Exercise and Thyroid Function

Dorina Ylli, Joanna Klubo-Gwiezdzinska,
and Leonard Wartofsky

Introduction

Thyroid hormone receptors are present in virtually every tissue in the body, thereby permitting an important physiologic role for the two thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Skeletal and cardiac muscle function, pulmonary performance, metabolism, and the neurophysiologic axis are only a few of the important areas affected by thyroid hormone level [1]. Any abnormality in thyroid function causing either an excess or deficiency in circulating thyroid hormone levels can lead to changes in body function at rest and during exercise. The presence of thyroid disease can have a major impact on exercise tolerance resulting in reduced performance of strenuous activities. On the other hand, exercise itself may have direct or indirect effects on thyroid function, either secondary to acute alterations in the integrity of the pituitary thyroid axis or to more long-lasting changes. In well-trained athletes, alterations in thyroid function can be viewed as an adaptive mechanism associated with enhanced performance possibly serving to provide a better balance between energy consumption and expenditure. Underlying energy balance does appear to play an important role in the effects that exercise may have on the hypothalamus–pituitary–thyroid axis. Reports in the literature indicate that athletes with excessive weight loss may exhibit a "low T3 syndrome" accompanied by amenorrhea (in women) as well as other alterations in pituitary function [2]. Fortunately, thyroid diseases usually can be treated effectively, and most individuals with thyroid disorders should expect to obtain resolution of their thyroid-related symptoms, including those associated with a negative impact on their exercise tolerance. The track athlete, Gail Devers, who has been very public about her experience with Graves' disease, is a well-known sprinter who went on to win Olympic fame following treatment for her Graves' disease and may act as a case in point.

After a brief overview of normal thyroid physiology, this chapter will provide a survey of the literature describing effects of abnormal thyroid hormone levels on exercise tolerance, with a special focus on alterations in cardiac, muscle, and respiratory function. The chapter will conclude with a review of existing data on the response of the pituitary–thyroid axis to varying levels and types of exercise.

D. Ylli
MedStar Health Research Institute, Thyroid Cancer Research Center, Washington, DC, USA

J. Klubo-Gwiezdzinska
National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease/ Metabolic Disease Branch, Bethesda, MD, USA

L. Wartofsky (✉)
Thyroid Cancer Research, Georgetown University School of Medicine, MedStar Health Research Institute, Department of Endocrinology, Washington, DC, USA
e-mail: leonard.wartofsky@medstar.net

Thyroid Physiology

All steps in thyroid hormone (TH) biosynthesis are driven by thyrotropin (TSH) and are intimately linked to iodine metabolism. Dietary iodine is reduced to iodide, is absorbed by the small intestine, and then enters the circulation. Iodide "trapped" by the thyroid gland subsequently undergoes oxidation by thyroid peroxidase (TPO), iodinating tyrosyl residues in the storage protein, thyroglobulin, to form the iodothyronines, monoiodotyrosine (MIT), and diiodotyrosine (DIT). MIT and DIT molecules can then couple to form either tetraiodothyronine (T4) or triiodothyronine (T3), which are the two major thyroid hormones. T4 and T3 are bound within thyroglobulin and stored in thyroid follicles. Under control of TSH, thyroglobulin undergoes endocytosis and proteolytic digestion, releasing T4 and T3 into the circulation. The feedback loop is completed at the hypothalamic level where declining levels of circulating T4 or T3 will prompt secretion of thyrotropin-releasing hormone (TRH), which stimulates synthesis and secretion of TSH. After binding to its specific receptor on the thyroid cell membrane, TSH leads to stimulation of T4 and T3 production. Only 20% of circulating T3 is derived from thyroid secretion, whereas 80% is derived from the monodeiodination of T4 by 5′-deiodinase (type I and type II) in the periphery (see Fig. 6.1) [3]. Since T3 is some 10–15 times more biologically potent than T4, this latter conversion has been termed the "activating" pathway of thyroid hormone metabolism. Alternatively, in certain physiologic and pathologic states, the deiodination of T4 proceeds via a 5-deiodinase (type I and type III), which leads instead to reverse T3 (rT3). Since rT3 is a biologically inactive compound [3], this route of metabolism has been termed the "inactivating" pathway. A precise metabolic role for rT3 has not been described, but diversion of T4 metabolism from the activating to the inactivating pathway serves a nitrogen-sparing and protective effect for the body during times of stress and has been viewed as homeostatic. After binding to a cellular receptor, the thyroid hormones have both genomic and nongenomic effects, the former leading to modulation in expression of nuclear actions, whereas the latter appears to involve plasma membrane/mitochondrial responses [4] (Table 6.1).

Thyroid Hormone Effects

Hyper- and hypothyroidism, associated with either excess or deficiency of TH, respectively, may have a negative impact on exercise performance. Although TH has pervasive effects on virtually
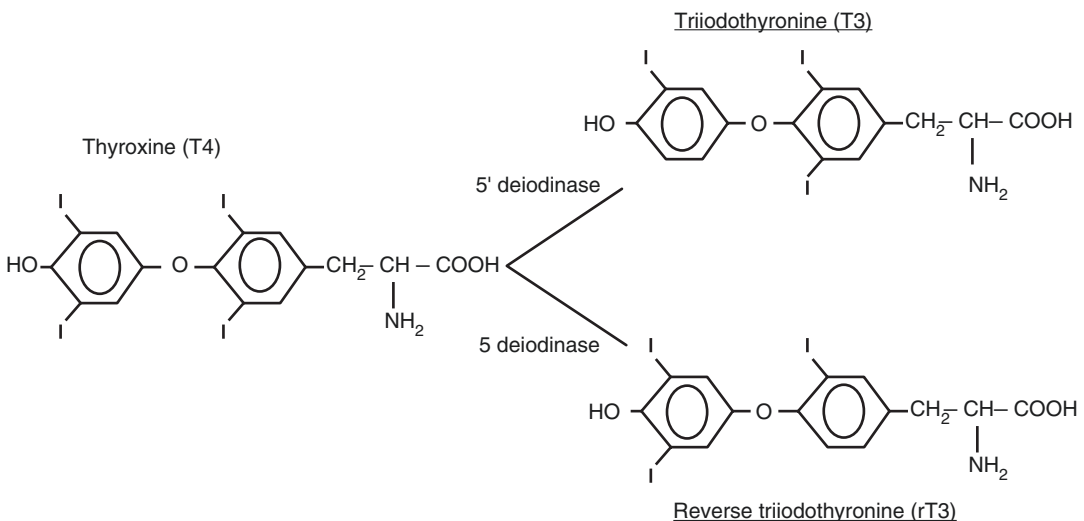

Fig. 6.1 Thyroxine, triiodothyronine, and reverse triiodothyronine

Table 6.1 Genomic and nongenomic actions of thyroid hormones

Genomic actions of thyroid hormones
-Positive regulation
Sarcoplasmic reticulum calcium adenosine triphosphatase
Myosin heavy chain α
β1-adrenergic receptors
Sodium/potassium adenosine triphosphatase
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)
Adenine nucleotide translocator 1
-Negative regulation
T3 nuclear receptor α1
Myosin heavy chain β
Phospholamban
Sodium/calcium exchanger
Adenylyl cyclase types V,VI
Nongenomic actions of thyroid hormones
Conductivity of sodium, potassium, and calcium channels
Actin polymerization status
Activation of PI3K/Akt/mTOR signaling pathway
Deiodination and decarboxylation of T4 resulting in thyronamine synthesis

all functions of the body, the following discussion emphasizes thyroid-related influences on exercise tolerance as mediated via involvement with cellular metabolism and the function of skeletal muscle and the cardiac, vascular, and pulmonary systems.

Cardiovascular Effects of Thyroid Hormones

Cardiac performance is dependent on the contractility of the heart as well as systemic vascular resistance. Resting tachycardia is very common in hyperthyroidism, and many patients complain of having a "racing" or "pounding" heart. The heart, being itself a muscle, is affected by thyroid hormone levels as is skeletal muscle. The heart relies mainly on serum T3 because there is no significant myocyte intracellular deiodinase activity [5].

TH can affect cardiac action via direct genomic and nongenomic effects on cardiac myocytes and hemodynamic alterations in the periphery that result in increased cardiac filling and modification of cardiac contraction [6]. TH mediates the expression of both structural and regulatory genes in the cardiac myocyte [5]. Thyroid hormone-responsive cardiac genes include sarcoplasmic reticulum calcium/adenosinetriphosphatase ($[Ca^{2+}]$/ATPase) and its inhibitor phospholamban, which are involved in regulation of calcium uptake by the sarcoplasmic reticulum during diastole [7], α- and β-myosin heavy chains, the ion channels coordinating the electrochemical responses of the myocardium: sodium/potassium ATPase (Na^+/K^+-ATPase), voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3), and sodium/calcium exchanger [6]. TH increases the expression of β1-adrenergic receptors and downregulates TRα1 receptors [8, 9].

In summary, the genomic action of TH on the heart involves genes which are largely responsible for enhanced contractile function and diastolic relaxation. Thus, T3 markedly shortens diastolic relaxation, i.e., the hyperthyroid heart relaxes with a higher speed (lusitropic activity), whereas diastole is prolonged in hypothyroid states.

The nongenomic effects of TH on the cardiac myocyte and on the systemic vasculature tend to occur rapidly. Schmidt et al. documented that T3-enhanced myocardial contractility and reduced systemic vascular resistance occur within 3 min [10]. These rapid T3-mediated effects include changes in membrane ion channels for sodium, potassium, and calcium; effects on actin polymerization; adenine nucleotide translocator 1 in the mitochondrial membrane; and a variety of intracellular signaling pathways in the heart and vascular smooth muscle cells [11, 12]. The actions on channels may determine set points of myocardial excitability and duration of the action potential and contribute to development of tachyarrhythmias [13].

Additional mechanism of T3 actions observed in vitro includes rapid activation of phosphoinositide 3-kinases (PI3K) leading to protein kinase B (Akt) phosphorylation that in turn translocates to the nucleus and promotes mammalian target of rapamycin (mTOR) phosphorylation [14]. As mTOR is important to regulate ribosomal biogenesis and protein translation, the signaling pathway described in these studies may underlie at least one of the nongenomic mechanisms by which T3 regulates cardiac growth and hypertrophy.

Moreover, it has been discovered that deiodination and decarboxylation of T4 could generate a biologically active metabolite, thyronamine, which is characterized by actions opposite to those of TH [15, 16]. It has been demonstrated that thyronamine reduces cardiac output, heart rate, systolic pressure, and coronary flow in isolated heart within minutes [16]. Conceivably, a balance between T3 and thyronamine might be responsible for maintaining cardiac homeostasis. Changes in this equilibrium might contribute to the cardiovascular alterations that occur in patients with thyroid disease [17].

In Vivo Animal Studies on the Role of Abnormal Thyroid Function in the Regulation of Cardiac Response to Exercise

It has been believed that one of the main mechanisms of increased cardiac work during hyperthyroidism was the sensitization to catecholamines. However, Hoit et al. in a study on thyrotoxic baboons refuted a role of βl- or β2-adrenergic receptors in any cardiac response to hyperthyroidism [18]. Interestingly, abnormal cardiac response to exercise has been described as being due to an inefficient use of chemical energy stored in adenosine triphosphate (ATP). In hyperthyroid hearts, a larger fraction of energy goes to heat production, whereas in euthyroid animals more is spent for useful contractile energy. Finally, TH modifies the secretory activity of the heart—i.e., T3 has been found to increase mRNA and protein levels of atrial natriuretic factor [19].

Several studies have indicated overactivation of the renin–angiotensin–aldosterone (RAA) system in hyperthyroid animals, documenting increased plasma renin [20, 21] and upregulated synthesis and secretion of angiotensinogen [22] in hyperthyroid rats. In contrast, the plasma renin activity is reduced in experimental hypothyroidism [20]. There is also an evidence of tissue-specific regulation of RAA. TH activates some components of cardiac RAA, and hyperthyroidism can promote an increase in cardiac levels of renin, stimulate Ang II generation [23], and

raise levels of AT1 and AT2 receptors [20]. In the heart, Ang II exhibits growth-promoting effects by inducing hypertrophy and fibrosis, mediated by the AT1 receptor [24]. Although most of the effects of Ang II related to cardiac remodeling have been attributed to the AT1 receptor, the AT2 receptor is also involved in the development of some cardiac hypertrophy models [25]. There are several literature reports showing that AT1 receptor blockade and ACE inhibition attenuate or prevent the development of cardiac hypertrophy induced by TH in vivo [21, 26, 27]. Some authors suggest that the mechanism of action of these compounds is associated with the alterations in calcium handling [28], while others suggest that these drugs may inhibit AT1 receptor-induced activation of PI3K/Akt/mTOR pathway [29, 30].

In hyperthyroidism structural remodeling such as hypertrophy, left ventricular fibrosis, myocyte lengthening, chamber dilatation, and decreased relative wall thickness have been observed and have been considered as likely to contribute to global left ventricular functional impairment [31].

Clinical Findings

In thyroid disease, cardiac structures and function may remain normal at rest; however, impaired left ventricular (LV) function and cardiovascular adaptation to effort become unmasked during exercise [32].

Hypothyroidism
Hypothyroidism has been associated with a decrease in intravascular volume, stroke volume, and cardiac index and an increase in systemic vascular resistance, resulting in diastolic hypertension (Table 6.2) [33]. In patients with transient hypothyroidism owing to thyroidectomy, radionuclide ventriculography and right heart catheterization revealed lower cardiac output, stroke volume, and end-diastolic volume at rest, but increased systemic peripheral resistance [34]. In the same individuals, during exercise, heart rate, cardiac output, end diastolic volume, and stroke volume were higher when the patients were euthyroid than when they were hypothyroid.

Table 6.2 Cardiovascular changes observed in hyper- and hypothyroidism

	Hyperthyroidism	Hypothyroidism
Heart rate	↑ NC	↓NC
Vascular volume	↑	↓
Stroke volume	↑	↓
Cardiac output	↑	↓
SVR	↓	↑NC
LVEF		
Rest	↑↓NC	↓NC
Exercise	↓	↓
Diastolic blood pressure	↓	↑NC
Systolic blood pressure	↑NC	↓NC
LV pre-ejection period	↓	↑
LV ejection time	↓	↑

↑ increased, ↓ decreased, *NC* no change, *SVR* systemic vascular resistance, *LVEF* left ventricular ejection fraction, *LV* left ventricular

The baseline LV ejection fraction (LVEF) and peak LVEF were shown to be lower in hypothyroid subjects compared with their euthyroid state, although with exercise, the rise of LVEF in the two states was similar [35]. As assessed by radionuclide-gated pool ventriculography in a younger group (average age 24 years), there was no noticeable change in LVEF with hypothyroidism, although exercise tolerance did improve after levothyroxine (LT4) replacement [36]. Even hypothyroidism of brief duration of only 10 days was associated with an impaired LVEF response to exercise; LVEF response returned to normal with restoration of the euthyroid state [37]. Of interest, the patients still achieved the same workload in either state.

Interesting observations have been found in patients with subclinical hypothyroidism (Sc-HypoT) defined as mild elevations of TSH with normal levels of T4, fT4, T3, and fT3. It has been a matter of investigative interest whether the mild hypofunction associated with subclinical hypothyroidism affected any measureable cardiac parameters.

An accurate assessment of left ventricular function performed by Doppler echocardiography in patients with stable Sc-HypoT showed no changes in left ventricle morphology. However,

the prolonged isovolumic relaxation time and a reduced early-to-late ratio of the transmitral peak flow velocities are suggestive of impaired diastolic function in the sense of slowed relaxation [38].

In the same study, ten randomly selected patients were re-evaluated after achieving euthyroidism by means of 6 months of LT4 administration. The treatment caused no change in the parameters of left ventricle morphology, whereas it normalized systolic and diastolic function. Interestingly, although systemic vascular resistance was comparable in untreated patients and control subjects, it was significantly decreased after LT4 therapy. Similar findings have been documented by Kahaly et al. [39], who assessed cardiac function on effort and physical exercise capacity showing no abnormalities in various cardiac parameters at rest, either before or after LT4 treatment. However, stroke volume, cardiac index, and peak aortic flow velocity were significantly lower, and the pre-ejection period was significantly prolonged during exercise in the untreated patients versus controls. Other authors confirmed early myocardial dysfunction unveiling a difference in longitudinal systolic and diastolic function reserve indexes during exercise in Sc-HypoT patients compared to controls [40]. However, in a large-scale study, structural changes were not observed when comparing patients with normal TSH with patients with TSH > 5 mIU/L [41]. Tadik et al. performing 3-dimensional echocardiography in 94 subjects observed significantly reduced LV cardiac output and ejection fraction in patients with Sc-HypoT compared to both controls and the same patients 1 year after treatment [42]. Furthermore, when women with Sc-HypoT perform physical activity, a slower HR kinetics (intended as time to reach 63% of the HR at steady state) has been observed in the transition from rest to exercise compared with euthyroid women [43].

Evidence supporting reversible left ventricle diastolic dysfunction in patients with subclinical hypothyroidism was documented employing radionuclide ventriculography [44]. The authors found that the time to peak-filling rate was prolonged in ten patients with Sc-HypoT compared

to ten normal control subjects. This accurate index of diastolic function normalized after achieving euthyroidism with LT4 therapy.

Abnormal diastolic function may impair coronary flow reserve. Hypothyroid individuals may have a form of reversible coronary dysfunction as found in a study of six patients undergoing stress testing before and after LT4 replacement therapy. Prior to replacement therapy, SPECT scanning revealed notable regional perfusion defects in four of six patients, which resolved within 8 weeks of LT4 therapy [45]. Similarly, Oflaz et al. [46] found that coronary flow reserve was lower in patients with Sc-HypoT than in euthyroid subjects. On the contrary, Owen et al. [47] using stress echocardiography with i.v. dobutamine found no differences in resting global, regional left ventricular function or regional myocardial velocities during maximal dobutamine stress between patients and controls or in patients treated with replacement therapy compared with baseline values.

To summarize, the vast majority of clinical studies show impaired LV systolic and diastolic function during exercise in patients with both overt and subclinical hypothyroidism.

Hyperthyroidism

The effects of hyperthyroidism on cardiac function both during rest and exercise are numerous (see Table 6.2) [33]. In thyrotoxicosis, the extent of the various cardiac responses to excess TH is somewhat dependent on the duration and severity of the disorder. Resting tachycardia, a slow decline in postexercise heart rate (HR), atrial fibrillation, decreased exercise tolerance, and, rarely, congestive heart failure (CHF) are seen in thyrotoxic patients. Cardiac complications from hyperthyroidism tend to occur in patients with a history of prior cardiac disease. Atrial fibrillation, atrial enlargement, and CHF are more common in patients over 60 years old with toxic multinodular goiter. Instead, cardiac valve involvement, pulmonary arterial hypertension, and specific cardiomyopathy are more common in Graves' disease [48]. Augmented blood volume and blood flow to the skin, muscles, and kidneys are seen and may be owing to vasodilators released

secondary to increased cellular respiration [49]. A rise in cellular oxygen consumption leads to a higher demand for oxygen and the need to get fuel to the peripheral tissues [49]. An increase in the velocity of cardiac muscle contraction is present, as well as a rise in myosin ATPase activity [50]. Evaluation of systolic time intervals in thyrotoxic subjects reveals a shortening of the LV pre-ejection period along with quicker LV ejection time and isovolumetric contraction [33, 51].

Kahaly et al. analyzed alterations of cardiovascular function and work capacity using stress echocardiography as well as spiroergometry in subjects with untreated thyroid dysfunction, then again after restoration of euthyroidism. At rest, LVEF, stroke volume, and cardiac indices were significantly increased in hyperthyroidism, but exhibited a blunted response to exercise, which normalized after restoration of euthyroidism. During exercise, negative correlations were found between free T3 (fT3) and diastolic blood pressure, maximal workload, HR, and LVEF. This impaired cardiac response to exercise was specifically apparent in older subjects [52–54].

Of note, combined oral LT4/LT3 overdosage has been reported to cause ST wave depressions with treadmill stress testing that resolve with the euthyroid state [55]. In general, diagnostic treadmill testing is best delayed until patients are euthyroid.

"Subclinical" hyperthyroidism (Sc-HyperT) is a term that has been applied to patients with undetectable levels of serum TSH, but with normal levels of T4, fT4, T3, and fT3. In one study, there was no difference in LVEF at rest and exercise between Sc-HyperT and controls, whereas overt hyperthyroid subjects had a reduction in LVEF with exercise, increased HR, and cardiac output at both rest and exercise [56]. Supporting evidence was provided by a study performed in 1112 subjects with a 5-year follow-up in which left ventricular mass divided by height did not differ between subjects with and without Sc-HyperT [57].

However, studies by Kaminski et al. indicated worse physical capacity in subjects with Sc-HyperT and the possibility of improvement after therapy. Compared with results after treat-

ment, the end-diastolic and end-systolic volume indexes, stroke volume index, and cardiac index were significantly larger in patients with Sc-HyperT. Stroke volume index was negatively correlated with TSH and positively with fT4 and fT3 values, and cardiac index was positively correlated with fT4 and fT3 levels in Sc-HyperT [58].

Analysis of the Framingham Heart Study revealed that TSH was related to left ventricular contractility in women with TSH < 0.5 mU/L TSH [41]. Furthermore, thicker left ventricular posterior wall, higher HR, and a lower achieved maximum workload have been reported in women with nontoxic multinodular goiter treated with mildly suppressive levothyroxine therapy compared to women not under treatment [59].

To summarize, LVEF, stroke volume and cardiac index, may be greater at rest in hyperthyroidism, but the lack of an increase in LVEF with exercise seems to be a reproducible finding.

Effects on Systemic Vascular Resistance (SVR)

TH causes decreased resistance in peripheral arterioles through a direct effect on vascular smooth muscle and decreased mean arterial pressure, which, when sensed in the kidneys, activates the RAA system and increases renal sodium absorption. T3 also increases erythropoietin synthesis, which leads to an increase in red cell mass. The combination of both leads to an increased blood volume and preload. In hyperthyroidism, these effects increase cardiac output by 50–300%, while a 30–50% reduction is seen in hypothyroidism [5].

In the vascular smooth muscle cell, TH-mediated effects are the result of both genomic and nongenomic actions. Nongenomic actions target membrane ion channels and endothelial nitric oxide (NO) synthase, which serves to decrease SVR [60, 61]. Indeed, it was recently reported that the PI3K/Akt signaling pathway plays a role in T3-induced NO production by vascular smooth muscle cells and by endothelial cells [11, 62].

Furthermore, T3 has been shown to inhibit vascular remodeling via the inhibition of the cAMP response element binding protein, a nuclear transcription factor involved in the remodeling process [63]. It seems also that voluntary exercise training can improve long-lasting endothelial dysfunction resulting from transient thyroid hormone deficiency in early life [64].

Clinical Findings

Hypothyroidism

Vascular control mechanisms may be abnormal in hypothyroidism with blunted vasodilatation secondary to reduced endothelium-dependent vasodilatation [65, 66]. In overt hypothyroidism, arterial compliance is reduced, which leads to increased arterial stiffness with higher central augmentation pressure and lower pulse wave velocities. These abnormalities were reversible with adequate LT4 treatment [67, 68]. However, in subclinical hypothyroidism, the study results have been equivocal. Several studies have not found any association between Sc-HypoT and blood pressure at rest [69–71]. In one cross-sectional study [69], Sc-HypoT was not associated with increased resting blood pressure. Similar results were observed in the cross-sectional Busselton thyroid study [70] that included 105 subjects with Sc-HypoT and 1859 euthyroid controls from Western Australia. On the other hand, two large population-based studies with 5872 [72] and 30,728 [73] subjects reported a modest association between high-normal serum TSH levels and resting blood pressure. This observation has been confirmed in other studies, suggesting that mild thyroid hormone deficiency also may affect vascular tone [74–77]. Several studies documented an improvement of SVR after LT4 replacement [38, 78]. Endothelial dysfunction in patients with hypothyroidism, borderline hypothyroidism, and those with high-normal TSH values using flow-mediated arterial dilation (FMD) has been demonstrated with TSH levels correlating inversely to endothelium-dependent dilatation [77]. Impaired endothelium-dependent

vasodilatation as a result of a reduction in nitric oxide availability has been demonstrated in Sc-HypoT by Taddei et al. [79].

Studies have also shown that FMD is associated with plasma osteoprotegerin levels in hypothyroid patients [80]. Osteoprotegerin is a member of the tumor necrosis factor (TNF) receptor family involved in vasculature regulation and related with increased cardiovascular mortality. In vitro studies suggest that TH and TSH are involved in regulation of osteoprotegerin expression [81].

Hyperthyroidism

Endothelium-dependent arterial dilatation is increased in hyperthyroid patients and is reversible after subtotal thyroidectomy [82]. Ojamaa et al. [83] demonstrated vascular relaxation due to the action of excess TH on the vascular smooth muscle cells. Conceivably, an inability to lower SVR during exercise in the hyperthyroid state might lead to impaired exercise tolerance [84]. In this regard, phenylephrine administration was associated with an increase in SVR and a decrease in cardiac output not seen in euthyroid subjects [85]. On the contrary, a case-control study of 42 patients with untreated overt hyperthyroidism documented similar systolic and diastolic blood pressures during maximal exercise as in 22 healthy controls. Moreover, no changes in systolic and diastolic blood pressure responses to exercise were observed in these patients after restoration of euthyroidism during 6-month follow-up [52]. Similar findings hold true for the patients with Sc-HyperT. In a recent population-based prospective cohort study, Völzke et al. [86] found that Sc-HyperT is not associated with changes in blood pressure, pulse pressure, or incident hypertension. Some smaller studies have reported similar results [52, 87].

Effects in Muscles

TH plays a critical role in maintaining homeostasis and influencing the rate of metabolism and energy expenditure. Skeletal muscles contribute to about 20–30% of resting metabolic rate [88].

TH control the expression of myocyte-specific genes coding for myosin isoforms [32], the Na^+–K^+ ATPase pumps, and the Ca–ATPase canals of the sarcoplasmic reticulum. This explains the increase of contractility and relaxation of skeletal muscles observed in hyperthyroidism, as opposed to hypothyroidism. In both cases muscle performance is reduced, with accumulation of lactic acid at exercise. This is because of defective pyruvate oxidation and proton expulsion in hypothyroidism and of acceleration of glycolysis in hyperthyroidism. Muscle glycolysis exceeds mitochondrial oxidation enhancing the shunting of pyruvate to lactate, thus leading to an increased lactic acid concentrations resulting in intracellular acidosis. Furthermore, TH increases fast myosin and fast-twitch fibers in skeletal muscle, which are less economic in oxygen utilization during contraction than slow-twitch muscle fibers explaining impaired exercise tolerance.

In Vivo Animal Studies on the Role of Abnormal Thyroid Function in the Regulation of Muscle Response to Exercise

Animal studies of hypothyroidism reveal that glycogen levels in muscle appear to be normal to increased at rest, whereas during exercise, muscle utilization of glycogen rises as may lactate production [89, 90].

In hypothyroidism, studies reveal a reduction in flow to the fast-twitch type II fibers of high-oxidative type muscles [91] compromising exercise capacity via reduced oxygen delivery and endurance through decreased delivery of blood-borne substrates [92, 93]. Additionally, decreased mobilization of free fatty acids (FFA) from adipose tissue leads to reduced lipid delivery to skeletal muscle [94]. After exercise the rate of glycogenolysis exceeded those in controls, showing diminished oxidative capacity resulting in lowering the ATP content. Thus, inadequate fuel utilization may be considered as a factor limiting ability for heavy exercise in hypothyroidism [89] probably triggering compensatory mechanisms in gene expression resulting in a slower striated

muscle phenotype [95, 96]. Moreover, in distinction to hypothyroid individuals, muscle blood flow is enhanced in hyperthyroid subjects including fast-twitch sections of muscle [94].

In induced hyperthyroidism, compared to euthyroid control rats, the energy cellular potential was increased during exercise, and it remained higher after the recovery period [97] testifying for an impaired cellular energy. THs also promote expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1a), which mediates mitochondrial biogenesis and oxidative capacity in skeletal muscle. Acute exercise increases deiodinase-2 expression in skeletal muscle accelerating conversion of T4 to T3 which induces PGC-1a and its downstream effect on mitochondria [98].

Whether physical activity can be recommended in hyperthyroidism is questionable. The effect of T3-induced thyrotoxicosis on exercise tolerance has been studied, with increases noted in resting oxygen uptake and increased lactic acid levels, protein breakdown, and loss of lean body mass [99]. However, Venditti et al. demonstrated in vivo that moderate training attenuated T3-induced increases in hydrogen peroxide (H_2O_2) production and, therefore, oxidative damage increasing antioxidant protection and decreasing the reactive oxygen species (ROS) flow from the mitochondria to the cytoplasmic compartment [100]. Another study of leucine supplementation in hyperthyroid rats demonstrated a positive effect in physical performance compared to the non-treated group [101].

Clinical Findings

Hypothyroidism

Hypothyroidism is characterized by a decrease in Ca^{2+} uptake and ATP hydrolysis by sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA; see Table 6.3) [102]. At least mild elevations in creatine kinase levels are seen in about 90% of hypothyroid patients [103]. In hypothyroid subjects, the alterations in lipid, protein, and carbohydrate metabolism in muscle may have pronounced effects on muscle function.

Table 6.3 Muscle changes observed in hyper- and hypothyroidism

	Hyperthyroidism	Hypothyroidism
Muscle strength	↓	↓
Type II fibers	↑	↓
Lactate: exercise response	↑	↑
Sarcoplasmic reticulum Ca^{2+} uptake	↑	↓
PCr/Pi ratio—exercise	↑	↓
PCr recovery rate	↑	↓

↑ increased, ↓ decreased, *PCr/Pi* phosphocreatine/inorganic phosphate, *PCr* phosphocreatine

Exercise may exacerbate this situation and be associated with rhabdomyolysis [104]. Several cases of rhabdomyolysis have been reported [105, 106], and a relation to a reversible defect in muscle glycogenolysis has been suggested [107].

In Hoffmann's syndrome, another muscle disorder related to hypothyroidism, abnormalities include increased muscle mass, muscle stiffness and weakness, creatine kinase of as much as >10 times normal levels, and repetitive positive waves on electromyography (EMG) [108]. Resolution of symptoms is expected with thyroid hormone replacement. EMG patterns that can be seen with hypothyroidism include fibrillations, increased polyphasic waves, unusual high-frequency discharges, and reduced motor unit recruitment [108].

An abnormal increase in lactate during exercise but not at rest has been described in subclinical hypothyroidism [109]. It was hypothesized that mitochondrial oxidative dysfunction was present and that this dysfunction worsens with length of disease; glycolysis may exceed pyruvate oxidation explaining the lactate buildup.

Phosphorous nuclear magnetic resonance spectroscopy (MRS) has been extensively used to investigate noninvasively the energy metabolism of human muscle. It allows tracking of real-time changes in the relative concentrations of the metabolites that are involved in high-energy phosphate metabolism [110]. A study by Kaminsky et al. performing MRS in hypothyroid women subdivided into either moderate hypothyroidism, subacute thyroid deficiency, or severe/

chronic hypothyroidism demonstrated dysfunction of muscle bioenergetics with even mild TH deficiencies [111]. Khushu et al. documented similar abnormalities in the bioenergetic profile in 32 hypothyroid patients [110]. Similarly, Bose et al. showed shifting of equilibrium of ATP breakdown to ADP and inorganic phosphate (Pi) after exercises confirming impaired oxidative phosphorylation in mitochondria [112].

Haluzik et al. compared metabolic changes in 12 hypothyroid women with those in 6 hyperthyroid and 12 euthyroid women. Compared to healthy subjects, hypothyroidism was associated with significantly decreased noradrenaline and glycerol concentrations, whereas the opposite is applied to hyperthyroid patients. These findings suggest altered adrenergic and lipolytic activities in thyroid disorders [113].

Whether the changes occurring in hypothyroidism are observed in subclinical hypothyroidism has been investigated. Changes in phosphometabolites (increased phosphodiester levels and Pi concentration) were similar in patients with overt hypothyroidism compared to Sc-HypoT. However, impaired muscle oxidative metabolism was not observed in Sc-HypoT patients [114].

Sc-HypoT in 3799 otherwise healthy subjects was associated with a lower resting HR and a significantly lower recovery HR [115]. While Reuters et al. observed no changes in muscle functional capacity in Sc-HypoT, symptoms of cramps, weakness, and myalgia were more frequent compared to controls [116], and a lower HR after exercise was observed [115]. Furthermore, Tanriverdi et al. observed Sc-HypoT subjects to have a higher arterial stiffness and lower physical activity duration with a significant difference in neuromuscular symptoms, muscle strength, and functional exercise capacity assessed by a 6-min walk test [117].

Hyperthyroidism

Hyperthyroid subjects also have impairment in cellular respiration and reduced exercise endurance [109]. Excess heat generation from the elevated metabolic activity associated with thyrotoxicosis and secondary hyperthermia may adversely impact heat dissipation during exercise and exercise tolerance. However, despite a baseline temperature increase of 0.5 °C in thyrotoxic subjects, exercise-induced temperature rise has been observed not to differ from that in controls [118]. Reduced duration of action potentials and increased polyphasic potentials can be seen with thyrotoxicosis [119]. Muscle weakness is a common complaint in patients with TH excess, and a variety of investigations have addressed muscle changes secondary to hyperthyroidism. Hyperthyroidism is associated with an increase in fast and a decrease in slow-twitch muscle fibers. Thyrotoxicosis appears to induce an oxidative muscular injury secondary to an increase in mitochondrial metabolism and a decrease in glutathione peroxidase, which may be protective against such injury [120]. Glycogen is lower at baseline in thyrotoxicosis and is utilized at a faster rate with an associated increase of serum lactate [121]. According to studies of Ribeiro et al., glycogen storage in hyperthyroidism can be differently distributed in tissues with lower levels in the heart, liver, and soleus and higher levels in mixed fiber type of gastrocnemius during regular swimming [122].

Thyrotoxic periodic paralysis (TPP) is an unusual complication of hyperthyroidism more typically seen in thyrotoxic Asian subjects, although not exclusively so. Patients with TPP suffer from attacks of para- or quadriplegia incited by exercise, high-carbohydrate meals, or high-salt intake [123].

The muscular function of these patients may appear grossly normal before and between episodes, although some patients have a prodrome of muscle stiffness and aching. The pathophysiology revolves around an imbalance in the Na+/ K+ pump. EMG studies reveal that the muscle has reduced excitability during TPP episodes, and low-amplitude muscle action potentials are seen following a paralytic episode [124]. Decreased compound motor action potential amplitudes are found postexercise in TPP [125] and improve following treatment [126]. Of note, muscle fiber conduction velocity measured in two patients with TPP was within normal limits during paralysis episodes, although muscle strength

was reduced by 40% during an attack [127]. A comparison of the electrophysiologic response to prolonged exercise between thyrotoxic patients with and without TPP demonstrated a preexisting latent abnormal excitability of the muscle membrane in TPP [128]. TH regulates muscle membrane excitability by increasing Na^+/K^+ pump-dependent potassium influx [129]. Adding to our insight into the pathophysiology of TPP is the recent discovery of KCNJ18 gene mutations in a third of TPP patients which alter the function of an inwardly rectifying potassium channel named Kir2.6 [130].

There are also a few case reports documenting rhabdomyolysis as a complication of hyperthyroidism [131–133].

Some authors describe significant metabolic changes in exercising muscle exposed to excess TH. Reduced metabolic efficiency of skeletal muscle energetic with decreased phosphocreatine (PCr) in hyperthyroid patients has been documented by MRS [134]. Under thyrotoxic conditions, ATP is promptly depleted, and myopathy easily develops, as the intramuscular glycogen content decreases due to the suppression of glycogenesis and glycogenolysis. During vigorous exercise, glycogen is rapidly consumed, and ATP consumption by the skeletal muscles increases more than the ATP supply. At that time, the compensatory mechanisms include involvement of purine catabolism as a source of energy [135, 136]. Fukui et al. compared the levels of glycolytic metabolites (lactate and pyruvate) as well as purine metabolites (ammonia and hypoxanthine) in treated and untreated Graves' disease patients vs. normal controls [137]. The study revealed that glycolysis and purine catabolism were remarkably accelerated in hyperthyroidism and thyrotoxic myopathy could be closely related to the acceleration of purine catabolism, which can be normalized only after long-lasting euthyroidism. Moreover, such acceleration of the purine nucleotide cycle is thought to be in part a protective mechanism against a rapid collapse of the ATP energy balance in exercising muscles of patients with hyperthyroidism [137, 138].

Another important question facing clinicians is the effect of treatment with suppressive doses of LT4 necessary in some patients with differentiated thyroid cancer. Vigario et al. [139] addressed this question and documented that muscle mass was lower in the patients on suppressive LT4 treatment than in euthyroid control subjects, but aerobic training, twice a week, during 3 months partially reversed this deteriorating effect of excess TH on muscle mass. Greater attention should be paid to elderly men with subclinical hyperthyroidism who may have accelerated poor physical performance. Also in euthyroid man, higher FT4 was predictive of a lower Short Physical Performance Battery score at the 3-year follow-up [140].

Effects on Pulmonary Function

Performance of any strenuous activity especially of endurance training requires the ability of the respiratory system to augment oxygen utilization. Exercise capacity, the maximal capacity for oxygen consumption (VO_2 max), and endurance, the ability to perform prolonged exercise at 75% VO_2 max, are the two main components of exercise tolerance [141].

Clinical Findings

Large goiters, especially firm, nodular substernal goiters, can cause an extrathoracic tracheal obstruction, which can limit air flow to the lungs [142].

Hypothyroidism
Altered TH levels can lead to impairment in optimal pulmonary function. Myxedema or profound hypothyroidism is associated with alveolar hypoventilation related to a reversible reduction in hypoxic ventilatory drive [143]. Reductions in lung volumes are seen and include vital capacity, total lung capacity, functional residual capacity, and expiratory reserve volume, as well as a decrease in diffusing capacity for carbon monoxide (DLCO) [144]. LT4 replacement therapy is associated with resolution of the aforementioned changes, but a concomitant reduction in

patient weight may also be an important factor in pulmonary function improvement [145]. Frank respiratory failure is unusual. During exercise, hypothyroid subjects were characterized by reduced forced vital capacity and tidal volume at the anaerobic threshold [146]. Also, the increment of minute ventilation and oxygen uptake was significantly lower.

A study in women with subclinical hypothyroidism demonstrated a slower VO2 kinetics (defined as the time needed to reach 63% of change in VO_2) in both the onset and recovery of exercise and a higher oxygen deficit compared to euthyroid subjects [147]. Conceivably therefore, it seems that levothyroxine treatment of mild or subclinical hypothyroidism can decrease oxygen uptake, improve minute ventilation and cardiopulmonary exercise performance, and improve the ability in these patients to carry out activities of daily life [148].

Hyperthyroidism

Thyrotoxicosis has been implicated as a primary cause of decreased cardiorespiratory exercise tolerance [52, 149, 150]. In hyperthyroidism, already at rest, cardiorespiratory capacity is maximally increased, leading to a limited functional reserve, which may explain the inadequate response of ventilation [53]. Dyspnea on exertion is a common complaint although the causes of this symptom remain unclear and may vary from one patient to another [151]. In hyperthyroidism, the respiratory systems adjust to the increased oxygen demand by increasing respiratory rate and minute ventilation [149]. Alveolar ventilation remains normal, but a rise in dead space ventilation is seen, and also the amount of oxygen diffusion from alveoli to the blood may be reduced during periods of strenuous exercise in thyrotoxicosis [152].

Pulmonary function is dependent on not just intrinsic lung function but also the accessory muscles for respiration. Pulmonary compliance and airway resistance tend to remain unchanged, whereas vital capacity and expiratory reserve volume are reduced, implicating respiratory muscle weakness [153]. Other supporting evidence for respiratory muscle dysfunction in thyrotoxic patients is the reduction of maximal inspiratory and expiratory efforts, which are seen to resolve on restoration of euthyroidism [154]. It appears that ventilation increase beyond the oxygen uptake is related to the dead space ventilation [155]. These changes also appear to resolve with appropriate therapeutic intervention [155]. Furthermore, changes in TH levels modify diaphragmatic function as well as muscle fiber type. Goswami et al. documented a more marked functional weakness of the diaphragm in Graves' disease during maximal respiratory maneuvers, indicating a diminished diaphragmatic reserve that could cause dyspnea on exertion. These changes were reversible after achieving euthyroidism [156].

With cardiac and muscular function being adversely affected by excess TH, one would postulate that work capacity must be reduced in hyperthyroid individuals. A study of maximum power output in hyperthyroid individuals with measurements of work capacity both while thyrotoxic and then euthyroid revealed a 19% increase from a low maximum power output during the thyrotoxic phase compared to the euthyroid state 3 months later. A subset of patients were retested 12 months later, and maximum power output in comparison to controls was in the low normal range and represented a +13% rise from the 3-month test [157]. Oxygen uptake at maximal effort was low during thyrotoxicosis and did not increase at 3 and 12 months. Net mechanical efficiency was also low at baseline and returned back up to normal only by 12 months. Kahaly et al. showed reduced forced vital capacity, 1-second capacity, and increased respiratory resting oxygen uptake (VO_2) rate in hyperthyroid patients compared to euthyroid controls. During exercise, decreased tidal volume at the anaerobic threshold was observed as well as a lowered increment of minute ventilation, VO_2, and oxygen pulse [53].

The studies are equivocal in terms of the effect of treatment with suppressive doses of LT4 on exercise capacity. Some studies revealed similar blood pressure, heart rate, VO_2, VCO_2, and anaerobic threshold response to exercise in LT4-treated patients as in healthy control subjects [158]. Other studies found that ventilation parameters

between patients and controls were comparable only at rest, but the patients treated with suppressive doses of LT4 had a worse response to exercise (i.e., lower maximal workload, lower peak VO$_2$, and lower anaerobic threshold) [159].

In conclusion, analysis of respiratory gas exchange showed low efficiency of cardiopulmonary function, respiratory muscle weakness, and impaired work capacity in hyperthyroidism which was reversible with restoration of euthyroidism.

Exercise and Thyroid Axis Response

Exercise is a stressful situation that challenges body homeostasis, so that the organism has to reestablish a new dynamic equilibrium in order to minimize cell damage.

One of the systems affected is the hypothalamic–pituitary–thyroid (HPT) axis [160].

Data demonstrate that voluntary exercise adapts the status of the HPT axis, through pathways that are distinct from those observed during food restriction or repeated stress [161]. Lesmana et al. suggested that alteration in TH signaling (increased TRβ1 expression) and TSH reduction observed in vitro after moderate training can contribute to the metabolic adaptation of skeletal muscle to physical activity [162].

Although the belief that a different normal range for thyroid hormones may apply in athletes compared to healthy nonathletes may be considered, data on the effects of exercise on TH metabolism have been inconsistent or even contradictory (see Table 6.4). These divergent results may be due to differences in the intensity of work, duration of exercise, and frequency and design of the training program and to differences in gender, age, and baseline individual physical status of the subjects. In addition, different duration of studies, timing of sampling after exercise, and methodological factors in hormonal assay and data analysis may also be responsible for the discrepancies.

Some studies indicated no major changes in the thyroid axis response to exercise. For example, a study of 26 healthy males, given identical diet and physical activity for a week before the test, revealed an increase in T3, T4, and TSH imme-

diately after exercise. However, it seems that the changes were mainly due to hemoconcentration, since they became insignificant after adjustment for hematocrit (Hct) [163]. Another study in subjects undergoing different exercise endurance showed similar results: no significant change in FT4 and a small increase (partially from hemoconcentration) in serum T3 and rT3 [164].

Interestingly, some studies indicate that TSH increases after exercise with the response dissipating with repetitive testing, which was suggested to indicate a psychological influence on the TSH rise [165]. In another study a fT4 increase of 25% was seen postexercise [166], but the increase may have been confounded by assay interference by an associated rise in FFAs. TSH also rose by 41%, but could not be correlated with T4/T3 levels.

A rise in TSH was seen with both short-duration graded exercise and prolonged exercise, but the latter had a peak of 33% lower than with graded exercise [167]. Another study compared the effect of submaximal and maximal exercise effect on TH levels [168]. Maximal exercise was associated with a decrease in TSH, FT4, and stable rT3 and rises in T3 during activity, whereas submaximal exercise was associated with an increase in TSH, but T3, rT3, and FT4 were unchanged. [168]. Also, when comparing intensive exercise intervals with steady-state endurance exercise, Hackney et al. observed that the change in TH levels was present 12 hours post exercise only in the intensive exercise group implying a longer period necessary for TH to return to normal. In both groups an increase in fT3, fT4, and rT3 was present immediately post exercise with a decrease in fT3 and increase of rT3 12 hours post exercise only in the intensive exercise group [169].TH changes in ultradistance and long-distance runners have also been investigated. Hesse et al. studied the effect of three distances of 75 km, 45 km, and marathon (42.2 km) with the subjects performing the 45-km run being slightly older than the other two groups. T4 increased in the 75 km and marathon group and decreased together with T3 in the 45-km group postrace. rT3, measured only in the marathon and 75-km groups, rose in both groups. The authors

Table 6.4 Reported changes in hypothalamus–pituitary–thyroid axis in association with exercise

Reference	Exercise type	Caloric status	TSH	T4	fT4	T3	fT3	rT3	Comments
[165]	Pre-exercise	NA	↑						Anticipation of exercise
[166]	Ergometry	NA	↑	↑		↑			Normal TRH stim
[173]	Ergometry	NA		NC		↑		↓	Untrained athletes
[173]	Ergometry	NA		↓		NC		↑	Well-trained athletes
[188]	Ergometry	NA		↑		↓		↑	Glucose infusion[a]
[181]	Chronic ergometry	NA	NC						Recreational athletes NC TSH response to TRH
[163]	Maximal treadmill exercise	Sufficient	NC	NC		NC			Transient changes in TH values reflected transcapillary movements of water
[2]	Aerobic exercise	Deficient		↑		↓	↓	↑	Not seen in energy-balanced group
[168]	Running	NA	↓		↓	↑		NC	Maximal exercise
[174]	Running	NA	NC	NC		NC			Endurance athletes[b] versus controls
[168]	Running	NA	↑		NC	NC		NC	Submaximal exercise
[183]	Runners	Deficient	NC	↑		↓			Prevented by caloric increase
[170]	Ultradistance	NA		↑		NC		↑	75 km[c]
[170]	Ultradistance	NA	↓	↓		↓			45 km[c]
[170]	Ultradistance	NA	NC	↑		↓		↑	42.2 km[c]
[169]	Intensive exercise	NA			↑	↑		↑	Post exercise
[169]	Intensive exercise	NA				↓		↑	12 hours post exercise
[169]	Steady state exercise	NA			↑	↑		↑	Post exercise
[169]	Steady state exercise	NA				NC		NC	12 hours post exercise
[164]	Swimming	NA			NC	↑		↑	
[176]	Swimming	NA	↑		↑	NC			20°C[d]
[176]	Swimming	NA	NC		NC	NC			26 °C
[176]	Swimming	NA	↓		↓	NC			32 °C
[197]	Ballet	NA	NC	NC		NC			
[195]	High-intensity resistance training	NA	↓			NC	↓		Leptin levels correlated with TSH levels
[195]	High-intensity endurance training	NA	↑			NC	NC		Same group of rowers underwent 3 weeks of resistance and 3 weeks of endurance training
[180]	Chronic endurance exercise	NA		↓		NC	↓	↓	Identical twins
[183]	Chronic endurance exercise	NA	NC	↓	↓	↓	↓	↓	Amenorrheic[e]
[196]	High-altitude exercise	NA	NC	NC		↓			Increased GH/IGF-1 axis and low T3 syndrome

T4 thyroxine, *T3* triiodothyronine, *fT4* free thyroxine, *fT3* free triiodothyronine, *rT3* reverse triiodothyronine, *TSH* thyrotropin, *TRH* TSH-releasing hormone, *NA* not applicable, *NC* no change, ↑ increase, ↓ decrease

[a]A glucose infusion blunted the exercise-induced changes of rT3, T3, and T4

[b]Endurance athletes had balanced increase in T3 production and disposal rates in comparison to active and sedentary men

[c]TSH, T4, and T3 are lower in older runners, whereas faster runners had higher T4 and TSH in relation to slower runners

[d]High TSH with longer cold water exposure

[e]T4/fT4, T3/fT3, and rT3 were lower in exercising amenorrheic versus sedentary group. The eumenorrheic exercise group only has a slightly lower fT4 level, but T4 and T3 were slightly lower than the eumenorrheic sedentary group

speculated whether the increase in rT3 might be protective against excess glucose metabolism, especially if intracellular glucose deficiency were present [170]. Semple et al. reported on marathon runners revealed no change in TSH, T4, T3, or rT3 levels before and after the marathon [171]. However, another study revealed an increase in TSH and fT4 post-marathon, with a decrease in fT3 and rise in T4 to rT3 conversion, which was still detectable 22 hours following race completion [172].

The level of training of athletes has been shown to affect the TH response to acute exercise. In one investigation, untrained athletes had a rise in T3, a decrease in rT3, and no change in T4, whereas the well-trained athletes were found to have a rise in rT3, no change in T3, and a decrease in T4 levels. It was hypothesized that the rT3 elevation in well-trained athletes might be adaptive to a more efficient cellular oxidation process [173]. Of note in another study, Rone et al. found an increase in T3 production and turnover in well-trained male athletes in comparison to sedentary men [174]. Following a treadmill stress test, TH levels and TRH simulation revealed responses similar in nature among sedentary subjects, regular joggers, and trained marathon runners [175].

Variation in ambient temperature appears to alter the body's TH response to exercise. One study looking at TH differences in swimmers exercising in different water temperatures demonstrated that TSH and fT4 rose in the colder water, were unchanged at 26 °C, and fell at the warmer temperature, but T3 levels were not affected [176]. Cold receptors appear to regulate a rise in TRH and TSH level in cold water, and exposure duration may affect the peak TSH with higher levels owing to longer times in the water [177, 178].

The chronic effects on thyroid hormone parameters have also been studied in endurance-trained athletes. The results of the studies conflict with regard to whether or not baseline TH levels are shifted in well-trained athletes [179]. Identical twins studied during 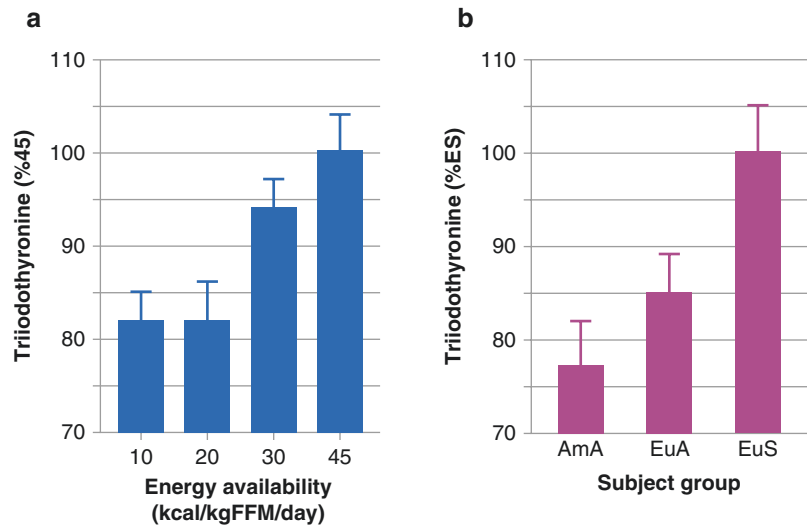an observed 93 days endurance training period with stable energy intake had an average 5-kg weight loss (primarily fat) and lower baseline fT3, T3 by the end of the exercise period [180]. A shorter study in recreational athletes over 6 weeks revealed no change in TSH or TSH response to TRH stimulation during exercise although the exercise endurance improved [181]. Also no difference was reported in baseline values for T4, T3, and TSH between endurance athletes and sedentary controls over time [174].

Radioactive iodine uptake (RAIU) may be altered secondary to chronic exercise since a lower thyroid uptake of ^{123}I has been found in regular exercising rats and humans in comparison to sedentary subjects [179].

Energy balance plays a role in the body's TH response to exercise. Data on the response of TH to fasting or malnutrition [182] suggest that the T3 decrease and rT3 increase could reflect a regulatory mechanism to regulate catabolism and energy expenditure. Of note, T3 and rT3 return to normal with refeeding. Loucks and Heath [183] found a decrease in T3 (–15%) and fT3 (–18%) along with an increase in rT3 (+24%) in healthy women undergoing aerobic exercise testing with low-caloric intake. However, this "low T3 syndrome" was not seen in individuals receiving a normo-caloric diet in balance with their energy expenditure. Other studies demonstrated that the reduction of energy availability from 45 kcal/kgFFM/day to 10 kcal/kgFFM/day was associated with a decrease in T3 levels in women undergoing 5 days of exercise (see Fig. 6.2a) [184, 185]. Especially in amenorrheic athletes, T3 levels have been found to be lower than in eumenorrheic athletes and sedentary women perhaps suggesting a generalized reduction of the energy-consuming process (see Fig. 6.2b) [185]. Furthermore, the observed correlation between T3 levels and osteocalcin suggests a possible role in collagen formation and matrix mineralization, thus contributing to the athlete triad characterized as a low energy availability or eating disorder, dysmenorrhea, and low bone density [186].

Interestingly, low-caloric diets high in carbohydrate appear to blunt the drop in T3 compared

to low-carbohydrate intake [187]. Moreover, glucose infusion has been found to diminish the increase in rT3 and T4 along with decrease in T3 [188].

In a military study, rangers were assessed over 4 days of grueling training in conjunction with sleep and caloric deprivation. The training was associated with an initial increase of TH during the first 24 h. After 4 days of training, there was a gradual decrease in T4, fT4, and T3 (65%), whereas rT3 continued to rise. The group that received a higher caloric intake, and therefore less energy deficiency, had a continued increase in T3 and T4. In the energy-deficient groups, TSH decreased during the first day and remained low throughout the training period. The response of TSH to TRH was reduced in all groups, but much less so in the energy-sufficient group [189]. The detected energy deficiency correlated with a decrease in T3 and increase in rT3 in this study [189]. Hackney et al. have demonstrated that these responses to military exercises and their relation to energy deficiency exist in extreme cold as well as hypoxic environments [190, 191].

Higher-altitude exposure has been shown to be associated with an increase in T4 and fT4 [192]. Furthermore, although Stock et al. reported that exercise at elevated altitudes is also notable for a significant increase in T4 and fT4 with even mild activity [193], not all studies entirely agree with these observations [191].

Animal studies revealed an increase in serum T3 immediately after exercise, with a gradual decrease thereafter to significantly lower values than in controls. Concomitantly, T4 levels progressively increased, resulting in the T3/T4 ratio being significantly decreased 60 and 120 min after the exercise, indicating impaired T4-to-T3 conversion [194].

Simsch et al. assessed hypothalamic–thyroid axis and leptin concentrations in six highly trained rowers. After 3 weeks of resistance training, a reduction in TSH, fT3, and leptin was found, while fT4 was unchanged. Interestingly, leptin levels correlated with basal TSH levels. In contrast, after 3 weeks of endurance training, a significant increase of TSH was observed. The authors interpreted these data to indicate that depression of the hypothalamic–thyroid axis and leptin is associated with training intensity [195]. Studies of Benso et al. also support the concept of low T3 syndrome as an adaptive mechanism to intense training as was seen in nine male well-trained climbers studied after climbing Mt. Everest and resulting in a low T3 syndrome with no significant change in ghrelin and leptin despite decrease in body weight [196].

Relative to women, amenorrhea is commonly seen in well-trained female athletes. One study found that amenorrheic subjects had lower T4 and T3 levels than the eumenorrheic groups, but the trained eumenorrheic females had slightly

lower T4 and T3 levels than the eumenorrheic nonathletes as well [197]. Of interest, the amenorrheic athletes tended to eat less fat and eat more carbohydrates with a similar caloric intake in comparison to the two other groups with more normal menstrual function. Also, the amenorrheic exercise group trained more hours and more strenuously than the other two groups. Oxygen uptake (VO_2) was similar in the trained groups, who also weighed less and had lower body fat. As measured by ^{31}phosphorous magnetic resonance spectroscopy (31P-MRS), inorganic phosphate/phosphocreatine (Pi/PCr) was not different at rest or at exercise, and pH did not differ at any activity level. However, PCr recovery was substantially faster in the eumenorrheic endurance-trained group than in the eumenorrheic nonathletes and amenorrheic athletes, and the Pi/PCr recovery was only different between the eumenorrheic-trained athletes and nonathletes [197]. PCr recovery is related to oxidative metabolism, and the fast recovery in trained eumenorrheic athletes indicates a potentially more efficient metabolism. The other parameters examined for exercise metabolism in these subjects were similar. Contrastingly, in another study, levels of TSH, T3, and T4 were not found to be different in oligomenorrheic heavily trained adolescents versus adolescent athletes without "strenuous" exercise with regular menses [198].

Summary

In summary, the thyroid function changes secondary to exercise represent complex physiologic responses, which are difficult to characterize fully. Mitigating factors in the TH response to exercise include age, baseline fitness, nutrition status, ambient temperature, altitude, as well as time, intensity, and type of exercise performed. Another important factor in interpretation of the extant literature is that not all TH blood tests were assessed in every study. Moreover, older studies employed less sensitive assay techniques, whereas various assays have improved over time. The detection of increased FFA in several studies, which may interfere with some TH assays,

also cannot be overlooked. However, despite these issues, a review of the literature does reveal certain trends (Table 6.4). One of the more consistent findings is that rT3 tends to increase with exercise especially with associated caloric energy deficiency or ultradistance exercise activities. However, TSH appears to be unaffected by exercise in about 50% of studies with an increase in TSH secondary to cold exposure being a noted exception. T4 was found to increase in 46%, decrease in 26%, and be unchanged in 28% of investigations, although an increase was more typically found with caloric energy deficiency, cold exposure, or ultradistance exercise; fT4 follows a similar pattern to T4. T3 was found to be decreased or be unchanged in 73% of study samples and usually is low with caloric energy deficiency (as in low T3 syndrome); fT3 when measured tended to follow the T3 pattern.

Many of the TH changes seen especially in athletes with negative energy balance appeared to be reversed with either a high-carbohydrate intake or even glucose infusion. Although well-trained athletes may exhibit an increased production and turnover of T4, baseline TH levels do not appear to be affected substantially by chronic exercise (i.e., endurance).

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