3-mediated regulation of bone formation. In addition, the TR β -specific agonist GC-1 not only helped to reduce the number of bone marrow-derived adipocytes in *Tshr*^{-/-} mice but also increased the expression of several brown/beige fat markers in bone marrow mesenchymal stromal or mouse marrow stromal ST2 cells, indicating that TH regulation of marrow adiposity was mediated at least in part via activation of TR β signaling[34].

3.1.1.4 Thyroid hormone The skeleton is an important TH-targeted tissue. THs play important roles in linear growth

and skeletal maturation and enhance the response to growth hormone and insulin-like growth factor-1 (IGF-1)[35]. In addition, T3 induces FGFR1 expression and FGF-induced MAPK signaling in osteoblasts[36]. For children, severe untreated hypothyroidism leads to delayed skeletal development, defective endochondral ossification, and short stature[1]. Timely diagnosis and TH replacement therapy helped to reverse the situation. For adults, THs are key regulators of bone health; the excess caused high bone turnover-mediated bone loss with a shortened remodeling time[26], and the deficiency caused low bone turnover-mediated bone loss for reduced osteoclastic bone resorption together with decreased osteoblastic activity[1]. Meanwhile, T3 promotes the differentiation and activation of osteoclasts directly[37] or indirectly by acting on osteoblasts[38]. Some researchers hold that the action of T3 on osteoclastic bone resorption is mediated predominantly by osteoblast-derived osteotropic cytokines[39]. Thyroid homeostasis is critical for the maintenance of bone homeostasis.

3.1.2 TSH and bone metabolism

Currently, the role of TSH itself in bone homeostasis has been debated. There is growing evidence showing that TSH has physiologically relevant effects on bone or bone cells and may exert a direct protective effect against osteoporosis (Fig. 1; Table 1). In euthyroid postmenopausal Greek women, higher TSH levels were associated with a lower risk of vertebral fracture[40]. TSH in the low-normal range correlated with a high incidence of vertebral[41], hip[42], spine, forearm, and humerus fractures[43]. Similarly, the results of the OPENTHYRO cohort showed a relevance between the risk of fractures and decreasing levels of TSH in euthyroid people[43]. By using genetic biobank data, genetically raised serum TSH concentrations were noticed to causally associated with decreased bone fracture risk in men [44]. Another study found that TSH levels were positively correlated with BMD in men with normal thyroid function[45]. In addition, TSH was positively correlated with osteoprotegerin (OPG), indicating that the level of OPG was directly affected by TSH[46]. However, a study including 993 euthyroid postmenopausal females and 968 euthyroid males found no association between TSH and BMD[47].

Therefore, further researches are needed to determine the role of TSH in bone. Compared with ovariectomized controls, intermittent injection of TSH significantly improved BMD in ovariectomized rats or mice[48]. Baliram et al. found greater bone loss and resorption in *Tshr*-KO hyperthyroid mice than in wild-type hyperthyroid mice, demonstrating that the absence of TSH signaling contributed to bone loss[49]. In *ex vivo* cultures of bone marrow-derived

osteoclast precursors, the inhibitory action of TSH on osteoclasts lasted more than 4 weeks after the cessation of TSH exposure, manifesting as reduced expression of key genes for osteoclastogenesis[48]. TSH inhibits osteoclast formation and survival by attenuating JNK/c-jun and NF κ B signaling triggered in response to RANK-L and tumor necrosis factor-alpha (TNF- α)[50]. TSH also directly inhibited TNF- α production and reduced the number of TNF- α -producing osteoclast precursors[51]. In the process of osteoblast differentiation, TSH stimulates osteoblast differentiation[45], primarily through the activation of protein kinase C δ and the upregulation of the noncanonical Wnt components frizzled and Wnt5a[52]. Further investigations showed that the presence of a macrophage-derived TSH- β splice variant (TSH- β v) exerted an osteoprotective effect by inducing osteoblastogenesis[53]. However, some researchers have suggested that TSH also inhibits osteoblast differentiation and type 1 collagen expression in a runt-related transcription factor 2 (RUNX2) and osterix independent manner by downregulating Wnt (LRP-5) and VEGF (Flk) signaling[50]. The exact mechanisms of action need further investigation. In addition, small molecules have received increasing attention as therapeutic options for modulating TSHR signaling. It has been reported that signal activation mediated by the small molecule β -arrestin-1 is involved in the TSH-induced enhancement of osteoblast differentiation[54].

3.1.3 Thyroid function status and bone metabolism

Some patients with HT have euthyroid function. Others present as subclinical or overt hypothyroidism, with a low progression of subclinical to overt hypothyroidism occurring at an average rate of 5% per year. In addition, few HT patients have concurrent hyperthyroidism at the same time, named “Hashitoxicosis”. Hashitoxicosis is the hyperthyroid phase of HT, caused by the destruction of thyroid follicles for thyroid inflammation[55], usually followed by a euthyroid or hypothyroid state[56], and it resolves in a few weeks to months[57]. Therefore, HT patients may have an effect on bone for various thyroid function statuses.

HT was the most common cause of hypothyroidism in the USA[58]. In addition to the autoimmune condition of HT, hypothyroidism also affects the bone. For patients with overt hypothyroidism, the duration of bone resorption was twofold longer, and the duration of bone formation and subsequent bone mineralization was fourfold longer[59]. From this perspective, hypothyroidism has the ability to boost bone mass and bone stiffness. However, with the increase in bone stiffness, the risk of fractures also increases[35]. A nationwide follow-up study in 16,249 patients demonstrated that fracture risk increased in hypothyroidism patients[60].

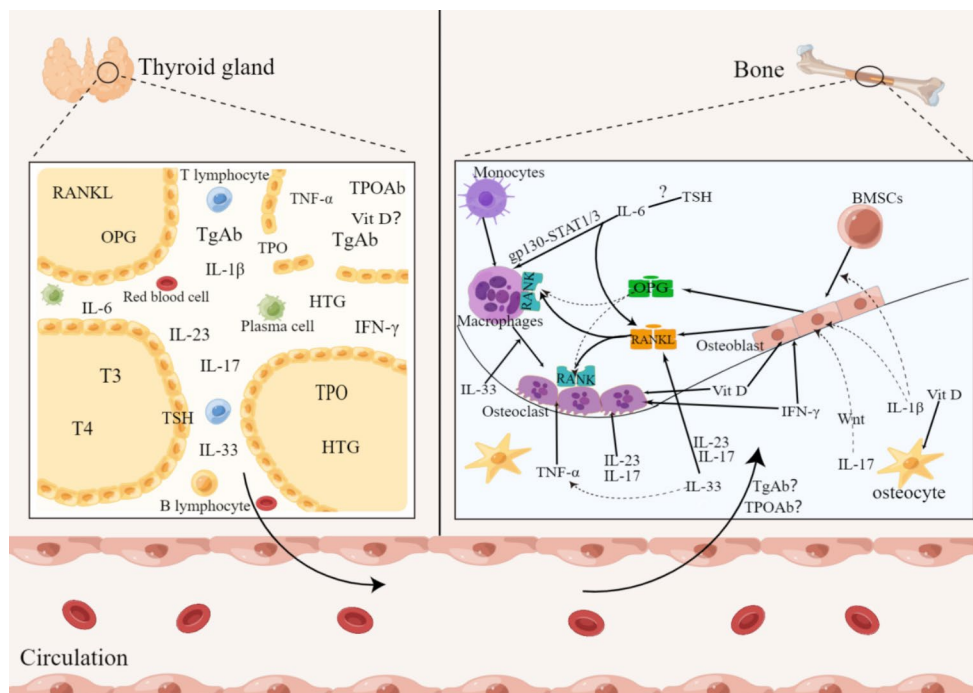
In addition, a study using mice carrying mutations showed that THs lacking rather than excess thyrotropin may cause abnormal skeletal development in hypothyroidism[61]. Whether hypothyroidism leads to osteoporosis remains controversial. Bone microarchitecture in women with hypothyroid HT did not differ considerably from healthy control subjects[62]. Hypothyroidism in premenopausal females was reported to have no influence on bone density[63]. For subclinical hypothyroidism, there is no consensus on its role in osteoporosis. A meta-analysis found no association between subclinical hypothyroidism and fracture risk[64]. However, some researchers noticed that subclinical hypothyroidism appeared to decrease serum calcium and low bone density[65]. Postmenopausal women with subclinical hypothyroidism tended to have a higher risk for low-trauma hip fracture[66] and a lower heel quantitative ultrasound[67].

At present, there is a consensus that patients with thyrotoxicosis tend to have a higher risk of osteoporosis and fracture, with high bone turnover and shortened bone remodeling. The uncoupling of osteoclast and osteoblast activities results in a 10% loss of bone per remodeling cycle[68]. Subclinical hyperthyroidism is commonly seen in patients undergoing TSH suppression therapy with levothyroxine (LT4) after thyroid tumor surgery. Previous studies have suggested that long-term LT4 therapy and decreased TSH levels usually have negative effects on bone metabolism and bone mass[69, 70]. However, a cross-sectional study suggests that long-standing suppressive therapy with LT4 may have no significant adverse effects on bone mineral density or microarchitecture[71]. A meta-analysis suggested that for patients with differentiated thyroid cancer, TSH suppression therapy was associated with lower BMD of the spine and total hip in postmenopausal women but not in premenopausal women and men[72]. Similarly, evidence from observational studies suggests that postmenopausal women treated with TSH suppression therapy are at risk for lower BMD[73]. Therefore, more researches are required to figure out the relationship between thyroid status and bone, and whether the status of HT will aggravate the influence.

3.2 HT patients' thyroid autoimmunity and bone metabolism

Current studies indicate that for patients with HT, the bone is affected not only by thyroid function but also by the setting of the autoimmune background. HT patients could develop thyroid dysfunctions, such as hyperthyroidism and hypothyroidism, that will lead to the disturbance of bone homeostasis. Meanwhile, abnormal immune activation in HT patients will also affect bone metabolism. Autoimmune diseases are a heterogeneous group of diseases characterized by inflammatory responses directed against self-tissues

Fig. 2 Thyroid autoimmunity could interact with bone through these molecules. By Figdraw



by the activation of abnormal immune cells[74]. Based on the main mechanisms and cell types involved in the pathogenesis, they can generally be characterized as antibody-mediated humoral immunity and T lymphocyte-mediated cellular immunity[75]. Immune cells are capable of producing various cytokines and interacting with other cells, further regulating and aggravating immune disorders. The destruction of thyroid cells in autoimmune thyroid disease (AITD) involves different mechanisms, including autoreactive T-lymphocytes, natural killer (NK) cells, and cytokines[75]. HT is a typical T-cell-mediated disease with severe parenchymal inflammatory infiltrates[76]. Antibodies against thyroglobulin (TgAb) and antibodies against thyroid peroxidase (TPOAb) are produced. In HT, the cytokines IL-1 β , IL-17, and IL-23 are the key players[77]. Thyroid autoimmunity interacts with bone through these molecules (Fig. 2; Table 1). The pathophysiological mechanisms between thyroid autoimmunity and bone metabolism have not been well ascertained, and they might involve multiple factors.

3.2.1 Thyroid autoantibodies

The presence of thyroid autoantibodies is one of the main characteristics of HT. A positive thyroid autoantibody test with a normal thyroid function often indicates an early-stage of HT. At this stage, abnormal autoimmune status is sufficient to affect bone homeostasis. TPOAb induces cell death through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) to attack thyroid tissues, accompanied by a changed immune

microenvironment. Thyroid autoantibodies may have direct effects on bone function with unclear mechanisms. For euthyroid patients with HT, the BMD values of the lumbar spine and femoral neck were lower than those without HT, and the longer the course of HT, the higher the prevalence of osteoporosis[78]. The presence of TPOAb was associated with decreased BMD at both the spine and hip in euthyroid postmenopausal women[79]. Lambrinouadaki et al. reported that positivity for TgAb and TPOAb was associated with the risk of vertebral fractures in postmenopausal women. TSH and TgAb both independently help to predict the presence of vertebral fractures[40]. Polovina et al. found that the presence of TPOAb was associated with a higher Fracture Risk Assessment Tool (FRAX) score in postmenopausal women[66]. It is known that FRAX score is used to quantify a patient's 10-year probability of a hip or major osteoporotic fracture, which is applicable to both postmenopausal women and men aged 40 to 90 years[80]. As HT is also one of the most common disease affecting middle-aged and elderly population. It is unknown whether the positivity of TPOAb should be added and what proportion they should occupy in the FRAX score. In addition, For patients with subclinical hypothyroidism, TSH was a better indicator for future fragility fractures than TPOAb[79]. The effect of thyroid hormone on bone homeostasis is more prominent than that of immune activation, when HT patients developed thyroid dysfunction.

3.2.2 Vitamin D and HT

The classical role of vitamin D is in the regulation of calcium and phosphate metabolism and bone mineralization[81]. It was reported that 1,25-dihydroxyvitamin D (1,25(OH)2D) induces the transcriptional activity of the vitamin D receptor (VDR) to increase calcium absorption in the intestine and calcium reabsorption in the kidney. VDR is expressed in osteoblasts, and 1,25(OH)2D modifies the gene expression of various osteoblast differentiation- and mineralization-related genes[82]. 1,25(OH)2D also plays important roles in the formation of osteoclasts through its actions on osteoblastic cells[83]. In recent years, the “noncalcemic” effect of vitamin D has drawn attention. It has been regarded as a potent immunomodulator. Some immune cells, such as B cells, T cells, and antigen-presenting cells, express 1-hydroxylase (CYP27B1) in cells and have the ability to generate the active compound vitamin D, exerting immunomodulatory effects[84]. According to the study of Hosseinezhad et al., supplementation with vitamin D was closely related to the expression of genes involved in the regulation of more than 160 pathways linked to autoimmune disorders, cancers and cardiovascular diseases[85]. Chronic inflammatory diseases may lead to the deactivation of the VDR[86].

There is growing evidence showing that vitamin D may participate in the pathogenesis of HT. Vitamin D supplementation can be helpful for alleviating disease activity in HT patients[87, 88]. A recent study indicated that vitamin D deficiency or insufficiency can increase the rate of autoimmune diseases such as HT[89]. After vitamin D treatment, TPOAb titers significantly reduced without a change in thyroid function[90]. It could also change the balance of CD4+T-cell subsets to improve disease control[91]. Therefore, some researchers held that vitamin D supplementation was advisable because it could not only correct vitamin deficiencies but also potentially improve autoimmune status[92].

However, the relationship between vitamin D and HT is still a controversial issue. Some studies found that lymphocytic thyroiditis was associated with neither vitamin D deficiency nor vitamin D levels[93, 94]. A study based on a Caucasian Polish population suggested that vitamin D receptor gene polymorphisms were not a major susceptibility factor for AIT development[95]. However, a study based in India found that vitamin D levels were low in AITD patients and vitamin D supplementation in HT patients increased thyroid autoantibody titers, reduced serum TSH levels, and increased free T4 levels[96]. In fact, the effect of vitamin D on thyroid function is also controversial. Some studies reported that Vitamin D treatment may not influence thyroid functions[90, 97]. But other studies reported it may be beneficial to thyroid function, especially during

pregnancy and postpartum[98, 99]. Therefore, there is a need for large double-blind clinical trials to investigate the effects of vitamin D supplementation on HT.

3.2.3 RANK/RANKL/OPG axis and HT

It is well known that RANKL and OPG are produced by a variety of tissues, including epithelial and mesenchymal cells, and play important roles in bone metabolism and immune responses. RANKL secreted by osteoblast lineage cells (osteoblasts and osteocytes) binds to its receptor RANK on the cell membrane of osteoclast progenitors, promoting subsequent osteoclast activation[100]. Osteoblasts secrete OPG, blocking RANKL/RANK signaling by acting as a decoy receptor.

Existing studies have shown that, not only in the bone, the RANK/RANKL/OPG axis also functions in the thyroid gland. Studies found that RANKL and OPG were produced by thyroid follicular cells, regulated by cytokines and TSH, and capable of modulating dendritic cell functions, indicating that immunoregulatory factors were involved in the pathogenesis of autoimmune thyroid diseases[101]. At the cellular level, pronounced OPG mRNA levels in normal human thyroid were noticed, while RANKL mRNA levels were low[101]. OPG mRNA expression was upregulated and RANKL mRNA was inhibited by TSH stimulation[101]. Patients with hypothyroidism had higher serum levels of OPG, and the correction of thyroid status led to a decrease in OPG[102], which might be related to endothelial dysfunction[103]. A study found that RANKL levels were lower and OPG levels were higher in premenopausal women with AIT than in nonthyroiditis controls[46], indicating that thyroid autoimmunity may regulate the level of RANKL/OPG. However, a study reported no correlation between OPG and RANKL in patients with a history of thyroid diseases[104], and another study did not observe a significant increase in OPG or RANKL levels after recombinant human TSH administration[105]. Therefore, further studies are needed to clarify the actions and mechanisms behind thyroid autoimmunity in the RANK/RANKL/OPG axis and to determine whether the change results in alterations of osteoimmunology.

3.2.4 Cytokines

Osteoporosis has been considered a chronic immune-mediated inflammatory disease with the discovery of the RANK/RANKL/OPG axis engaging in bone homeostasis[106]. The etiology of thyroid autoimmunity and osteoimmunology is complex and involves a number of immune cells, cytokines, and chemokines. T lymphocytes and their secreted cytokines play vital roles in modulating the immune response.

The same cytokines may affect and connect different tissues and organs. Proinflammatory cytokines might be primary mediators of accelerated bone loss in postmenopausal osteoporosis[107].

IL-6: Interleukin (IL)-6 is involved in the pathogenesis of osteoporosis, which is characterized by a negative balance between bone resorption and formation[108]. In ovariectomized mice, IL-6 appears to be crucial in bone turnover acceleration[109]. It increases RANKL mRNA expression and inhibits bone formation[101]. IL-6 may exert its inhibitory effect on bone formation directly through gp130-STAT 1/3 signaling[110] or indirectly by influencing the balance between the RANKL/RANK/OPG pathway[111]. In addition, IL-6 suppressed the differentiation of osteoclast precursors into osteoclasts by inducing chondrocytic PGE(2) production[112]. A study found a positive correlation between IL-6 and RANKL and a negative correlation between IL-6 and TSH[46]. When the status of thyroid function changes or thyroid autoimmunity occurs, cytokine levels altered. For example, hyperthyroidism leads to increased levels of IL-1 and IL-6, which are vital for bone resorption. It also plays a role in mediating the bone loss that results from excess THs[113].

IL-17: Recent studies on thyroiditis have focused on the imbalance between Th17 and Treg cells. Treg cells suppress immune responses. Th17 cells are a newly discovered lineage of effector CD4+ T cells that are different from Th1 and Th2 cells[114]. Th17 cells are necessary for the removal of extracellular bacteria and play an essential role in the pathogenesis of AITD[115]. The combination of IL-17 and IL-17 A motivates MAPK signaling, recruits macrophages and neutrophils, and results in proliferation of T cells and inflammation of the thyroid[116]. For patients with HT, significantly elevated levels of TH17 cells and IL-17 A were noticed in both the peripheral blood and thyroid tissues[114, 116–118]. The reciprocal role of Th17 cells and Treg cells is involved in the pathogenesis of osteoporosis in ovariectomized mouse models[119]. Th17 cells promote osteoclastogenesis, while Treg cells exhibit anti-osteoclastogenic activity[119]. In experimental periodontitis, Th17 cells and the level of IL-17 were pathogenic drivers of inflammatory bone loss[120]. Increased Th17 cells and IL-17 levels are associated with low BMD in postmenopausal women[119]. However, the function of IL-17 on osteoblasts is controversial. Some studies have reported that IL-17 inhibited osteoblast differentiation and bone regeneration in rats[[121, 122]. Another study reported that IL-17 stimulated osteoblast differentiation and osteoblast-dependent osteoclastogenesis *in vitro*[123]. Since AIT accompanies elevated serum IL-17, whether this change is involved in the pathogenesis of osteoporosis has not been explored. Similar to chronic skin inflammation leading to bone loss by IL-17-mediated

inhibition of Wnt signaling in osteoblasts[124], there could also be a connection between AIT and osteoporosis.

IL-23: IL-23 is known to stimulate the development of Th17 cells and the production of IL-17, to obtain a pathogenic and sustained phenotype[125]. The IL-23/IL-17 axis plays a role in the pathogenesis of HT[77, 114, 126]. The data of Gerenova et al. showed that the significance of IL-23 was more pronounced than that of IL-17 in HT development and severity[114]. Furthermore, the IL-23/IL-17 axis also plays a role in the pathogenesis of inflammation and bone destruction[127]. In mice, systemic overexpression of IL-23 induced chronic arthritis and increased osteoclast differentiation and systemic bone loss[128]. According to Priyanka Shukla et al., the efficacy of anti-IL-23 therapy supported bone protective effects[127]. IL-23 directly mediates bone loss by augmenting osteoclast activity and RANKL expression in T cells[129], and promotes osteoclastogenesis in an osteoblast-osteoclast coculture system[130]. However, Razawy et al. demonstrated that IL-23R-deficient mice had a temporary defect in their bone formation, which resulted in temporal effects on trabecular bone and long-term effects on cortical bone[131]. Kamiya et al. reported that IL-23 and IL-27, both partly and indirectly through activated T cells, inhibited osteoclastogenesis[132]. IL-23 may have different effects on bone in different situations. So what is the role of IL-23 in the contest of HT needs more exploration.

IL-33: Recently, the IL-33/suppression of tumorigenicity 2 protein (IL-33/ST2) pathway revealed its participation in the process of several autoimmune diseases. ST2 is the receptor of IL-33. Wang et al. found that the elevated mRNA expressions of plasma IL-33 and sST2 perpetuated chronic inflammation in HT[133]. However, the results of elevated IL-33 and sST2 in bone are still debatable. Mune et al. reported that IL-33 stimulated the formation of functional osteoclasts from human CD14(+) monocytes[134]. Malcolm et al. found that IL-33 exacerbated periodontal disease through the induction of RANKL, leading to bone loss in a RANKL-dependent manner[135]. However, Zaiss held that IL-33 shifted the balance from osteoclast to alternatively activated macrophage differentiation and protects against TNF- α -mediated bone loss[136]. Therefore, how abnormal levels of IL-33 caused by thyroid autoimmunity affect bone is inconclusive thus far.

IL-1 β : The IL-1 family is known to play a unique role in innate immunity. IL-1 α and IL-1 β are two individual forms of IL-1 which are isolated from two distinct cDNAs but are indistinguishable in terms of biological functions[137]. Previous studies have shown that IL-1 stimulates thyroid cell growth[138], inhibits the synthesis and release of THs[139], promotes the exposure of hidden autoantigens to the immune system[140], and inhibits the expression of thyroglobulin[141] and thyroid peroxidase[142].

IL-1 β is a potent proinflammatory cytokine involved in a variety of cellular activities, including cell apoptosis and the promotion of autoimmune diseases[143]. Upregulated tissue expression of IL-1 β was noticed in the thyroid, and it may be an active etiologic factor in the pathogenesis of HT[144]. IL-1 β contributes to autoimmune arthritis by inducing osteoclastogenic capacity in Tregs[145]. In the early stages of fracture healing, IL-1 β leads to impaired recruitment of osteoblasts[146]. In human periodontal ligament fibroblasts, IL-1 β inhibits BMP-9-induced osteoblastic differentiation[147]. However, the effect of IL-1 β on bone marrow mesenchymal stem cells is unclear[148, 149]. IL-1 β is involved in multiple processes of HT autoimmunity and bone loss caused by various chronic inflammatory diseases. In patients with HT, whether the abnormal expression of IL-1 β is involved in the process of osteoporosis needs further study.

TNF- α : TNF- α is known to be produced by thyroid-infiltrating CD4+ T cells and B cells[150]. The secretion of TNF- α by infiltrating T cells in the thyroid is higher than that in normal human lymph nodes, indicating that TNF- α could directly damage human thyroid follicular epithelial cells[151]. The ratio of TNF- α /IL-6 in HT patients was higher than that in healthy patients or those with Graves' disease[152]. TNF- α and transforming growth factor- β promoted hyperplasia and the proliferation of thyrocytes in IFN- γ -/-Non-Obese Diabetic.H-2h4, resulting in a chronic state of thyroid dysfunction and fibrosis[153]. Local and systemic production of cytokines, including TNF- α , IL-1, IL-6 and IL-17, functions to recruit osteoclast precursors into the bone microenvironment, which is suitable for differentiation into mature osteoclasts[154]. TNF- α -mediated bone destruction has been confirmed, especially in rheumatoid arthritis, and its therapeutic monoclonal antibodies have been widely used in the clinic. In addition, TNF- α directly inhibits osteoblast differentiation and bone nodule formation by suppressing the expression of positive regulators of bone development and growth[45]. TNF- α has a promoting effect on thyroid immunity and bone loss, so whether the increase in TNF- α caused by one disease will lead to the aggravation of another disease requires more research.

IFN- γ : Interferon-gamma (IFN- γ), another immunogenic cytokine, is involved in both innate and adaptive immune responses. It plays a role by activating macrophages, inducing antigen presentation, upregulating adhesion molecules, and recruiting Th1 cells to sites of inflammation, etc.[155]. A previous study showed that IFN- γ played a dual role in the development of lymphocytic-spontaneous autoimmune thyroiditis (L-SAT). It is required for the development of L-SAT, and it also functions to inhibit thyroid epithelial cell hyperplasia and proliferation[156, 157]In addition, IFN- γ mediates thyroid follicular cell apoptosis by upregulating

the expression of Fas in HT[158]. Coincidentally, it also has dual functions in bone. IFN- γ not only blunts osteoclast formation by directly influencing osteoclast precursors but also indirectly promotes osteoclast differentiation and bone resorption by stimulating antigen-dependent T-cell activation and T-cell secretion of the osteoclastogenic factors RANKL and TNF- α [159]. IFN- γ promotes the degradation of tumor necrosis factor receptor associated factor 6 (TRAF6) via the proteasome, leading to blocked activation of the downstream transcription factors NF- κ B and JNK of the RANK-RANKL signaling axis and ultimately leading to reduced osteoclastogenesis[160]. Interestingly, this inhibition of osteoclastogenesis could be rescued by overexpression of TRAF6 in precursor cells. In addition, IFN- γ increases the expression of osteoblast-related genes, including RUNX2, osterix, alkaline phosphatase, and osteocalcin[161]. In the condition of estrogen deficiency and chronic inflammation, the net effect of IFN- γ is that of stimulating bone resorption and bone loss[159]. IFN- γ has dual effects on the regulation of both thyroid immunity and bone metabolism. How IFN- γ regulates bone in the setting of chronic thyroid immune dysfunction is unclear.

In addition to the cytokines discussed above, there are many cytokines or small molecules involved in the pathogenesis of HT and osteoporosis at the same time, and potentially affect both diseases by interacting with each other, such as TNF- β , IL-10, IL-18, IL-34, IL-38, et al. However, it remains unclear whether changes in circulating immune complexes caused by HT have an impact on the development of osteoporosis.

3.3 Reduce the effects of HT on osteoporosis

HT is a slowly progressive chronic disease that affects bone differently at different disease stages. At the early stage, patients often maintain euthyroid status but have a disordered immune system, manifesting as abnormal levels of relevant cytokines or positivity for thyroid-related immunoglobulins. At this time, disturbance of the immune system caused by HT interacts with osteoimmunology, thereby affecting bone remodeling. As the disease progresses, when the aggravation of thyroid immune inflammation leads to thyroid dysfunction, patients gradually develop permanent hypothyroidism, while a few patients show a short stage of hyperthyroidism. At this time, HT affects patients through TSH and/or THs in addition to the immune system, which significantly exacerbates the impact on bone.

Therefore, different treatment regimens at different stages should be applied to reduce the impact of HT on bone. However, no effective treatment for immune abnormalities in the early stage of HT has been developed. Some studies have proven that selenium (Se) has an immunomodulatory effect.

For HT patients, Se supplementation was able to decrease TPOAb, TgAb, and TSH levels, increase glutathione peroxidase 3, increase activated Tregs[162], decrease INF- γ and increase IL-1 β [163], exerting a beneficial effect on thyroid autoantibodies and thyroid function by increasing antioxidant activity and upregulating activated Treg cells[162]. *In vitro* studies showed that Se nanoparticles (SeNPs) promoted osteoblast differentiation by modulating alkaline phosphatase (ALP) activity and promoting calcium nodule formation and collagen content[164]. *In vivo* studies have shown that SeNPs stimulate osteoblast differentiation via the BMP-2/MAPKs/ β -catenin pathway in diabetic osteoporosis[164]. In addition, inverse associations of Se levels with osteoporosis risk were observed[165]. Within the reference range, Se levels were positively correlated with BMD in healthy elderly men[166]. In euthyroid postmenopausal women, Se levels were inversely related to bone turnovers and positively correlated with BMD[167]. A study, based on population in the US, reported that higher Se status was correlated with lower FRAX scores and a lower incidence of previous bone fractures[168]. Therefore, Se supplement to patients in the early stage of HT may not only delay its progression but also may reduce the possibility of the occurrence and progression of osteoporosis. In addition, when HT patients develop abnormal thyroid function, it is particularly important to correct thyroid status.

4 Conclusion

Osteoporosis is not only a disease of bone-metabolic abnormalities, but also a disease featuring immune disorders. HT is the most common thyroid autoimmune disease and is also a common autoimmune disease. Immune changes caused by HT may be one of the factors that exacerbate osteoporosis. In this review, we summarized the mechanisms of the long-term effects of thyroid dysfunction on bone and the relationship between thyroid autoimmunity and osteoimmunology. We speculate that HT affects the occurrence and development of osteoporosis at least through endocrine and immune pathways. However, there are currently no drugs that can effectively modulate immunity in HT. Long-term thyroid function monitoring should be performed in patients with HT to avoid thyroid dysfunction promoting or exacerbating osteoporosis.

Declarations

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