



Thyroid Hormones and Skeletal Muscle Beyond Thermogenesis

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Abstract

Thyroid hormones are widely studied for their involvement in energy metabolism and thermogenesis. However, their role on muscle fibers and the structure and organelles of this tissue has yet to be reviewed. This mini-review aims to show the involvement of thyroid hormone signalings in the function of muscle fibers. Serum levels of thyroid hormones depend on the hypothalamic–pituitary–thyroid axis, which, in turn, acts depending on changes in homeostasis and the environment. In skeletal muscle, thyroxine (T4) and triiodothyronine (T3) participate in contractile function, metabolism, myogenesis, and regeneration. T3 regulates skeletal muscle gene expression through the interaction with the specific nuclear isoforms receptors for thyroid hormones: α (THRA) and β (THRB). In addition, T3 activates phosphoinositide 3-kinase (PI3K), which ultimately increases the transcription of hypoxia-inducible factor 1-alpha (HIF-1 α). They can bind to a membrane integrin, Alpha-5 beta-3 integrin ($\alpha v \beta 3$), and activate the PI3K and mitogen-activated protein kinase (MAPK) signal transduction pathways. T3 and T4 also increase Fibroblast Growth Factor 2 (FGF2) gene transcription. These initially nongenomic, nonclassical actions serve as additional interfaces for transcriptional regulation by thyroid hormones. In addition, di-iodine (T2), the thyroid hormone metabolite, has been shown to play a role in this process.

Keywords TSH · T3 · T4 · Myogenesis · Skeletal muscle

Introduction

Thyroid hormones play a key role in regulating metabolism. It is known that the hypothalamus releases thyrotropin (TRH) stimulates thyroid-stimulating hormone (TSH) secretion by the pituitary gland in response to peripheral and central stimuli. TSH will promote the release of triiodothyronine (T3) and thyroxine (T4) hormones from the thyroid gland. In a downregulation mechanism, these hormones can inhibit the production of TSH, and an impaired regulation will lead to functional disorders (hyper or hypofunction of the thyroid) [2]. The action of thyroid hormones on target tissues results from the interaction of T3, the active form of the hormone, with its nuclear receptor isoforms. T3 and T4 showed metabolic activity and release into the bloodstream,

differently from T1 (mono-iodine) and T2 (di-iodine) molecules. Thus, TSH becomes a good indicator in diagnosing alterations in the production of thyroid hormones since small changes in the concentrations of these hormones in their free form result in significant changes in serum TSH concentrations [2].

Thyroid hormones (T4 and T3) are widely studied for their involvement with energy metabolism and thermogenesis. However, its role in the structure and organelles of muscle fibers has yet to be reviewed. The signals from these hormones can affect thermogenesis, which regulates body temperature through brown adipose tissue (BAT) and in less active tissues. In addition, thyroid hormones have roles such as participating in contractile function, metabolism, myogenesis, and regeneration of skeletal muscle [25, 54, 60]. The hypothalamic–pituitary–thyroid axis activity might also stimulate serum levels of thyroid hormones, depending on homeostasis and the environment [51]. Blood concentrations of thyroid hormones and their tissue-specific concentrations in skeletal muscles depend on levels of transporters, receptors, and the activity of hormone converter enzymes [11]. Therefore, in this review, we aim to discuss the main effects of thyroid hormones on physiological processes of muscle.

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In addition to thermogenesis, this mini-review aims to show thyroid hormone signalings are involved in muscle fibers' functions.

Overview (Intracellular Signaling for T3 and T4)

The hormone T3 acts on the skeletal muscle by regulating gene expression via interacting with nuclear receptors for thyroid hormones α (THRA) and β (THRB). This interaction happens in specific promoter regions [51]. THR also act as ligand-independent transcription factors [52]. For example, the main isoform in skeletal muscle is THRA [25, 46].

The gene expression of thyroid hormones is more diverse than researchers believed. For instance, T3 activates phosphoinositide 3-kinase (PI3K) via the TRHA and TRHB, which ultimately increases the transcription of specific genes, e.g., hypoxia-inducible factor 1-alpha (HIF-1 α /HIFk-1 α). In addition, they can bind to a membrane integrin, Alpha-5 beta-3 integrin (α v β 3), and activate the PI3K and mitogen-activated protein kinase (MAPK) signal transduction pathways. T3 and T4 also increase gene transcription, e.g., of the Fibroblast Growth Factor 2 (FGF2) gene. Therefore, these initially nongenomic actions serve as additional interfaces for transcriptional regulation by thyroid hormones [47] (Fig. 1).

On the other hand, thyroid hormones also induce short-term effects independent of receptors on muscle fibers, for example, by regulating the activity of membrane proteins [19]. T4 stimulates the activity of Sodium Potassium Pump (Na⁺, K⁺-ATPase) in skeletal muscle, increases the transmembrane resting potential and thus the frequency of action potentials [7]. At the same time, T3 increases the pH

in rat L6 myoblasts via phospholipase C and mobilization of intracellular calcium ions [22]. T3 also modifies p38 and AMPK kinase activity, which is fundamental in the mitochondrial biogenesis of muscle fibers [37].

T3 and T4 cross the membrane by facilitated diffusion mediated by specific transporters. In skeletal muscle tissue, the primary transporters are the monocarboxylate transporters MCT10 and MCT8, which are found in both humans and rodents [26, 44], encoded by the solute carrier family 16 member 10 (*SCL16A10*) (localized on human chromosome 6, mapped to 6q21-q22) and solute carrier family 16 member 2 (*SLC16A2*) (chromosome Xq13.2) genes, respectively. Both transporters mediate uptake of T3, but MCT8 has more affinity to the sum of both hormones than the T4 transporter, whereas MCT10 presented less affinity at transporting T4 but is capable of aromatic amino acid uptake [34, 57].

In addition, the activity of iodothyronine deiodinases type 2 (D2) and iodothyronine deiodinases type 3 (D3) contributes to the control of intracellular levels of thyroid hormones. D2 converts T4 to T3, which increases the availability of T3 and its effects. However, D3 converts T4 into reverse T3 (rT3) and T3 into diiodothyronine (T2), decreasing the nuclear effects of T3 [9]. The balance between D2 and D3 activity in muscles alters the intramuscular levels of T3, affecting THR occupancy, even though the serum levels of T3 and T4 remain unchanged [3, 11].

D2 is constitutively expressed in rodents and human muscles. The activity is higher in muscles with a predominance of type I fibers than in muscles with a predominance of type II fibers [43, 64]. In humans, the modulation of D2 by changes in circulatory levels of T4 is controversial. Analysis of D2 and D3 expression in muscle biopsies

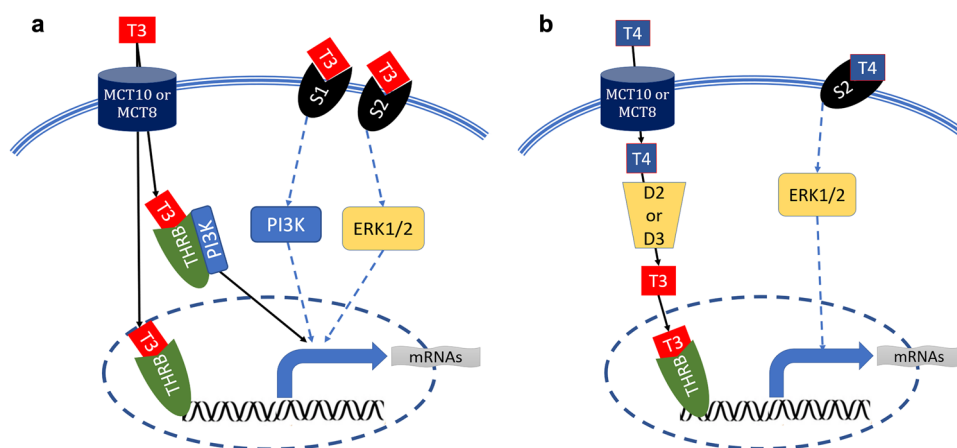


Fig. 1 Thyroid hormones (triiodothyronine or T3 (a) and thyroxine or T4 (b)) participate in contractile function, metabolism, myogenesis, and regeneration. Tissue-specific thyroid hormone concentrations in skeletal muscles depends on levels of transporters, receptors, and the activity of hormone converter enzymes. T3 triiodothyronine, T4

thyroxine, MCT8 monocarboxylate transporter 8, MCT10 monocarboxylate transporter 10, D2 Deiodinase type II, D3 Deiodinase type III, THRB receptors for thyroid hormones β , PI3K phosphoinositide 3-kinase, ERK1/2 extracellular signal-regulated kinase 1/2 cascade, S1 and S2 binding sites for thyroid hormones

of thyroidectomized patients before and after T4 therapy showed no differences in iodothyronine deiodinase 2 (DIO2) activity or iodothyronine deiodinase 3 (DIO3) mRNA expression [32, 64]. However, short-term fasting decreased circulating T3 and increased D2 activity in euthyroid muscles [64].

The functioning of muscle fibers (contraction and relaxation) depends on maintaining ionic gradients across cell membranes. Maintenance of gradients is accomplished by ATPases, constantly pumping ions against their concentration gradients. To achieve this, they use energy from the hydrolysis of adenosine triphosphate (ATP). Muscle contraction is triggered by an increase in sarcoplasmic Ca^{2+} concentration due to the opening of dihydropyridine receptors in the sarcoplasmic reticulum (SR), releasing Ca^{2+} into the sarcoplasm. Calcium ions bind to the troponin of the myofilaments, setting the myosin-actin cross-bridge cycle in motion, which subsequently activates the sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA). SERCA ensures that, under optimal coupling conditions, two Ca^{2+} ions are pumped back into the reticulum lumen at the expense of hydrolysis of an ATP molecule [62]. In skeletal muscle, the SERCA 1 isoform is expressed in type II muscle fibers. In contrast, type I muscle fibers express SERCA 1 and SERCA 2a [40]. Important regulators of SERCA activity are thyroid hormones and sarcolipin (SLN) [6].

Uncoupling protein 1 (UCP-1) plays an important role in Brown adipose tissue (BAT)-mediated thermogenesis by uncoupling oxidative phosphorylation and dissipating energy as heat [33]. Thyroid hormones mediate this mechanism. In skeletal muscle, Uncoupling protein 3 (UCP-3), a homolog of UCP-1, is primarily expressed and observed to play a role in metabolism and is also mediated by thyroid hormones [12, 63]. However, the mechanisms of UCP-3 were shown not to be analogous to UCP-1 in BAT. The main roles of UCP-3 in skeletal muscle are to prevent damage mediated by mitochondrial oxidative stress [12].

Thyroid hormones also play an essential role in myogenesis, a multistep process responsible for development, maintenance, and repair of adult myofibers [37]. Part of the process is activating satellite cells, their amplification, differentiation, and fusion to form new myofibers. Correct progression through these phases is orchestrated by myogenic regulatory factors (MRFs), such as myogenic transcription factor 5 (Myf5), myogenic transcription differentiation (MyoD) and Myogenin (MYOG). Several studies have shown that a finely tuned sequential expression of D3 and D2 is more important than plasma levels of T3 to customize the intracellular level of thyroid hormones in satellite cells during myogenic lineage phases [24, 25]. Satellite cells and C2C12 cells grown under proliferative conditions express high levels of D3 that decrease after differentiation. Genetic ablation of D3 from satellite cells increases the intracellular concentration

of T3 and induces massive apoptosis through activation of the transcription factor forkhead box O-3 (FoxO3) signaling pathway [24, 25].

D2 has an expression pattern opposite to D3. Dio2 expression increases during differentiation, similar to MyoD. Genetic ablation of Dio2 in these cells impairs myogenic differentiation, a phenotype that is reversed by culturing the cells in the presence of T3 [24].

Skeletal muscles depend on the thyroid hormone receptor alpha 1 (TRa1) for the actions of T3 and T4. Mice with loss of skeletal muscle-specific TRa1 function demonstrated the crucial role of TRa1 receptors in thyroid hormone-mediated skeletal muscle functions [49]. Skeletal muscle composition was altered for the oxidative phenotype (predominance of type I fibers).

3,5-Diiodo-L-thyronine (T2) is an endogenous derivative of thyroid hormones with influences on metabolism and thermogenesis, acting mainly at the mitochondrial level [58]. In skeletal muscle, T2 induces muscle phenotypic change (from type I to type II fibers) and increases AMPK phosphorylation associated with fatty acid oxidation; additionally, an increase in glucose transporters 4 (GLUT4) has been observed [39], increasing insulin-induced glucose uptake in muscle cells.

Hypothyroidism and Hyperthyroidism

Hypothyroidism is the reduced production of thyroid hormones. It manifests through various symptoms (e.g., tiredness, sensitivity to cold, weight gain, constipation, depression, slow movements, thoughts, muscle aches and weakness, and muscle cramps). Skeletal muscle is one of the affected organs, resulting in muscle weakness and cramps [15]. The cellular mechanisms of hypothyroidism-induced skeletal muscle weakness [65] are related to reduced autophagy in skeletal muscle and decreased mitophagy proteins and factors involved in mitochondrial biogenesis. There is also downregulation of genes related to lipid metabolism and changes in skeletal muscle fibers [65].

Hyperthyroidism is the opposite, with thyroid hormone levels above normal [59, 60]. Animal models have shown a link between hyperthyroidism and increased skeletal muscle thermogenesis. There was a 0.8-fold increase in SERCA activity in type I fibers. In contrast, there was a four-fold increase in type II fibers, suggesting that SERCA activity may contribute to heat generation in hyperthyroidism [5]. Furthermore, Meis et al. [45] found a significant increase in the SERCA 1 subtype in muscles with a predominance of type I fibers and a smaller increase in type II fibers, with muscles predominantly composed of type I fibers storing more Ca^{2+} and producing more heat. There was a 40-fold increase in heat production by SERCA in the muscle with

predominance of type I fibers in the hyperthyroid state of rabbits, mainly due to the expression of SERCA1 (Fig. 2).

Corroborating in humans, patients with hyperthyroidism suffer from skeletal muscle weakness, paralysis, cramps, and pain is referred to as thyrotoxic myopathy [20]. Muscle strength and cross-sectional area (the area of the cross-section of a muscle perpendicular to its fibers, generally at its largest point) were reduced in patients with hyperthyroidism. In contrast, muscle proteolysis was observed in women with hyperthyroidism [54]. Surprisingly, normalization of thyroid function in women with hyperthyroidism results in gains in fat mass without change in muscle mass [55].

Myogenesis

Skeletal muscle function depends on energy turnover, rates of contraction and relaxation, and tissue regeneration. Myogenesis must occur for skeletal muscles to grow and regenerate, which means the proliferation and differentiation of satellite cells. Satellite cells are between the basal lamina and the sarcolemma (muscle fiber membrane) of muscle fibers [16, 38]. The location of satellite cells, which are close to the blood vessels (muscle capillaries), allows them to receive extrinsic signals (from other organs and tissues) and intrinsic signals (produced by the muscle fibers themselves).

Both stimuli can modulate the proliferation and differentiation of progenitor cells [8, 37, 38]. In this way, they are also exposed to variations in T3 and T4 concentration in the bloodstream.

Myogenesis occurs in the intrauterine phase for the maturation of muscle tissues. It also happens during muscle strains and exercise-induced micro-injuries. It is a complex process that depends on extrinsic and intrinsic factors and an intracellular signaling pathway. Myogenesis is controlled by the expression of transcription factors [7, 29], such as the paired protein box 7 (Pax7), which regulates the expression of myogenic regulatory factors (MRF). MRFs are a family of myogenic transcription factors, mainly myogenic factor 5 (Myf5) and myogenic differentiation 1 (MyoD1) [8, 17, 53]. These two factors have redundant roles in myogenesis and induce the expression of myogenin (MYOG) and myogenic regulatory factor 4 (MRF4) by myoblasts [28]. MyoD1 and MYOG are involved in terminal myogenic differentiation and are stimulated to a greater or lesser extent by intracellular concentrations of T3 [14, 28]. The expression of MyoD1 after muscle breakdown or exercise-induced microdamage is similar between healthy and hypothyroid mice; however, satellite cells of hyperthyroid regenerative myoblasts express more MyoD1 compared to euthyroid cells [4] (Fig. 3). Intracellular levels of T3 are critical for myogenesis [3]. The D3 enzyme (converts T4 to reverse T3) is highly expressed

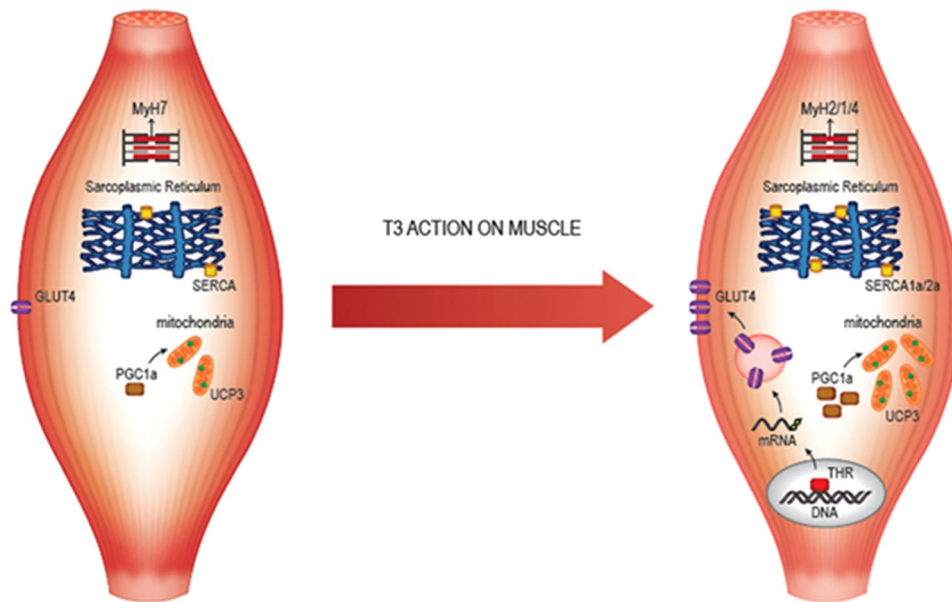
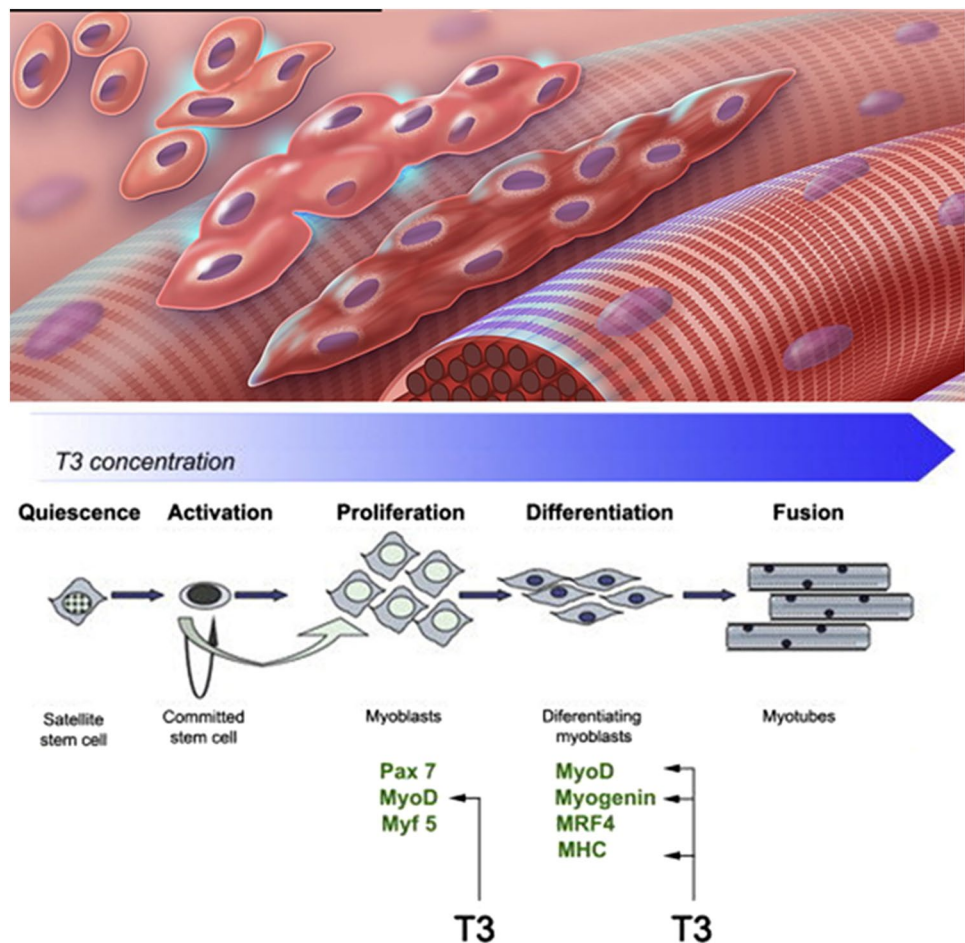


Fig. 2 Local conversion of T4 to T3 via D2 represses type I fibers but stimulates the rapid type II fibers. Thyroid hormones increase oxidative capacity due to increased mitochondrial content and protein activity. T3 stimulates UCP-3 expression that uncouples ATP synthesis (adapted from Bloise et al. [10]). *MyH7* myosin heavy chain 7 gene, *MyH2/1/4* myosin heavy chain types 2, 1, and 4 genes, *GLUT4*

glucose transporter 4 gene, *SERCA* sarcoplasmic reticulum Ca^{2+} -ATPase gene, *SERCA 1a/2a* sarcoplasmic reticulum Ca^{2+} -ATPase isoform expressed in muscle fibers gene, *PGC1a* peroxisome proliferator-activated receptor gamma coactivator 1-alpha gene, *UCP3* uncoupling protein 3 gene, *THR* receptors for thyroid hormones, *mRNA* messenger ribonucleic acid, *DNA* deoxyribonucleic acid

Fig. 3 Thyroid hormone levels and myogenesis of satellite cells. The T3/T4 hormones signal is essential for differentiation, while thyroid hormone downregulation is required to retain muscle progenitor cells in a proliferative phase. *T3* triiodothyronine, *Pax 7* paired box protein, *MyoD* myoblast determination protein 1, *Myf 5* Myogenic factor 5, *MRF4* myogenic regulator factor, *MHC* myosin heavy chain. ① Quiescence, ② Activation, ③ Proliferation, ④ Differentiation, and ⑤ Fusion



in activated and proliferating satellite cells; however, this enzyme is inhibited during myoblast differentiation [3, 24]. The reduction of D3 facilitates the expression of *FoxO3*, which is important in the self-renewal of satellite cells as it is associated with the return of quiescence after cell division [41]. The expression of D3 is downregulated during the differentiation process, and the activity of D2 (the enzyme that catalyzes the conversion of T4 to T3) is increased. Differences between D2 and D3 expression lead to changes in T3 and T4 levels, which modulates myogenesis. The intracellular concentration of T3 is kept low only at the beginning of the myogenic process [24, 25]. The myogenic process is associated with the intrauterine phase and the regeneration of micro-injured tissues during physical exercise [35].

THRA1 represses the transcriptional activity of MyoD1 and MYOG independent of T3, during the myoblast proliferative phase [23]. However, MyoD1 induces transcriptional activity of THRA1, presenting a negative feedback loop for the MyoD1 activity [13]. In cultured avian myoblasts, the administration of T3 reduced the proliferation rate and increased the myotube fusion index, after the induction of myoblast differentiation [42]. Further on, there is

a hypothesis that the joint effects of T3 and T4 could be associated with the regeneration of muscle micro-damage induced by physical exercises, especially eccentric ones (contractions that occur when the muscle is being lengthened). These micro-damages are responsible for delayed onset muscle soreness (DOMS), with the release of muscle enzymes such as myoglobin and creatine kinase, in addition to the production of pro-inflammatory factors [35].

An increase in intracellular levels of T3 is essential for the terminal differentiation of myocytes, while T3 upregulates the expression of MyoD1 and MYOG [3]. Furthermore, T3, MYOG, and myogenic transcription factor 4 (MYF4) are essential for terminal differentiation of myotubes, inducing expression of MYH and SERCA [3, 43, 56].

Types of Fiber, Exercise, T3 and T4

In older men, reduced muscle mass and strength with aging (called sarcopenia) are associated with decreased type II fibers and minimal changes in type I fiber profile [50]. Aging-associated sarcopenia is multifactorial and is related

to decreases in myogenesis and changes in biochemical profiles and fiber types [18, 27, 29]. These findings have almost exclusively been associated with reductions in important anabolic hormones, such as growth hormone (GH) and insulin-like growth factor I (IGF-I). In addition, the increase in cortisol secretion has a predominant catabolic, potentially proteolytic action in skeletal muscles. Controversially, T3 and T4 have been barely associated with anti-sarcopenic players, because of their association with catabolic metabolism. Recent studies however, have shown that sarcopenia correlates with altered thyroid hormone signaling. It has been observed that serum thyroid hormone levels decrease with aging, which seems to influence skeletal muscle physiology [21].

It is important to note that thyroid hormones induce the transition from a slower fiber type (type I) to a faster fiber type (type II), and the reduction in their production may be involved in the induction of sarcopenia [56, 61]. In an experiment with old rats treated with T3, no significant changes were observed in the extensor *digitorum longus* (which has a predominance of fast-twitch fibers) after treatment. However, there was increased expression of myosin heavy chain 2 (Myh2), responsible for type II myosin gene expression, and myosin heavy chain 1 (Myh1), accountable for type I myosin gene expression in the soleus, which has a predominance of type I fibers [36]. These results give evidence (even if limited) that these hormones may also be closely linked to the reduction of sarcopenia in humans. Even subclinical hypothyroidism negatively affects cross-sectional muscle area compared to euthyroid, and treating these patients with radioactive iodine improves muscle strength and cross-sectional area [48].

The practice of physical exercises is extremely important for increased release of TSH, which will consequently stimulate the thyroid gland to release its hormones [31]. The volume-intensity of exercise regulates TSH secretion. For example, long-duration (> 60 min) and moderate or low-intensity exercise does not appear to modulate TSH secretion, but more intense, short-duration exercise may increase TSH secretion. This increase in circulating TSH induces an increase in T4 concentration without increases, or even reductions in free or total T3 [31]. High-intensity interval training increases free T4, free T3, and total T4 levels. However, after 12 h of recovery, free T3 reduced, and rT3 increased, probably caused by a reduction in the peripheral conversion of T4 to T3 [1, 30]. This response to high-intensity interval training differed from moderate continuous training at the same total work, which showed a recovery to pre-condition level for T3 after 12 h (into recovery) [30]. Once high-intensity interval training is part of several training programs and athletes very often participate in multiple training sessions on the same day, recovery of less than 12 h may occur. The impaired thyroid

hormones by recurrent short recovery between sessions may lead to overreaching or overtraining. Especially after high-intensity interval training, more extended recovery periods should be addressed for thyroid hormonal levels to return to typical values.

Conclusion

Thyroid hormones are strongly associated with skeletal muscle function and phenotypes. The mechanisms underneath the effect of T3 and T4 hormones on skeletal muscle have been explored by studies involving in the enzymes SERCA, UCP-3, TRa1 and deiodinase. SERCA, UCP-3 and deiodinase enzymes are playing a role, while TRa1 appears to have no effect. In addition, T3 and T4, the thyroid hormone metabolite T2, have been shown to play a role in the process.

Physical exercise, as a potent stimulator of TSH secretion, will induce acute increases in the mobilization and use of lipids, mitochondrial oxidation, and heart rate. Exercise is also indirectly associated with a late increase of T3 and T4 secretion. This increase in the availability of thyroid hormones has been classically proposed as a stimulator of thermogenesis and an important factor in programs to reduce obesity and prevent overweight. Of note, these assumptions are factual. However, it should be noted that the structural changes occurring in skeletal muscle induce 2 phenomena: (a) acceleration of the regenerative capacity of muscles, damaged during exercise by mechanical and oxidative stresses; and (b) medium and long-term adaptations that will increase the ability of muscles to withstand greater training loads (improvement of muscle fitness).

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. The authors declare that the results are reported honestly and without inappropriate data manipulation. They also declare no conflicts of interest.

Ethical approval As a review study, ethical approval is not applicable.

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