Chapter 4

Complications of Hyperthyroidism

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1. Introduction

Some clinical views which appear during hyperthyroidism can be called complications of hyperthyroidism. These clinical events are as follows.

1. Thyrotoxic heart disease
2. Progressive infiltrative ophtalmopathy in hyperthyroidism
3. Hyperthyroidism and bone
4. Thyroid chrisis
5. Thyrotoxic periodic paralysis
6. Thyrotoxicosis related psychosis and convulsion
7. Thyrotoxicosis related diabetes mellitus

2. Thyrotoxic heart disease

2.1. Effects of hyperthyroidism on heart-from pathophysiology to clinical complications

Cardiovascular signs and complications are generally the first alarming signs of hyperthyroidism for any physician. Effects of thyroid hormones on the heart and cardiovascular system could be direct or indirect. Palpitations and exercise intolerance are the most frequent signs [1, 2]. Although effects of iodization and world-wide use of radiocontrast agents may change the incidence, overt hyperthyroidism is common and affects 2-5% of the population [3,4]. In hyperthyroid patients mortality is increased 20% and the major causes of death are cardiac problems [5]. Atrial fibrillation is the most common and fearful arrythmic complication of

hyperthyroidism which occurs in an estimated 10-25% of all overtly hyperthyroid patients [6]. Susceptibility to arrhythmic effects of thyroid hormones may have a genetic basis and recently the studies on molecular details of cardiac actions of thyroid hormones revealed some important knowledge [7]. Meanwhile, the cause of hyperthyroidism may also change the cardiovascular risk; patients with toxic multinoduler goitre have higher cardiovascular risk than patients with Graves' disease, probably because of older age, and patients with Graves disease may have autoimmune complications, such as valvular involvement, cardiomyopathy and pulmonary arterial hypertension [8]. Effects of thyroid hormones on the heart may be grouped as molecular or cellular mechanisms and hemodynamic effects. On the other hand, thyroid hormones have 2 types of effects on every tissue; genomic effects which occur more slowly, and non-genomic effects. Severity of hyperthyroidism may also cause differences in clinical presentation of the patient, overt hyperthyroidism and subclinical hyperthyroidism bring differing degrees of risks to patients.

2.2. Molecular and cellular mechanisms of thyroid hormone effects on heart

Both T3 and T4 are lipophylic and they pass through the cellular membranes and the conversion of T4 to T3 occurs in many cells. Triiodothyronin (T3) is the active thyroid hormone and it has genetic and cellular effects on cardiac muscle and blood vessels. It acts on THRs (thyroid hormone receptors) in the nucleus, creating dimers of 9-cis-retinoic acid receptor (RXR) (9): the formed complexes recognize some specific DNA consensus sequences, the thyroid response elements (TRE), located in the enhanced region of the genes initiate the transcription [9].

In myocytes, thyroid hormones act on many TREs, such as alpha myosin heavy chain fusion (MHC-α), sarcoplasmic reticulum calcium-activated ATPase (SERCA), the cellular membrane Na-K pump (Na-K ATPase), β1 adrenergic receptor, cardiac troponin I, atrial natriuretic peptide (ANP) [10-12] and some genes are also suppressed such as β-myosin heavy chain fusion (MHC-β), adenylic cyclase (IV and V) and the Na-Ca antiporter [13].

Thyroid hormone upregulates α, but downregulates β-chain in myocytes [14]. The final effect of thyroid hormones in animal studies is an increased rate of V1 isoform of MHC (MHCα/α) synthesis that is characteristically faster in myocardial fibre shortening [13,15]. A similar effect has been also observed in preliminary human studies [16,17].

Thyroid hormones also have effects on SERCA, which is responsible for the rate of calcium uptake during diastole, by actions on calcium activated ATPase and its inhibitory cofactor phospholamban [18,19]. Thyroid hormones enhance myocardial relaxation by upregulating expression of SERCA, and downregulating expression of phospholamban. The greater reduction in cytoplasmic calcium concentration at the end of the diastole increases the magnitude of systolic transient of calcium and augments its ability for activation of actin-myosin subunits. As a confirmation, phospholamban deficient mice showed no increase in heart rate after thyroid hormone treatment [20].

On the plasma membranes, T3 exerts direct extragenic actions on the functions other ion channels such as Na/K ATPase, Na/Ca++exchanger, and some voltage gated K channels (Kv

1.5, Kv 4.2, Kv 4.3) affecting myocardial and vascular functions [21,22] coordinating electrochemical and mechanical responses of myocardium [23,24]. It prolongs the activation of Na channels in myocardial cells [25] and induces intracellular Na uptake and secondary activation of the Na-Ca antiporter, which can partly explain the positive inotropic effect. T3 exerts direct effect on L-type calcium channels resulting in abbreviation of action potential duration and possibly L-type calcium channel mRNA expression [26,27].

The strong inotropic activity of thyroid hormones is probably due to an increased number of β-adrenergic receptors [28]. Circulating cathecholamine levels are in fact the same, but G protein and β-receptors increase [29]. The sensitivity of cardiovascular system to adrenergic stimulation does not change by thyroid hormones [30,31]. The changes in the heart rate result from both an increase in sympathetic tone and decrease in parasympathetic tone [32,33].

These genomic effects fail to explain the fast actions of thyroid hormones on the cardiovascular system. Non-genomic effects promote rapid changes, such as increased cardiac output [34-36]. The hemodynamic consequences of hyperthyroidism and nongenomic changes on plasma membranes occur acutely and contribute to these rapid changes. Studies indicate that thyroid hormone activates acute phosphorylation of phospholamban, and that also partly explains the homology between thyroid hormone and adrenergic system on the heart [32].

In an experimental study on rats, thyroid hormones upregulate connexin-40, a gap junction protein of myocardium important for the transport of electrical activity, and this may be one of the pathogenetic mechanisms of atrial fibrillation in hyperthyroidism [37]. In another animal study the authors suggested that the connexin-43 phosphorylation was downregulated by T3 in diabetic rats and decrease adaptation of heart to hyperglycemia and this may render the heart prone to ventricular arrythmias [38]. In fact thyroid hormone receptor alpha 1 is predominantly expressed in cardiac myocardium and may have an important role in cardiac myoblast differentiation by ERK kinase dependent process, but its clinical relevance is not known [39]. Also ERK (extracellular signal-regulated kinase) pathway may have a role in negative cardiac remodelling and decreased cardiac contractile function in hyperthyroidism, by inhibition of the Raf-1/ERK pathway by T3 [40,41].

Meanwhile, the thyroid hormone may have direct (without autonomous nervous system) effects on the sinoatrial node [42,43] and oxidative stress in animal studies [44]. The heart rate increases due to increased sinoatrial activity, a lower threshold for atrial activity, and a shortened atrial repolarisation [45,46]. Together with hemodynamic changes, i.e. the volume preload increases due to activation of the renin-angiotensin system [47], contractility increases due to increased metabolic demand and the direct effect of the thyroid hormone on heart muscle [48] and systemic vascular resistance decreases because of triiodotyronine-induced peripheral vasodilatation [49]. The result is a dramatic increase in cardiac output [50].

Local type 2 iodothyronine deiodinase up-regulation may also be involved in cardiac remodelling via activation of thyroid hormone signalling pathways involving Akt and p38 MAPK (mitogen-activated protein kinase) in thyrotoxic-dilated cardiomyopathy [51]. Animal studies show the effects of thyroid hormones on soluble fractions of 5′-nucleosidase activity, via protein kinase C-related pathway [52]. Preclinical studies blocking Akt by angiotensin-II type

2 receptor blocker showed that this blockage might prevent thyroxine-mediated cardiac hypertrophy [53]. Meanwhile, hypertrophied myocytes may be susceptible to apoptotic stimulation by angiotensin II in hyperthyroidism [54].

Studies on rats show that mitochondrial ultrastructure was damaged in T3 treated hyperthyroid rat heart, leading to energy depletion and cardiac dysfunction [55]. Another study on hamsters revealed that long term hyperthyroidism cause increased left ventricular interstitial fibrosis, significant cardiac hypertrophy and deleterious cardiac remodeling characterized by myocyte lengthening, chamber dilatation, decreased relative wall thickness, increased wall stress, and impaired global cardiac function whereas cardiomyocyte functions may be enhanced [56]. Some animal studies Show beneficial effects of angiotensin receptor blockers on myocytes as improved left ventricular longitudinal strain, heart rate and reduced cardiomyocyte width, affecting structural remodelling beyond the anti-tachycardic effect of beta-blockers [57].

2.3. Hemodynamic effects of thyroid hormones

Hemodynamic effects of thyroid hormones are generally nongenomic and faster, by direct effects on the heart and blood vessels. In the peripheral vascular system, the rapid use of oxygen, increased production of metabolic end products and relaxation of arterial smooth muscle fibres by thyroid hormone cause peripheral vasodilatation [21]. This fall in peripheral vascular resistance (PVR) plays the central role in all hemodynamic changes caused by thyroid hormones [58]. Decreased PVR causes an increase in heart rate and selective increase in blood flow of some organs (skin, skeletal muscles, heart), and a fall in diastolic pressure with consequent widening of pulse pressure. Vasodilatation without an increase in renal blood flow causes reduction in renal perfusion and activation of the renin-angiotensin system which causes sodium retention and increased blood volume [59]. In addition, thyroid hormones regulate erythropoietin secretion and increased red cell mass may also contribute to blood volume increase [60]. Improved diastolic relaxation and increased blood volume increased left ventricular end-diastolic volume (LVEDV). Reduced PVR and increased LVEDV means increased preload and decreased afterload, thus the stroke volume increases. Increased stroke volume and increased heart rate leads to a doubling or tripling of cardiac output which cannot be solely explained by the increased metabolic rate of the body [61].

The importance of the contribution of decreased systemic vascular resistance to the increase in systemic blood flow in patients with hyperthyroidism is evidenced by studies in which the administration of arterial vasoconstrictors, atropine and phenylephrine, decreased peripheral blood flow and cardiac output by 34% in patients with hyperthyroidism but not in normal subjects [62,63].

2.4. Clinical aspects of hyperthyroidism and subclinical hyperthyroidism on heart

Increased rate and strength of the heart contractility, together with an exaggerated response of heart rate to exercise is present in hyperthyroid patients who describe this as palpitations. Diurnal heart rate variations are generally preserved. The most common ECG abnormality is

sinusal tachycardia and shortened PR interval, and frequently intra-atrial conduction is prolonged, which is seen as increase in P wave duration. Intraventricular conduction delay in the form of right bundle branch block is present in around 15% of patients, and atrioventricular block may also occur due to unknown reasons. The most common rhythm disturbance in hyperthyroid patients is sinus tachycardia [32]. Its clinical impact however is overshadowed by that of patients with atrial fibrillation. The prevalence of atrial fibrillation (AF) and less common forms of supraventricular tachycardia in this disease ranges between 2 to 20 percent [64,65]. AF is generally accompanied by rapid ventricular response. It is more common in men and its significance increases by age, after 40 years [65]. As in the case of angina or heart failure, the development of AF should not be attributed only to hyperthyroidism, and the underlying organic heart diseases should be investigated.

Atrial fibrillation usually reverses to a sinus rhythm by achievement of a euthyroid state, if the patient is younger and the duration of hyperthyroidism is not long. The beta-adrenergic blockade may be effective in controlling the ventricular rate. Increased plasma clearance of beta-blockers may necessitate higher doses [66]. Among them propranolol has the advantage of blocking the conversion of T4 to T3 in peripheral tissues, however other cardioselective beta-blockers have a longer half-life and can be equally effective on the heart. In cardiac arrhythmias intravascular infusion of calcium blockers should be avoided due to the risk of a further fall in PVR [67]. It is still controversial whether the patients with AF should have anticoagulant therapy to prevent systemic embolization. It is advised to evaluate each patient on a case-by-case basis, and determine the risk of bleeding over embolization [68,69]. In younger patients with hyperthyroidism and AF, who do not have other heart disease, hypertension, or independent risk factors for embolization, the risk of anticoagulant therapy may suppress its benefits. But it would be appropriate to administer anticoagulant agents to older patients with known or suspected heart diseases, or AF with longer duration. When oral anticoagulants will be used, it should be considered that hyperthyroid patients will need smaller doses than euthyroid ones, due to faster elimination of vitamin-K dependent clotting factors [70].

In the patients with AF the maintenance of sinus rhythm is not possible until the euthyroid state is restored, so electrical cardioversion is not recommended without confirming the euthyroid status.

Many hyperthyroid patients experience exercise intolerance and exertional dyspnea, in part because of weakness in the skeletal and respiratory muscle [71] and also due to inability to increase heart rate or lower vascular resistance further, as normally occurs in exercise [72]. The tem “high output heart failure” has not been used in recent decades, because it is clear that the heart is still able to increase cardiac output at rest and with exercise. In the setting of low vascular resistance and decreased preload, the cardiac functional reserve is compromised and cannot rise further to accommodate the demands of submaximal or maximal exercise [73]. About 6% of thyrotoxic patients develop heart failure and less than 1% develop dilated cardiomyopathy with impaired left ventricular systolic dysfunction, due to the tachycardia-mediated mechanism leading to an increased level of cytosolic calcium during diastole, with reduced contractility of the ventricle and diastolic dysfunction, often with tricuspid regurgitation [74]. In the recent study of Yue et al, diastolic dysfunction was more prominent in

thyrotoxic patients older than 40 years of age, whereas in younger ones marked reduction in peripheral vascular resistance and increased cardiac output were prominent [75].

Hyperthyroidism may complicate or cause pre-existing cardiac disease because of increased myocardial oxygen demand, increased contractility and heart rate, and may cause silent coronary artery disease, anginas or compensated heart failure and even endothelial dysfunction [76]. Treatment of heart failure with tachycardia should include a beta-blocker, by considering its contraindications in each patient. Furosemide may help to reverse the volume overload, but digoxin is less beneficial when compared with euthyroid heart failure patients because there may be relative resistance to its action, due to greater blood volume (distribution) and the need to block more Na-K-ATPase in myocardium [70].

Subclinical hyperthyroidism is a state characterised by low serum thyrotropin levels and normal serum thyroid hormone concentrations. Over recent decades this state has also been found to be associated with some abnormalities in cardiac function. Enhanced systolic function and impaired diastolic function due to slowed myocardial relaxation may cause increased left ventricular mass in these subjects, together with increased heart rate and arrhythmias by similar mechanisms as overt hyperthyroidism [77,78]. In people over 60 years of age subclinical hyperthyroidism was associated with a tripled risk of atrial fibrillation during a 10-year follow-up period [79]. In a recent cross-sectional study with 29 patients, subclinical hyperthyroidism was found to be related with impaired functional response to exercise with low oxygen consumption and exercise threshold, together with slower heart rate recovery [80].

Besides antithyroid treatment strategies, beta-blocker therapy reduces heart rate and improves left ventricular mass, but positive inotropic response persists. This subclinical hyperthyroidism is associated with increased cardiovascular mortality [81]. In the study of Heeringa et al with 1,426 patients, it was shown that even the high-normal thyroid function may increase the risk of AF [82]. Besides increased AF and thromboembolic events, increased left ventricular mass and left ventricular function may be the reason. Thus, it is advised to measure serum thyrotropin in all elderly patients with systolic hypertension, a widened blood pressure, recent-onset angina, atrial fibrillation and any exacerbation of ischemic heart disease and treat it [72,83].

3. Progressive infiltrative ophtalmopathy in hyperthyroidism

3.1. Hyperthyroidism and eye disease

Thyroid eye disease (TED), also called thyroid-associated ophthalmopathy (TAO) and Graves' ophthalmopathy (GO), affects 25–50% of patients with Graves' disease [84]. Regardless of whether hyperthyroidism occurs first, the signs and symptoms of GO become manifest in 85% of patients within 18 months [85]. The clinical features are usually mild. Most common symptoms are; ocular irritation with redness and tearing,, sensitivity to light, double vision, blurring of vision, and feeling a pressure sensation behind the eyes. On physical examination, extraocular muscle dysfunction, proptosis, periorbital and eyelid edema, conjunctival chemos,

lid lag and retraction (or stare), or exposure keratitis may be detected [86]. Most patients experience only the minor congestive signs of TAO (chemosis, injection, lid edema), with improvement in several months without treatment. Approximately 28% of TAO cases are severe and symptomatic for several years. Symptoms and signs include, restricted motility leading to diplopia, exposure keratopathy, optic neuropathy and loss of vision [87,88].

TAO can be divided into two clinical stages; congestive and fibrotic. In the congestive or inflammatory stage, auto-immunity leads to inflammatory cellular infiltration of the muscles and transformation of fibroblasts into adipose tissue. The fibrotic stage is characterized by fibrosis which causes proptosis and strabismus [89,90].

3.2. Pathophysiology

In TAO, the most important pathological changes are enlarged extraocular muscles and increased orbital fat. These changes result from a complex interplay among orbital fibroblasts, immune cells, cytokines, auto-antibodies, genetics, and environmental factors [84].

Interactions between orbital fibroblasts, immune cells, cytokines and autoantibodies

Patients with TAO, orbital tissue is infiltrated by inflammatory cells (T helper type 1 (Th1) and T helper type 2 (Th2) lymphocytes, B lymphocytes, mast cells, and macrophages) [91,92]. These cells release cytokines which participate in tissue reactivity and remodeling. Normally, the antigens to which lymphocytes respond are foreign, and several tolerance mechanisms act to prevent the development of reactivity to self-antigens or autoimmunity, but these tolerance mechanisms sometimes fail and autoimmunity develops [93,94]. Fibroblasts are a highly interactive cell type, described as “sentinel cells” [95]. They, respond to immune stimulation and actively participate in the inflammatory pathway [96,97]. In patients with TAO, orbital fibroblasts synthesize excess glycosaminoglycans (GAGs), including hyaluronan. These can differentiate into adipocytes, leading to the accumulation of fat [98]. Orbital fibroblasts do not express the IL-1 receptor antagonist at levels found in other fibroblasts, but also display lymphocyte costimulatory molecules such as CD40. These differentations result in excessively high levels of Cox-2 and PGE_2 in response to proinflammatory cytokines [99,100]. T lymphocytes in the orbital tissue interact with fibroblasts. This interaction results with activation and proliferation of fibroblasts, synthesis of extracellular macromolecules, and differentiation to adipocytes [101]. A summary of this model for the pathogenesis of TED is depicted in Figure 1 [102].

Autoantigen expression by orbital fibroblasts results in T lymphocyte accumulation to the orbit [103]. The autoantigen may be a TSH receptor (TSH-R) or an insulin-like growth factor-1 receptor (IGF-1R) [103,104]. T lymphocytes in the orbital tissue induce fibroblast proliferation and hyaluronan synthesis. This result in orbital tissue remodeling [101]. Stimulation of orbital fibroblasts by T lymphocytes results in production of chemokines (e.g. IL-16, RANTES) and cytokines (e.g. IL-6). These molecules initiate migration of T and B lymphocytes to the orbital tissue and increase fibroblast presentation of autoantigens [97,101,105). Costimulatory molecules, adhesion molecules, and cytokines like IFNγ, IL-1β, and TNFα play an important role in the interaction between T lymphocytes and fibroblasts. One of the communication

pathways of T lymphocytes and orbital fibroblasts is the CD40-CD40 ligand pathway [97,100,101]. In TAO orbital fibroblasts express high levels of CD40 [97,106]. Activation by CD40L induces hyaluronan synthesis, IL-6 and IL-8, Cox-2 and PGE2 [97,101,107].

T lymphocyte-mediated activated fibroblasts release factors which promote and activate the proliferation of T lymphocytes. In this way fibroblasts perpetuate inflammation [101,108]. Antonelli et al. found that orbital fibroblasts from TAO patients may modulate the activity of T lymphocytes through the production of CXCL10. Serum CXCL10 levels were higher in active TAO patients than in those with inactive disease. CXCL10 release enhances the migration of T lymphocytes into the orbital tissue. These lymphocytes secrete IFNγ and TNFα. There is a positive feedback between CXCL10 and IFNγ – TNFα. Peroxisome proliferator-activated receptor-gamma (PPAR-γ) activation has an inhibitory role in this process [108]. Feldon et al. found that activated human T lymphocytes drive the differentiation of human fibroblasts to adipocytes. They showed that human T cells, when activated, strongly express Cox-2 and produce PGs, possibly 15d-PGJ_2, that are PPAR-γ ligands and human T cells also produce PGD_2. These findings showed that PGD_2 converts to the PGJ series of PGs with the final product being 15d-PGJ_2, a notable potent PPAR-γ ligand [109-111]. Feldon et al. also showed that human orbital fibroblasts express PPAR-γ and that 15d-PGJ_2, PGD_2, and 15d-PGD_2 strongly induce adipogenesis [109]. Natural and synthetic activators of PPAR-γ stimulate lipid accumulation and the expression and secretion of adiponectin [112,113]. PPAR-γ levels are higher in orbital tissue from patients with active TAO [108,114].

Chen et al. showed higher mRNA levels of a macrophage chemoattractant called C-C motif chemokine ligand-2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1) and dense infiltration with macrophages in the orbital fat compared with normal controls [115].

3.3. Smoking

There is a strong and consistent association between smoking and TAO [116]. But the exact mechanism by which smoking affects TAO is not known. Formation of superoxide radicals and tissue hypoxia could be responsible. Cigarette smoke either contains or can generate a variety of oxidants and free radicals [117]. Orbital fibroblasts can be induced by tissue hypoxia (5% CO_2 and 95% N_2) and superoxide radicals, thus they proliferate and synthesize GAGs [118,119]. Mack et al. cultured orbital fibroblasts, obtained from patients undergoing orbital decompression for severe GO. They showed that, inreased human leukocyte antigen (HLA-DR) expression of orbital fibroblasts occurred in response to nicotine and tar only in the presence of interferon-γ. These findings suggest that there is an interaction between smoking and orbital immune responses [120]. Many studies demonstrated a dose-response relationship between the numbers of cigarettes smoked per day and TAO [121]. Smokers suffer more severe TAO than non-smokers. Smoking increases the progression of TAO after radioiodine therapy for hyperthyroidism [116]. Eckstein et al. demonstrated that smoking influences the course of TAO during treatment in a dose dependent manner. The response to treatment is delayed and considerably poorer in smokers [122]. Pfeilschifter et al. showed that former smokers had a significantly lower risk for the occurrence of proptosis and diplopia than active smokers with a comparable lifetime cigarette consump

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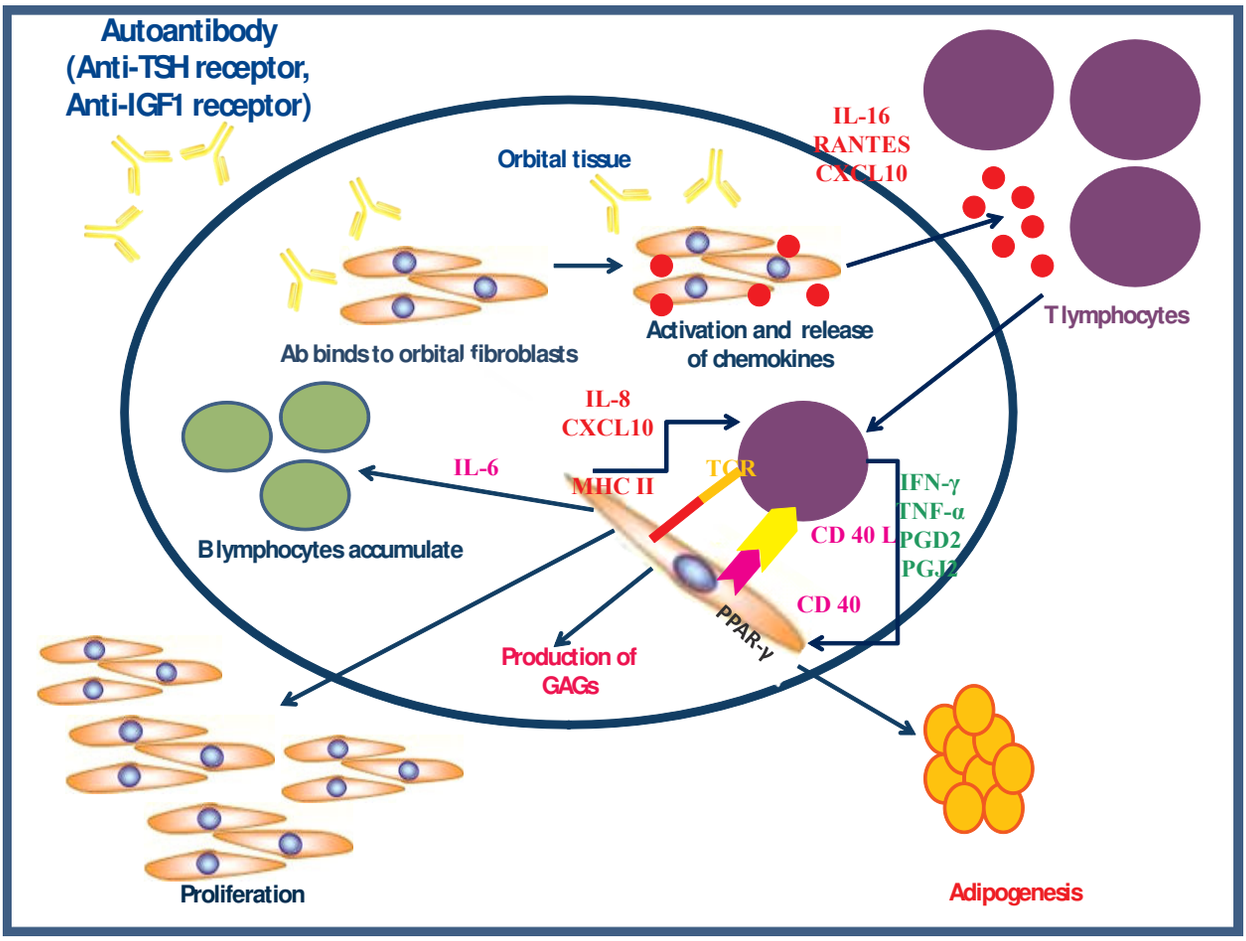


(Data adapted from reference 102)

Figure 1. Pathophysiology of thyroid eye disease

3.4. Genetics

For the development of TAO the presence of autoimmune thyroid disease appears to be necessary, but not sufficient [124]. The interaction between genetic and environmental factors plays a major role for the development of TAO in a patient with autoimmune thyroid disease. TAO and autoimmune thyroid disease share a common etiology; regardless of which occurs first, the other develops within 18 months in 80% of affected patients [125]. Polymorphic variations in individual somatic genes or groups of genes known to be involved in thyroid autoimmunity might also predispose to TAO.

Thymic stromal lymphopoietin (tslp) gene promoter polymorphisms

The role of TSLP in Th17 cell differentiation implicates TSLP in the pathogenesis of TAO. Tsai et al. genotyped 470 patients with TAO at 3 single nucleotide polymorphisms (SNPs) in TSLP and determined the serum concentrations of TSLP in 432 patients and 272 controls. They showed that TSLP polymorphisms are associated with TAO and that expression levels of TSLP are higher in patients than in control subjects. In addition, they concluded that TSLP mediates

the differentiation of CD4+T cells into Th17 cells. According to this study the *TSLP* gene may be a relevant candidate gene for susceptibility to TAO. *TSLP* genotypes may be used as genetic markers for the diagnosis and prognosis of TAO [126].

Toll-like receptor gene polymorphisms

Toll-like receptors (TLRs) are a family of pattern-recognition receptors, which play a role in eliciting innate/adaptive immune responses and developing chronic inflammation. Liao et al evaluated 6 TLR-4 and 2 TLR-9 gene polymorphisms in 471 GD patients (200 patients with TAO and 271 patients without TAO) from a Taiwan Chinese population. There was no statistically significant difference in the genotypic and allelic frequencies of TLR-4 and TLR-9 gene polymorphisms between the GD patients with and without TAO. In the sex-stratified analyses they showed that the association between TLR-9 gene polymorphism and the TAO phenotype was more pronounced in the male patients. Their data suggest that TLR-9 gene polymorphisms are significantly associated with increased susceptibility of ophthalmopathy in male GD patients [127].

Polymorphisms of B7 molecules (CD80 and CD86)

Liao et al. evaluated genotypes of CD80 and CD86 polymorphism in GD patients. They found that the frequency of C allele at position rs_9831894 of the CD86 gene is different in patients with GD (with and without TAO). They showed that the G-A haplotype has a protective effect in the development of TAO among patients with GD. Their data suggest that the polymorphisms of the CD86 gene may be used as genetic markers for making the diagnosis and prognosis of TAO [128].

Interleukin-1beta (IL1β) polymorphisms

Recent studies have demonstrated that IL1β plays a role in the development of TAO by inducing adipogenesis and accumulation of GAGs and prostaglandin E2 (PGE2) [129,130]. Liu et al. found that the SNPs rs3917368 and rs1143643 in the 3′ UTR and intron regions of *IL1β* and patients with the genotypes containing both rs3917368 A/A and rs1143643 A/A may bear a higher risk of developing TAO. Thus we can speculate that *IL1β* polymorphisms can be related with the development of TAO in GD [131].

Cytotoxic T lymphocyte antigen-4

Vaidya et al. firstly reported an association between *CTLA-4A/G* polymorphism at codon 17 and TAO [132], but this data was not confirmed by Allahabadia et al. in a larger cohort of patients [133]. Daroszewski et al. evaluated the relation between soluable CTLA-4 level and clinical manifestation of TAO and CTLA-4 gene polymorphisms. They found higher levels of Serum sCTLA-4 in the TAO group than in controls. The level of sCTLA-4 was higher in severe TAO patients than in non-severe cases. They showed for the first time that the presence of the *CTLA-4* gene polymorphisms Jo31 and CT60 were related with elevated sCTLA-4 levels [134]. These data suggest that the polymorphisms of the *CTLA-4* gene may be used as a genetic marker for making the diagnosis and prognosis of TAO. The role of sCTLA-4 and its full-length cell-bound analogue in autoimmunity remains uncertain.

PPAR-γ gene polymorphism

The PPAR-γ transcription factor is involved in both adipogenesis and inflammation which have been implicated in the pathogenesis of TAO. Alevizaki et al. found no difference in the distribution of the Pro(12)Ala PPAR-γ gene polymorphism between GD patients with and without TAO. But they showed that PPAR-γ polymorphism carriers had lower TSH-Rab levels and lower clinical activity scores (CAS). According to this study patients with TAO who have this polymorphism are associated with less-severe and less-active disease [135].

IL-23R polymorphisms

Huber et al. demonstrated that two IL-23R polymorphisms (rs10889677 and rs2201841) were associated with TAO. According to this study we can speculate that these variants may induce TAO by changing the expression and/or function of IL-23R, by promoting a pro-inflammatory signaling cascade [136].

Protein tyrosine phosphatase-22

Lymphoid protein tyrosine phosphatase (LYP, aka PTPN-22) represents another negative regulator of T cell activation. Syed et al. found an association between certain single nucleotide polymorphisms (SNPs) in the protein tyrosine phosphatase (PTP) called PTPN12 and increased risk of mild/moderate ophthalmopathy [137]. But this data should be confirmed in larger studies.

Nuclear factor (NF)-[kappa]B1

Kurylowicz et al. showed a correlation between a polymorphism in the NF-[kappa]B1 gene promoter (-94ins/del adenine, thymine, thymine, guanine) and the development of TAO [138].

Human leukocyte antigen (HLA)

HLA class I-II genes are related for the development of TAO [139]. Akaishi et al. found TAO patients with major extraocular muscle involvement have had a higher frequency of the HLA-DRB1*16 allele, but patients with minor extraocular muscle involvement have had a higher frequency of the HLA-DRB1*03 allele [140]. In another study an association between HLA-A11,-B5,-DW12 and-DR14 and TAO has been found [141,142].

3.5. Cytokines

Autoimmune thyroid disease involves the activation of multiple cytokine networks. Serum IL-6 levels were greater in the patients with TAO than in those without eye disease [143] and both Th1-and Th2-derived cytokines were elevated in TAO patients compared with control samples [144]. Chen et al. found that the exaggerated capacity of orbital fibroblasts to express high levels of both IL-6 and its receptor in an anatomic site-selective manner could represent an important basis for immune responses in TAO [145]. Higher serum levels of IL-17 were obtained in TAO patients than in controls. Serum IL-17 concentration had significant correlation with CAS [146]. Significantly higher PAI-1 [147] and IgE levels [148] were found in TAO patients than in the control groups.

3.6. Imaging procedures in TAO

Ultrasound (US)

US is of primary importance in orbital pathology because of its safety, non-invasiveness, short time of investigation, low cost, lack of radiation and application without need to prepare the patient. In endocrine orbitopathy; the A scan demonstrates echographical widening of the peripheral orbital space and a widening of the muscle echo, while the B scan shows a high internal echo of the connective tissue septa, increased reflection of the muscle belly and distension of the retrobulbar optic nerve sheaths, enlargement of lacrimal gland and dilatation of the superior ophthalmic vein [149]. Although it has many advantages, US cannot effectively display the muscles at the apex of the orbit. US is not as effective as other diagnostic procedures in delineating the relationship of orbital pathology to contiguous structures, nor is it reliable in imaging lesions of either the posterior orbit or those involving the bone walls [150].

Computed tomography (CT)

According to differential X-ray absorption CT can differentiate normal and abnormal structures of different tissue density. In CT orbital fat images as a black, low-density area, while in contrast to this extraocular muscles and the optic nerve image as higher-density areas [151]. The primary areas of orbital involvement are extraocular muscles, and CT findings correlate with clinical impressions of the severity of extraocular muscle enlargement [152]. Muscle involvement on CT of TAO is usually limited to the non-tendonous portion of the muscle. Due to compression of the optic nerve by enlarged extraocular muscles near the orbital apex, optic nerve dysfunction can be seen in TAO [153]. Other findings that may be noted on CT are lachrymal gland enlargement, a dilated superior opthalmic vein, muscle belly enlargement and increase in orbital fat volume [154,55]. CT imaging is a non-invasive, simple, fast, and cost effective imaging procedure. Furthermore, having high sensitivity and correlation with clinical findings, CT imaging should be considered first during diagnostic evaluation of TAO.

Magnetic resonance imaging (MRI)

Pulse sequences that examine T2 in MRI can estimate the water content of tissues. In TAO lymphocytes infiltrate the orbital tissue that causes fibroblast stimulation. Fibroblasts produce large amounts of GAGs. By binding large amounts of water, GAGs cause edema. Increased water content of thickened extra-ocular muscles cause elevated T2 [156]. In TAO there are two different phases with disease activity. Medical treatment can be effective in the active stage. Therefore, for predicting the outcome of medical management the evaluation of disease activity is important. Yokoyama et al. investigated whether MRI could assess the disease activity in TAO. They found that MRI is not only a useful tool for detection of extraocular muscle enlargement, but also for assessment of disease activity in TAO [157]. In conclusion, MRI is useful to assess TAO. But cost and availability are current limitations of this modality. Therefore, MRI should be used for the management of TAO in specialized patients and clinics.

Octreoscan (OCT)

It is thought that radionuclide accumulation is probably due to binding to somatostatin receptors on lymphocytes, myoblasts, fibroblasts and endothelial cells. Another explanation

is local blood pooling due to venous stasis by the orbital inflammation [158,159]. Krassas et al. found that OCT positivity is higher in Graves' patients with than in those without ophthalmopathy, and higher in patients with active TAO than in those with inactive TAO [160]. Postema et al. demonstrated that OCT positivity correlates with activity of the TAO such as high CAS [161]. Thus, a positive orbital OCT means clinically active TAO, in which immunosuppressive treatment might be of therapeutic benefit [162]. However, limitations such as cost, non-negligible radiation burden, non-specific examination for TAO, and finally, lack of evaluation of eye muscle swelling restrict the widespread use of this technique [163]. Orbital OCT is mainly indicated to select patients with TAO who will benefit from immunosuppression [162].

3.7. Other diagnostic techniques

Kuo et al. were first described in a positron emission tomography (PET/CT) study in a patient with TAO. The detection of inflammation by 18F-fluorodeoxyglucose (FDG) uptake was sensitive and objectively demonstrable by this semi-quantitative imaging method [164]. García-Rojas et al. carried out the first prospective study. FDG uptake of extra-ocular muscles was statistically different between patients with and without TAO. In cases with TAO where clinical doubt exists, PET/CT provides valuable and useful information for the diagnosis, characterization, and therapeutic decision [165]. Further research is required to define the role of FDG-PET/CT in the management of TAO.

Another tool to measure orbital inflammation is the uptake of radioactively labeled substances, such as ^{67}Gallium (Ga) citrate [166] and ^{99m}Technetium (Tc)-labeled agents [167,168]. In medical literature there are few studies about these nuclear imaging techniques.

3.8. Clinical classification systems

The treatment for TAO varies according to the level of disease activity. Thus, methods have been proposed to determine whether TAO is active (33). There are two main scoring systems [169,170]:

1. NOSPECS (No signs or symptoms; Only signs; Soft tissue involvement with symptoms and signs; Proptosis; Eye muscle involvement; Corneal involvement; Sight loss)
2. CAS (Clinical Activity Score) systems.

Neither NOSPECS nor CAS are both specific and completely reliable, but CAS is a simple office-based tool. The modified NOSPECS criteria include lid retraction, soft tissue inflammation, proptosis, size difference, extra-ocular muscle involvement, corneal defects, and optic nerve compression [169]. CAS demonstrates the presence or absence of seven symptoms or signs that indicate inflammation (Table-1) [171].

The score ranges from 0 to 7, with 0 to 2 characteristics indicating inactive TAO and 3 to 7 characteristics indicating active TAO. The CAS has a high predictive value for the outcome of immunosuppressive treatment in TAO. The main determinant of therapeutic outcome is disease activity, not disease duration [172]. In addition, the severity of disease should be

assessed (Table-2). Dysthyroid optic neuropathy, corneal breakdown or both indicate that the TAO is sight-threatening and requires immediate treatment [116].

• Spontaneous retrobulbar pain
• Pain with eye movement
• Redness of the eyelids
• Redness of the conjunctiva
• Swelling of the eyelids
• Swelling of the caruncle
• Conjunctival edema (chemosis)

Table 1. Components of the Clinical Activity Score

• Lid aperture	• Exophthalmos
• Swelling of the eyelids	• Subjective diplopia score
• Redness of the eyelids	• Eye muscle involvement
• Redness of the conjunctivae	• Corneal involvement
• Conjunctival edema	• Optic nerve involvement
• Inflammation of the caruncle or plica	

Table 2. Assesment of Disease Severity

3.9. Management

Smoking and TAO

Patients should be encouraged to quit smoking. In an observational study smoking cessation has been associated with a decreased risk of the development of exophthalmos and diplopia in patients with Graves' disease [171].

Management of hyperthyroidism in patients with TAO

Uncontrolled thyroid functions (both hyper-and hypothyroidism) are related to severe TAO. Patients with hyperthyroidism can be treated with anti-thyroid drugs (ATDs), radioactive iodine (RAI) therapy and surgical therapy. Some different studies have shown improvement in TAO [173] by indirect beneficial effects [174] and a gradual decrease in TSH-receptor antibody (TRAb) levels during ATDs treatment [175]. There are confliciting reports in medical literature about RAI therapy and severe TAO [176,177]. But this association cannot be excluded. This risk can be eliminated by therapy with oral glucocorticoids (GCs) after RAI therapy and avoiding post-treatment hypothyroidism [116]. Thyroidectomy is an effective treatment choice for the definitive cure of hyperthyroidism. Wilhelm et al. showed that near-total/total thyroidectomy is safe and superior to subtotal thyroidectomy for management of hyperthyroidism in Graves' disease [178]. According to the European Group on Graves' Orbitopathy (EUGOGO) Consensus Statement; ATD therapy and thyroidecto-

my do not affect the course of TAO. No particular ATD or regimen, nor any type of thyroidectomy (subtotal or total) has been demonstrated to have any advantages in terms of outcome of TAO in hyperthyroidism [116].

3.10. Pharmacologic treatments

TAO represents a complex therapeutic problem. Currently available pharmacologic treatment options result in a partial or absent response of the ophthalmopathy. Up to date available treatments for TAO are as follows:

Glucocorticoids

Glucocorticoids (GCs) are effective treatment options in TAO because of their antiinflammatory and immunosuppressive actions (96). Moreover they decrease GAGs synthesis and secretion by orbital fibroblasts [180].

GCs can be administrated by oral, local (retrobulbar or subconjunctival) and intravenous routes. Oral GCs are generally used in high doses (prednisone, 60–100 mg/day or equivalent doses of other steroids) and for long-time periods (several months). It has been demonstrated that high-dose oral GCs are effective on soft tissue changes and optic neuropathy. But when its dose is tapered down and/or withdrawn, recurrence of active eye disease is a frequent problem [181]. In slightly more than 60% of cases (range: 40–100%) favorable effects of high-dose oral GCs are reported. GCs have also been used intravenously. In most studies effects have been observed on inflammatory signs and optic nerve involvement. But the effects on extra-ocular muscle involvement, and especially proptosis, have not been constantly impressive [90].

In most studies patients treated with intravenous GCs have had more favorable results compared with patients treated with oral GCs [18,183]. But in almost all studies treatment with intravenous GCs have been associated with, in the interpulse periods, or followed by (often prolonged) treatment with oral GCs. Moreover there have been biases in patient selections (different degrees of disease activity and duration). Bartalena et al. compared the efficacy and safety of three doses of intravenous (IV) methylprednisolone (2.25, 4.98, or 7.47 g in 12 weekly infusions) in patients with moderate to severe and active TAO. They demonstrated that the use of a cumulative dose of 7.47 g of methylprednisolone provides short-term advantage over lower doses. This benefit was transient and associated with slightly greater toxicity. According to this study we can speculate that an intermediate-dose regimen be used in most cases and the high-dose regimen be reserved to the most severe cases of TAO [184]. Systemic glucocorticoid therapy relates with some side effects and complications. Therefore, local (retrobulbar or subconjunctival) glucocorticoid therapy has been raised. But in most studies local glucocorticoid therapy had been less effective than systemic administration. As a result, local glucocorticoid therapy can be a treatment option in patients with active ophthalmopathy and with major contraindications to the systemic administration [181].

GCs are generally used for severe and active TAO [90]. Furthermore, patients with sight-threatening dysthyroid optic neuropathy should be treated with high-dose intravenous or oral

glucocorticoid agents [116]. Additionally, there are some case reports in medical literature, who had severe complicatons related with high-dose glucocorticoid pulse therapy [185].

Somatostatin (SST) analogues

SST receptors (SSTR) are expressed in many tissues, including activated lymphocytes. OCT was proposed as a method to evaluate orbital inflammation in TAO. The use of the SST analog, octreotide, was first reported in TAO patients by Chang et al [186]. Uysal et al. evaluated the effect of octreotide treatment in nine patients with TAO. Seven of the patients showed improvement in CAS. Proptosis improved either slightly or significantly in seven patients. None of the patients has showed deterioration in the eye according to their findings [187]. A major disadvantage of octreotide is its short half-life, which requires multiple injections. To overcome this limitation, new long-acting SST analogs (lanreotide / octreotide-LAR) have been developed. Stan et al. carried out a randomized, double-blind, placebo-controlled trial of octreotide-LAR for treatment of TAO. In octreotide-LAR-treated patients, the CAS improved with a greater degree than in the placebo group. They noted improvement in eyelid fissure width, which suggest that octreotide LAR treatment may be effective in TAO patients with significant lid retraction [188]. In another study Krassas et al. aimed to investigate the orbital Indium-111-pentetreotide activity after treatment with octreotide and lanreotide in patients with TAO. All patients treated with SST analogs had a negative follow-up OCT, whereas controls had a positive OCT. Both NOSPECS score and CAS had improved in the treatment group, but there have been no changes in control subjects [189]. Most common side effects of SST analog therapy in TAO patients were mild gastrointestinal symptoms occurring during the first week of treatment. Because of minimal side effects and proven efficacy, SST analogs could be a treatment option in selected patients. But we need further large, multi-center, prospective and randomized clinical trials and a comparable series of patients with other established treatment options, to achieve more accurate outcomes. In addition, the high cost of this treatment must also be taken into account.

Intravenous immunoglobulins (IVIG)

Antonelli et al. was published as the first non-randomized study on the use of IVIGs for TAO. They treated 7 patients with high-dose IVIGs alone (400 mg/kg/day for 5 consecutive days; the cycle was repeated five times at 3-week intervals) and 7 patients with IVIGs associated with orbital radiotherapy. The results were compared with a historical group of patients previously treated with high-dose GCs and orbital radiotherapy. They found that IVIGs, either alone or combined with orbital radiotherapy, had improved the ocular conditions. This result did not differ from those obtained in the historical group [190]. In a randomized trial by Kahaly et al. 19 patients with active TAO were treated with a 20-week course of oral prednisolone (P, starting dose 100 mg/day), and 21 received 1g immunoglobulin/kg body weight for 2 consecutive days every 3 weeks. The immunoglobulin course was repeated six times. The degree of clinical improvement between two groups was not significant. There was a marked reduction of thyroid antibody titres in the immunoglobulin group. Side effects were more frequent and severe during P than during immunoglobulin therapy [191]. But another study by Seppel et al. failed to show any beneficial effects of IVIGs in TAO [192]. In summary, treatment studies with IVIGs include small numbers of patients and all of them are not randomized. In addition

to this, treatment is quite expensive and is related with disease transmission using plasma-derived products. More prospective, randomized and controlled trials, which includes large series of patients are required to obtain more accurate results.

Immunosuppressive drugs

a. Cyclosporine A (CyA): The first report by Weetman et al. showed that CyA had positive effects on ocular-muscle function, visual acuity, exophthalmos and orbital muscle swelling [193]. Prummel et al. compared two groups of 18 patients each of which were treated with either cyclosporine or prednisone. At the end of the study, treatment response was observed in 11 patients treated with prednisone, but only in 4 patients treated with cyclosporine [194]. Weissel et al. treated 8 patients with TAO, all of whom had compressive optic nerve disease (CON), by a combined treatment with CyA and cortisone. CON disappeared completely in all patients [195]. In summary, the use of CyA has been reported in several studies. Given the side effects of CyA, some of which can be severe, it should not be considered as a first-line treatment in TAO. The use of CyA might be maintained in patients who are resistant to GCs alone, and in whom the persistent activity of the disease warrants a continuing medical intervention. According to the recent European Thyroid Association survey CyA or azathioprine were indicated as suitable therapeutic options by only 6% and 2% of respondents respectively [196].

b. Methotrexate (MTX): MTX is not a novel drug, but it has not systematically been evaluated in TAO management. Smith et al. carried out the unique study on the use of MTX for non-infectious orbital inflammatory disorders like TAO. They included 14 patients, and three of them had TAO. All three patients with TAO had an improvement in their ocular conditions after MTX treatment [196] According to the recent European Thyroid Association survey MTX was indicated as a therapeutic option by only 1% of respondents [197]. MTX has many dose-dependent and reversible side effects and should not be used as a first-line treatment. In patients with GC dependency, it can be used at low doses with the aim of reducing the dose of GCs. However, to clarify the effectiveness of MTX in TAO management we need more controlled and randomized prospective studies.

Antioxidants

Bouzas et al. carried out a prospective, nonrandomized, comparative study on the effects of the antioxidant agents allopurinol and nicotinamide in TAO patients. Ocular conditions significantly improved in antioxidant-treated patients, more than placebo-treated patients [198]. Yoon et al. investigated the inhibitory effect of quercetin on inflammation in cultured whole orbital tissue. Quercetin had a significant suppression of tissue IL-6,IL-8, IL-1β and TNFα mRNA expression in cultured orbital tissues from three TAO samples relative to untreated control tissue [199]. Marcocci et al. demonstrated that selenium administration (100 μg twice daily) significantly improved quality of life, reduced ocular involvement, and slowed progression of the disease in patients with mild TAO [200].

There is limited data about treatment TAO with antioxidants. We need larger, prospective and randomized trials to clarify the role of antioxidant agents in the treatment of TAO.

Cytokine antagonists

Chang et al. aimed to determine the effects of pentoxifylline (Ptx); a cytokine antagonist, on fibroblasts derived from patients with Graves' ophthalmopathy. Ptx treatment caused a dose-dependent inhibition of serum-driven fibroblast proliferation and glycosaminoglycan synthesis [201]. Balazs et al. showed that Ptx has had beneficial effects on inflammatory symptoms of TAO and associated laboratory parameters [202]. In another study Ptx has improved the quality of life (QOL) of patients in the inactive phase of TAO [203]. According to these studies Ptx may be an effective and promising drug in the treatment of TAO.

TNF-α antagonists

Paridaens et al. assessed the effect of etanercept on clinical signs in TAO. After treatment the mean CAS and ophthalmopathy index (OI) had decreased significantly. No adverse effects were noted [204]. İnfliximab administration resulted with a significant reduction of inflammation and improvement of visual function without noticeable short-term side effects in two patients with active TAO [205,206]. But randomized prospective clinical trials are needed to obtain whether TNF-α antagonists are effective in reducing the inflammatory symptoms of TAO, and can be administered safely for a long-term period without serious side effects.

Rituximab (RTX)

A patient with TAO, who was unresponsive to steroids, was treated with RTX. The CAS declined from 5 to 2 in 3 months and the patient had peripheral B-cell depletion [207]. When the effect of RTX therapy was compared with IV GCs, RTX had positively affected the clinical course of TAO, independently of either thyroid function or circulating antithyroid antibodies, including TSH receptor antibody [208]. Silkiss et al. demonstrated a statistically significant decrease in CAS from the baseline value. B-cell depletion had been observed and was well tolerated, and there were no adverse effects from the RTX infusions [206]. There is currently insufficient evidence to support the use of RTX in patients with TAO. We need large randomised conrolled trials (RCTs) for investigating the efficacy and safety of RTX versus placebo or corticosteroids in patients with active TAO to make adequate judgement of this novel therapy for this condition

Rapamycin

A case of TAO, with dysthyroid optic neuropathy, who was refractory to steroids and orbital decompression surgery reported. Symptoms, visual acuity, color plate testing, and visual fields of the patient had been improved; despite the prednisone tapering [210]. On the basis the pathogenesis of TAO, rapamycin can be considered as a therapeutic option. But we need more RCTs to assess the efficacy and safety of this drug.

Colchicine

A randomized clinical study showed that colchicine had a beneficial effect on the inflammatory phase of TAO. Therefore, it was equally effective when compared to the classic treatment with corticosteroids, but safer and better tolerated [211]. Due to the lack of controlled trials, it is not clear that these effects were related to the natural history of the ophthalmopathy or to the effects of the drug.

Thalidomide

Thalidomide plays a role in inhibiting adipogenesis of orbital fibroblasts in TAO [212]. Han et al. demonstrated the immunoregulatory effect of thalidomide on peripheral blood mononuclear cells in patients with TAO [213].

Peroxisome proliferator-activated receptor (PPAR) agonists / antagonists

Orbital fibroblasts from patients with TAO have treated with rosiglitazone, and the results suggested that TSHR expression in TAO orbital preadipocyte fibroblasts is linked to adipogenesis [214]. Several case reports of TAO exacerbation following the initiation of PPAR agonists have been reported in the literature [215,216]. These findings suggest that novel drugs which antagonize the PPAR signalling system can also be considered as a treatment option in TAO. The effects of PPAR-γ activation on CXCL10, CXCL9 and CXCL11 secretion in orbital fibroblasts and preadipocytes were evaluated. The inhibitory role of PPAR-γ activation in the process demonstrated [217,218].These studies suggest that PPAR agonists can also be considered as a treatment option in TAO. There are conflicting reports in the medical literature, regarding the use of PPAR agonists and antagonists in the treatment of TAO.

3.11. Radiotherapy

Radiotherapy (RT) is a treatment option in TAO because of its non-specific anti-inflammatory and specific immunosuppressive effects (lymphocytes infiltrating the orbital space are highly radiosensitive) [219]. Moreover RT reduces GAG production by orbital fibroblasts [220]. RT has especially benefical effects on soft tissue changes and optic neuropathy. Unfortunately, in longstanding TAO, the benefical effects for reduction in proptosis and the improvement in ocular motility are not satisfactory [90]. A systematic review and meta-analysis of eight randomized controlled trials showed that, in patients with moderate to severe TAO, RT 20 Gy is a valid therapeutic option which improves lots of ocular symptoms. According to medical literature the dose of 20 Gy can be considered the optimal dose for orbital RT of TAO. The cumulative dose is usually fractionated in 10 daily doses over a 2-week period to reduce the cataractogenic effect [221]. Higher cumulative doses of RT does not improve the effectiveness of treatment [222]. Combined use of GCs and orbital RT was found to be more effective than using either one alone (140). Orbital RT is usually well tolerated. It may be associated with a transient exacerbation of inflammatory eye signs and symptoms, but this is unlikely to occur if GCs are concomitantly administered. Cataract is a possible complication of irradiation to the lens. Radiation retinopathy is an extremely rare complication of RT. Systemic microvascular disease due to diabetes mellitus (DM) or to previous chemotherapy may increase the risk for radiation retinopathy [221].

A major concern about orbital RT is carcinogenecity. In a small cohort of patients treated with RT for TAO, there was no significant evidence of radiation-induced cancer death [224]. Wakelkamp et al. evaluated the frequency of long-term complications of orbital RT for TAO (radiation-induced tumors, cataract, and retinopathy) in comparison with GCs. Mortality has obtained similarly in the irradiated and nonirradiated patients [225]. Haenssle et al. reported pigmented basal cell carcinomas 15 years after orbital RT therapy for TAO [226]. The long-

term treatment results seem to be satisfactory. But long-term follow up studies with greater numbers of patients are necessary to examine the risks and benefits more precisely. Orbital radiotherapy, when properly performed, appears to be a safe procedure with limited side effects.

3.12. Plasmapheresis

In the first report by Dandona et al., a patient with Graves's disease with acute progressive exophthalmos was treated with plasmapheresis. Their results has suggested that plasmapheresis could be a useful treatment option in acute and rapidly progressive ophthalmopathy [227]. Glinoer et al. observed significant clinical improvement immediately after plasmapheresis. The most significant effects were on soft tissue involvement, proptosis, intraocular pressure, and visual acuity [228]. In contrast to these, unfavorable effects of plasmapheresis have been reported [229,230]. Trials involving plasmapheresis provided conflicting results. We need RCTs to assess the efficacy and safety of plasmapharesis.

3.13. Total thyroid ablation

According to "shared" antigen(s) theory hypothesis; autoreactive T-lymphocytes which can recognize and interact with one or more antigens shared by the thyroid and the orbital tissue, trigger the event [231]. If this hypothesis is correct, in patients with appropriate genetic background and exposed to relevant environmental risk factors, the presence of thyroid tissue could be related with the development and progression of the ophthalmopathy [232,233]. A progressive decrease and disappearance of circulating auto-antibodies in initially antibody-positive thyroid cancer patients was demonstrated. This observation supports the theory that total thyroid ablation reduces thyroid autoimmunity [234]. Spinelli et al. reported major efficacy in the ophthalmopathy by total thyroidectomy(TT) [235]. De Bellis et al. evaluated the effect of TT alone or followed by post-surgical ^{131}Iodine with respect to methimazole treatment on the activity and severity of TAO. Patients in TT and ^{131}Iodine showed an early significant decrease and a further progressive reduction of the activity and severity of TAO during the follow-up, without statistically significant differences. These studies suggest that TT alone could be an appropriate alternative to improve TAO with a reduction of the cost/benefit ratio [236]. In conclusion, Total Thyroid Ablation (TTA) could be a possible treatment strategy for TAO. Its advantages are; better outcomes in the short term and a shorter period for the improvement of TAO. Because of its costs and risks TTA can not be recommended as a first-line treatment option in TAO.

3.14. Surgical therapy

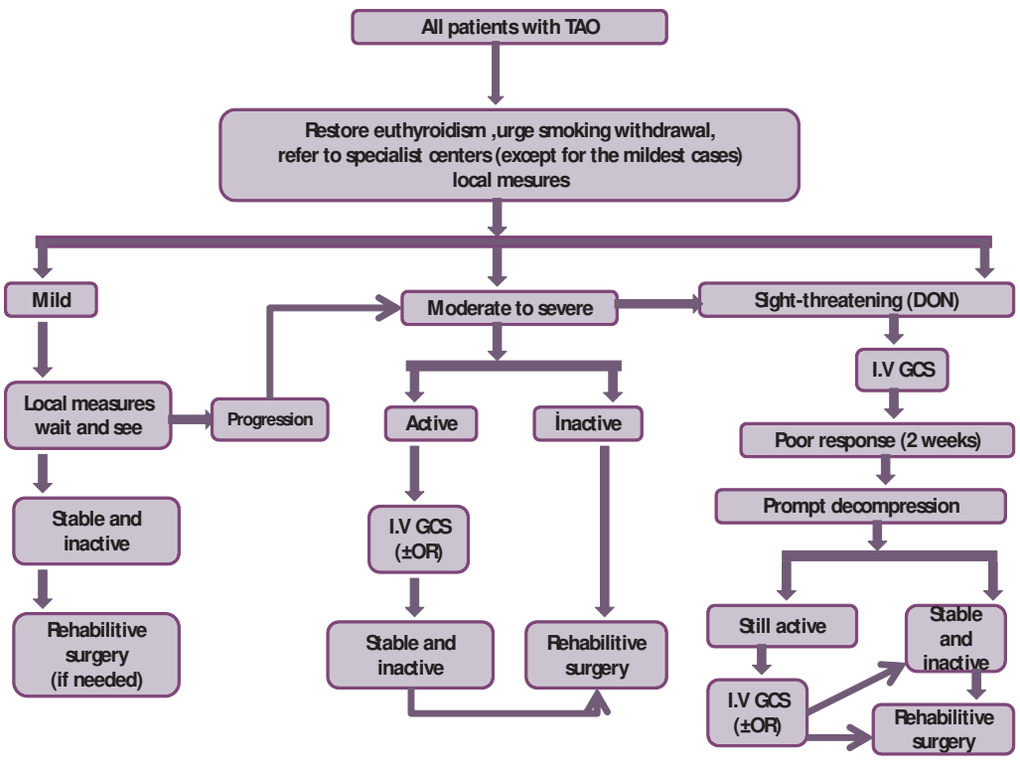
Orbital decompression

The goal of orbital decompression is to provide increased space for the increased orbital tissue, by removing the bony or fatty components of the orbit. In this way it is effective on proptosis and on the other ocular manifestations. This treatment could not act on the pathogenesis of the diesease. Several techniques have been used to remove portions of one to four walls of the orbit. The decision for which surgical techniques could be used, depends on the experience of the orbit surgeon and the clinical situation of the patient [237].

The studies in the medical literature could not make any meaningful comparisons between the surgical techniques. In the previous studies because of the risks of surgery, orbital decompression has been used in patients with marked proptosis and optic nerve compression, especially if no beneficial effect was obtained with other treatments. But in recent years the indications of orbital decompression has expanded. Garrity et al. reviewed the records of 428 consecutive eye surgery patients at the Mayo Clinic. These were; optic neuropathy, severe orbital inflammation, proptosis, and glucocorticoid side effects [238]. According to the EUGOGO consensus statement on TAO; orbital decompression for exophthalmos (rehabilitative surgery) could be delayed for at least 6 months, until the orbitopathy has been inactive for a period, because surgery yields the best results when TAO is inactive. But in patients with TAO who are intolerant or non-responsive to GCs, orbital decompression can be considered in the active phase. In conclusion, orbital decompression seems to be an effective and safe treatment for patients with TAO [116].

3.15. Medical and surgical recommendations

Bartalena et al. within the EUGOGO consensus statement on TAO, published the set of medical and surgical recommendations shown in Figure 2.

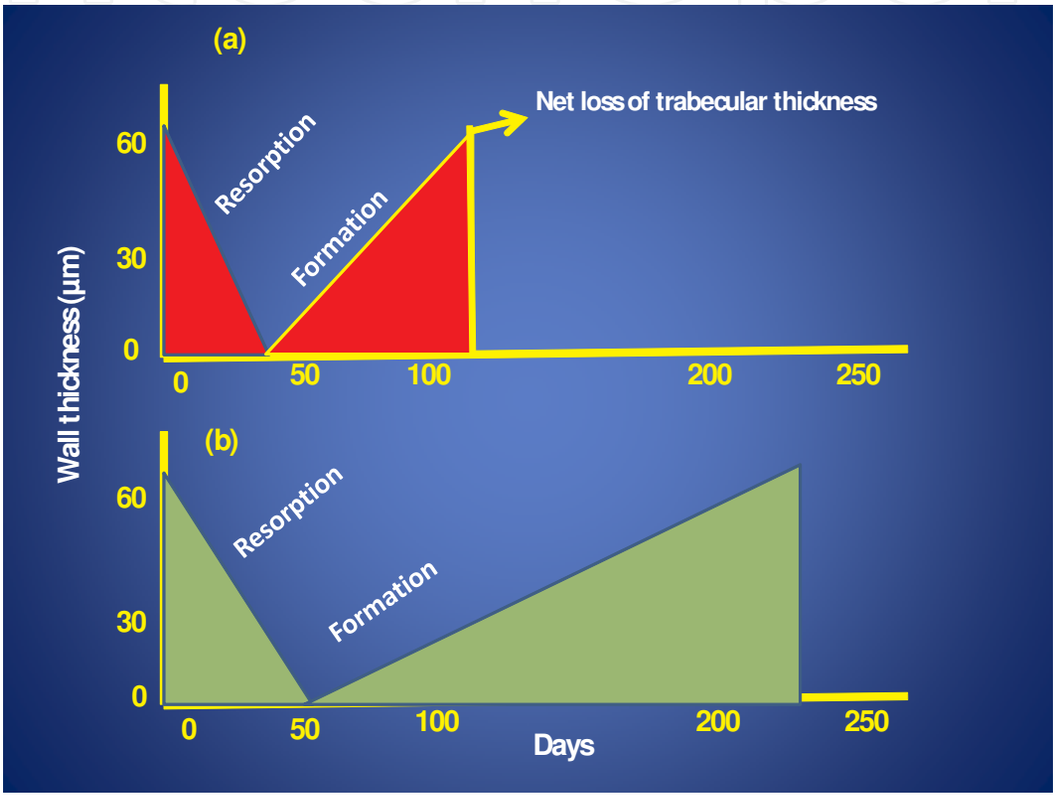


Commentary: Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. I.V.GCs: intravenous glucocorticoids; OR: orbital radiotherapy; DON: dysthyroid optic neuropathy.

Figure 2. Management of Thyroid-Associated Oophthalmopathy (TAO)

4. Hyperthyroidism and bone

In 1891 Von Recklinghausen firstly described reduced bone mass in untreated hyperthyroidism. Thyroid hormones (3,3',5-triiodothyronine [T3] and 3,3',5,5'-tetra iodothyronine [T4]) act on normal bone growth, development and turnover in both children and adults [239,240]. Hyperthyroidism increases bone turnover, acting mainly on bone resorption, but also on osteoblast activity [241,242] [Figure-3]. As a result, hyperthyroidism is an important etiology of secondary osteoporosis [243].



(Data adapted from reference 252).

Figure 3. Trabecular Bone Remoelling Cycle in (a) Hyperthyroid and (b) Normal Subjects

4.1. Mechanism

Direct stimulation of thyroid hormones on bone resorption in organ cultures have been demonstrated [244]. This action may be mediated by a nuclear T3 receptor [245,246]. Thyroid hormones may also affect bone calcium metabolism by a direct action on osteoclasts [247].

Besides the hormones of calcium metabolism, locally produced factors are important in maintaining normal bone metabolism. Serum interleukin-6 (IL-6) concentration increases in hyperthyroid patients and stimulates osteoclast production. Therefore, IL-6 may be an effector of the action of PTH on bone [248]. Thyroid hormones may influence the IGF-I/IGFBP system in vivo in hyperthyroidism. The anabolic effects of increased levels of IGF-I may be limited in

hyperthyroidism due to the increases of inhibitory IGFBPs that can counteract the anabolic effects and contribute to the observed net bone loss [249]. T3 activates fibroblast growth factor receptor-1 (FGFR1) in bone and this can be related with the pathogenesis of skeletal disorders resulting from thyroid disease [250].

4.2. Changes in hyperthyroidism

Histological changes in hyperthyroidism

Thyroid hormones increase the activation of new remodeling cycles. These effects include predominantly increased osteoclastic activity. Although; excess osteoblastic activity, osteoid deposition (osteomalacia) and rarefaction (osteoporosis) were also described. These changes were observed both in trabecular and cortical bone ([51]. In 1978 Mosekilde & Melsen demonstrated a unique histomorphometric pattern; with evidence of both increased osteoblast and osteoclast activity in hyperthyroidism. These changes have given rise to a net loss of bone volume and were evident in both cortical and trabecular bone. But cortical bone has been rather more influenced (Figure-4) [252]. An *in-vitro* organ culture of fetal rat bone, demonstrated a direct stimulation of bone resorption by prolonged treatment with T4 or T3 [244].

Biochemical changes in hyperthyroidism

a. Calcium homeostasis in hyperthyroidism

The majority of patients with hyperthyroidism have normal or near normal total serum calcium levels. However, ionized serum calcium levels are elevated in most of the patients. Changes in serum calcium levels correlate with serum T3 levels [253,254]. Generally hypercalcemia in hyperthyroidism tends to be mild or asymptomatic. Severe (>15 mg/dl) and symptomatic hypercalcemia is rare [255]. Hypercalcemia usually resolves after attainment of euthyroid state by all therapeutic modalities, i.e. subtotal thyroid resection, antithyroid drugs and radioiodine therapy. Symptomatic hypercalcemia can be treated by rehydration, use of corticosteroids, calcitonin and phosphate therapy. Reduced renal tubular and intestinal calcium reabsorption leads to increased urinary and fecal calcium [241]. The hyperadrenergic state of hyperthyroidism contributes hypercalcemia [256]. These changes correlate positively with thyroid hormone levels and cortical osteoclastic activity. Hypercalcemia in hyperthyroidism is unrelated to the parathyroid hormone (PTH) levels [253,254].

b. Phosphorous homeostasis in hyperthyroidism

Most of the patients have increased serum phosphorous levels. But some studies have shown normal or low levels of serum phosphorous. Increased bone and tissue catabolisms which lead to excess input of phosphorous to the plasma, lower clearance and increased renal tubular reabsorption of phosphorous may lead to hyperphosphatemia in hyperthyroidism. These changes are related to suppressed PTH levels and direct effects of thyroid hormones. Antithyroid treatment normalizes serum phosphorous concentration [253].

c. Parathyroid hormone secretion in hyperthyroidism

The reduction of serum PTH levels has been reported for the first time by Bouillon and DeMoor [257]. This observation confirmed by other clinical trials. Increased serum calcium levels inhibit

PTH secretion, so there is an inverse relationship between serum PTH and calcium levels. Additionally, serum parathyroid hormone-related peptide (PTH-rP) levels increase in hyperthyroidism. In hyperthyroid patients, a significant elevation in PTH-rP levels was obtained when compared with healthy controls. After treatment, levels of PTH-rP declined. PTH-rP could be a factor in the pathogenesis of hypercalcemia in hyperthyroid patients [258].

d. Vitamin D in hyperthyroidism

Serum concentrations of 25-hydroxyvitamin D_3 ($25(OH)D_3$)and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) in hyperthyroidism have been evaluated in many clinical trials. In most studies, serum $25(OH)D_3$ levels were normal [255,259]. However, few studies in medical literature obtained lower serum $25(OH)D_3$ levels in patients with hyperthyroidism than control subjects [260,261]. Karsenty et al. found a higher metabolic clearance rate of $1,25(OH)_2D_3$ in hyperthyroid patients than in control subjects [262]. These changes in serum concentrations of $25(OH)D_3$ and $1,25(OH)_2D_3$ are probably unrelated with the direct effects of thyroid hormones on bone metabolism. It is postulated that lower levels of serum $25(OH)D_3$ and $1,25(OH)_2D_3$, can be related with reduced intestinal absorption [261]. Biochemical changes in hyperthyroidism are shown in Figure-2.

4.3. Evaluation of bone turnover in hyperthyroid patients and serum markers

Alkaline phosphatase (ALP)

Patients with hyperthyroidism have elevated levels of serum [263]. Total, liver, and bone ALP activities obtained significantly higher in hyperthyroid patients. Bone ALP level are more markedly elevated than liver ALP. Intestinal ALP does not differ significantly between hyperthyroid and normal subjects. These changes correlate positively with thyroid hormone levels. After a euthyroid state is achieved, serum ALP level remains elevated for a prolonged time. This means increased bone turnover continues even after restoration of hyperthyroidism [264].

Other serum markers

Serum pyridinoline (PYD) and deoxypyridinoline (DPD) [265,266]., osteocalcin [267]., carboxy-terminal propeptide of type 1 procollagen (P1CP) and carboxy-terminal telopeptide of type 1 collagen (1CTP) [268]., serum bone Gla protein (BGP) [269]. and serum osteoprotegerin (OPG) [270]. levels were obtained significantly higher in hyperthyroid patients than in control subjects. These laboratory parameters can be considered as reliable non-invasive markers of bone turnover in hyperthyroid patients. All markers were correlated with serum thyroid function tests and were normalized after a eutyhyroid state was achieved.

4.4. Clinical implications

Hyperthyroidism causes reduction in bone mineral density (BMD) assessed by the measurement of lumbar vertebrae and femur by dual energy X-ray absorptiometry (DEXA) [271]. Hyperthyroidism affects bone mineralization especially during the early post-menopausal period and the effect is mainly at the cortical bone [272]. However, hyperthyroidism could be

associated with bone loss and may be a risk factor for the development of osteoporosis in pre-menopausal women [273]. It has been well established that hyperthyroidism leads to reduced BMD in female patients, but there is lack of acceptable data in male patients. Majima et al. evaluated BMD and bone metabolism in male patients with hyperthyroidism. The study demonstrated a high prevalence of cortical bone loss in male patients with hyperthyroidism, especially in elderly patients [274].

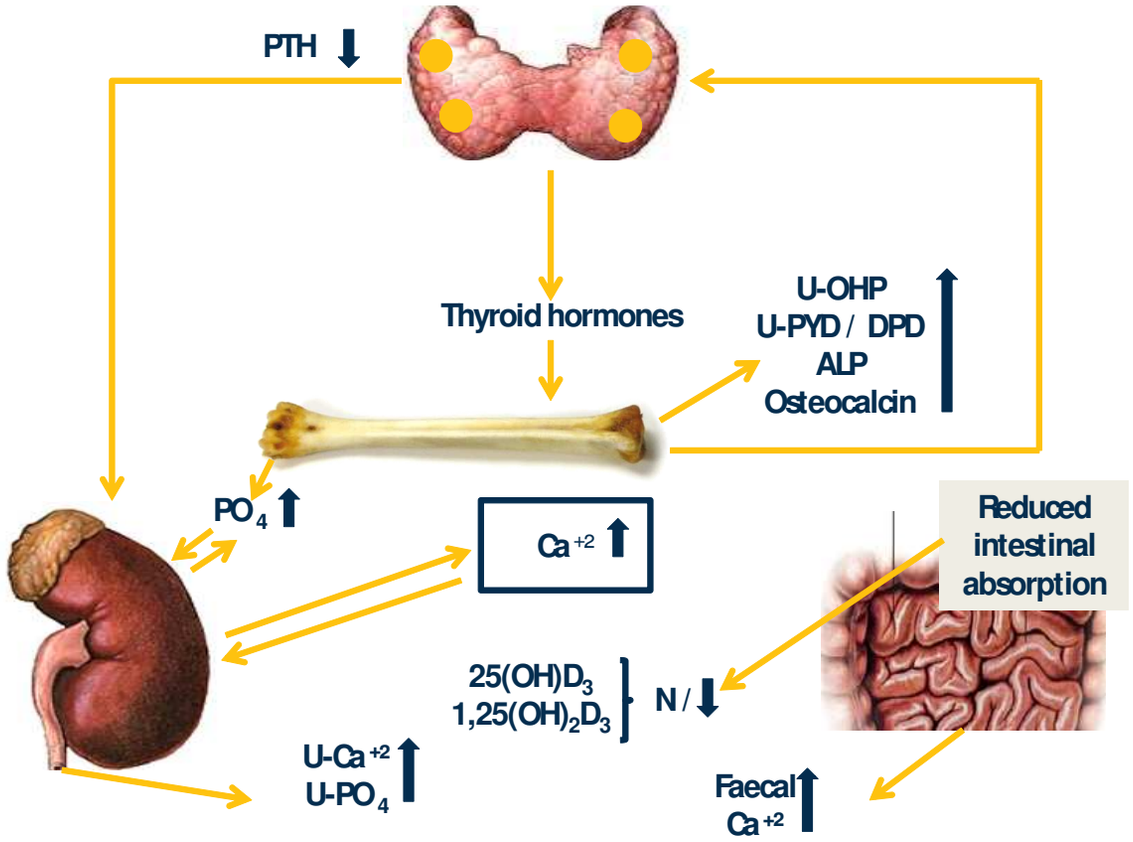
Also, endogenous subclinical hyperthyroidism can be a risk factor for osteoporosis. In several cross-sectional studies, BMD was decreased at multiple sites in pre-and post-menopausal women with endogenous subclinical hyperthyroidism [275-277]. This finding, however, was not confirmed in other cross-sectional observations in endogenous conditions [278]. Földes et al. demonstrated that numbers of pre-menopausal patients with endogenous sub-clinical hyperthyroidism BMD of the lumbar spine, femoral neck and the midshaft of the radius were not significantly decreased. But in post-menopausal women with long-lasting endogenous sub-clinical hyperthyroidism mean densitometric values were slightly, but significantly, lower [279]. Whether endogenous sub-clinical hyperthyroidism significantly affects bone metabolism and increases the risk of fractures remains controversial.

Prolonged hyperthyroidism due to L-thyroxine(L-T4) treatment has been associated with reduced bone mass and thus with the potential risk of premature development of osteoporosis. The effects of L-T4 treatment have been evaluated in many clinical trials. In several studies, bone mineral density was decreased at multiple sites in pre-and post-menopausal women treated with L-T4 [280,281]. In a study by Giannini et al. post-menopausal thyroidectomized patients showed significantly lower bone mass than pre-menopausal patients. A negative correlation between time since menopause and bone mass were obtained in post-menopausal L-T4 treated patients [282]. There is lack of acceptable data about the effects of L-T4 treatment on bone metabolism in male patients. A mild deleterious effect of thyroid hormone excess in the axial bone mass from male subjects obtained. Male patients with chronic TSH suppression by L-T4 or history of hyperthyroidism should be assessed by BMD [283]. However, several recent studies have failed to show such a harmful effect of L-T4 treatment on BMD [284-286].

It should be noted that other risk factors may affect BMD in hyperthyroid patients. These include a relative deficiency of insulin-like growth factor type I, dehydroepiandrosterone sulfate [287], vitamin D receptor (VDR) polymorphisms [288] and estrogen [289]. The question as to whether prolonged hyperthyroidism due to L-T4 treatment increases the risk of fractures also remains controversial.

4.5. Diagnosis

BMD measuring by DEXA scan is one of the best techniques to obtain the extent of bone changes in hyperthyroidism. DEXA scan offers monitoring for response to therapy and with little radiation it gives very reliable measurements [290]. Quantitative ultrasound (QUS) might give information about bone mass and also on bone elasticity and structure. Advantages are the lower expense, portability, and lack of radiation exposure [291]. Acotto et al. reported significantly lower QUS parameters in hyperthyroid patients in comparison with controls



Abbreviations are as follows: calcium (Ca), alkaline phosphatase (ALP), 25 hydroxy vitamin D_3 (25 OH D), 1,25 dihydroxy vitamin D_3 ($1,25\ (OH)_2D_3$), 24,25 dihydroxy vitamin D3 (S-24,25 (OH)2D), parathyroid hormone (PTH), phosphate (PO4), urinary calcium (U-Ca), urinary hydroxyproline (U-OHP), urinary phosphate ($U\text{-}PO_4$), urinary pyridinium and deoxypyrodinoline (U-PYD/DPD). (Data adapted from reference 292).

Figure 4. Biochemical Changes in Hyperthyroidism.

[292]. For practical use, the development of quality standards and criteria for diagnosing osteoporosis are necessary.

Prevention and treatment of reduced bone density

Patients with a history of hyperthyroidism and who are treated with L-T4 replacement/ supressive therapy should be considered at higher risk of reducing BMD and developing clinically significant osteoporosis. These patients should be encouraged to modify other risk factors for osteoporosis such as smoking, drinking excessive alcohol, low Ca^{+2} intake and lack of exercise [293]. In these patients adequate daily calcium intake should be provided. Kung et al. found that 1,000 mg. daily calcium supplementation prevents bone loss in post-menopausal women taking suppressive doses of L-T4 compared with a placebo [294]. Estrogen replacement therapy prevents a decrease of BMD in postmenopausal women with previous hyperthyroidism and subsequent L-T4 therapy [295,296]. These potentially beneficial effects of estrogen replacement on BMD in postmenopausal women with a history of thyroid disease suggests that estrogen administration should be encouraged in this group.

Titration of suppressive therapy to maintain serum TSH concentration between a slightly low (*e.g.* between 0.1-0.5 mU/l) range may prevent bone loss [297]. Guo et al demonstrated a reduction of L-T4 dose in post-menopausal women with suppressed serum TSH levels related with deceleration of bone turn over (serum osteocalcin and urinary excretion of bone collagen-derived pyridinium cross-links decreased) and increased BMD (lumbar/femoral) [298]. Careful titration of L-T4 dosage to maintain biochemical euthyroidism is the most important way to prevent the adverse effect of T4 on bone.

The major question is whether the decrease in BMD caused by hyperthyroidism can be reversible. Many clinical trials have obtained that there is some reversibilty of bone mass after treatment of hyperthyroidism [293,299-301]. Another question is whether antiresorptive treatment is effective on hyperthyroidism related osteoporosis. Two clinical trials evaluated the increase of BMD in osteoporotic/osteopenic hyperthyroid patients treated with only anti-thyroid drugs versus patients treated with anti-thyroid drugs and alendronate. The combination of anti-thyroid drugs and alendronate was found to be more efficacious than anti-thyroid therapy alone [302,303]. Majima et al. evaluated the efficacy of risedronate for the treatment of osteoporosis/osteopenia in patients with Graves' disease. The percentage increases in BMD at the lumbar spine and distal radius were significantly greater in patients treated with an anti-thyroid drug and risedronate than treated with an anti-thyroid drug only [304]. These findings conclude that bisphosphonates can be considered as a treatment option in decreased bone mass cases associated with hyperthyroidism. Kung et al. demonstrated intranasal calcitonin with calcium supplements was not more effective than calcium supplements alone in preventing bone loss induced by thyroxine suppressive therapy in post-menopausal women [305]. Jódar et al. designed a prospective study to evaluate the effects of antiresorptive therapy with nasal salmon calcitonin (CT) in hyperthyroid patients receiving standard medical treatment. They showed that treatment with nasal CT has no additional beneficial effect compared with the attainment of the euthyroid state [306]. But in another study by Akçay et al. the addition of intranasal calcitonin to the anti-thyroid drugs was found to be effective in preventing the degradation of bone [307]. More prospective, randomized and controlled trials, which include large series of patients, are required to obtain more accurate results about antiresorptive treatment in hyperthyroidism.

5. Thyroid storm

Thyroid storm (TS) [thyrotoxic crisis] is an uncommon, life-threatening condition reflecting the augmentation of the manifestations of thyrotoxicosis. Mortality rates are high (10-20%) and occur in less than 10% of patients hospitalized for thyrotoxicosis. TS occurs nine to ten times more commonly in women than in men, and the most common aetiology is Graves' hyperthyroidism. However, any aetiology of thyrotoxicosis can cause TS. This situation can be precipitated by a number of factors shown in Table-3 [308-312].

The pathophysiology of thyroid storm is not fully understood. The current theory is that; increased numbers of catecholaminergic receptors being exposed to increased catecholamine

levels in states of stress. Decreased binding to thyroxine-binding globulin (TBG), markedly increase in free thyroid hormone levels may also play an important role [313].

• **Severe infections (pulmonary)**	• Direct trauma or surgical manipulation of the thyroid gland
• **Diabetic ketoacidosis (DKA)**	• Biological agents such as interleukin-2 and α-interferon
• **Surgery**	• Discontinuation of anti-thyroid medications or poor patient adherence to the treatment
• **Trauma**	• Cerebrovascular disease
• **Pulmonary thrombo-embolism**	• Myocardial infarction (MI)
• **Salicylates ***	• Exogenous thyroid hormone intake
• **Administration of large quantities of exogenous iodine ****	• Pregnancy
• **Radioactive iodine therapy**	• Unknown factors

*They increase the concentration of circulating free thyroid hormones to critical levels

**Such as iodinated contrast agents or amiodarone

Table 3. Precipitating Factors for Thyroid Storm

Clinical presentation of thyroid storm

Symptoms of thyroid storm are similar to those of hyperthyroidism, but they are more sudden, severe and extreme. The main findings are high fever (38-41° C) accompanied by excessive sweating and flushing. Other common symptoms include; altered mental status (confusion, agitation, overt psychosis, and in extreme cases, even coma), cardiovascular complications [tachycardia, cardiac arrhythmias (including atrial fibrillation), high systolic bood pressure, low diastolic bood pressure and congestive heart failure], diffuse muscle weakness, tremor or fasciculations and neuropsychiatric syndromes. Gastrointestinal involvement presents with nausea, vomiting, diarrhoea and abdominal pain. Liver dysfunction (cardiac failure with hepatic congestion or hypoperfusion, direct effect of the excess thyroid hormones) could be present with jaundice [309,314]. Elderly patients often present with apathy, stupor, cardiac failure, coma and minimal signs of thyrotoxicosis so-called apathetic thyroid storm [313].

The scoring system suggested by Burch and Wartofsky (Table 4) illustrates the typical features of thyroid storm [315]. The clinical symptomatology is sometimes difficult to distinguish from other medical emergencies [308]. Differential diagnosis of TS is shown in Table-5.

5.1. Diagnosis

Diagnosis depends on primarily clinical findings. There are no specific laboratory tests available. Serum thyroid hormone levels (i.e. free T3 [FT3] and free T4 [FT4]) are elevated with suppressed TSH levels (with the rare exceptions being states of thyroid hormone resistance or TSH secreting pituitary adenomas). An immediate search should begin for precipitating factors. Pregnancy should be excluded urgently in any woman of childbearing age with urinary or plasma assessment of human chorionic gonadotropin (HCG) levels. Routine

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Clinical feature	Scoring points
1. Thermoregulatory dysfunction	
Temperature °F (°C)	
99-99.9 (37.2-37.7)	5
100-100.9 (37.8-38.2)	10
101-101.9 (38.3-38.8)	15
102-102.9 (38.9-39.4)	20
103-103.9 (39.5-39.9)	25
≥104 (40)	30
2. Cardiovascular dysfunction	
• *Tachycardia (beats per minute)*	
<99	0
99-109	5
110-119	10
120-129	15
130-139	20
≥140	25
• *Congestive heart failure*	
Absent	0
Mild (Pedal oedema)	5
Moderate (Bibasal rales or crackles)	10
Severe (Pulmonary oedema)	15
• *Atrial fibrillation*	
Absent	0
Present	10
3. Central nervous system dysfunction	
Absent	0
Mild (Agitation)	10
Moderate (Delirium, psychosis, extreme lethargy)	20
Severe (Seizures, coma)	30
4. Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (Diarrhoea, nausea/vomiting, abdominal pain)	10
Severe (Jaundice)	20
5. Previous episode of thyroid storm	
Absent	0
Present	10
TOTAL	
>45	Highly likely thyroid storm
25-44	Suggestive of impending storm
<25	Unlikely to represent storm

Table 4. Diagnostic Criteria for Thyroid Storm

biochemical tests, urinalysis, urine sediment, complete blood count, chest X-ray and related cultures should be made, to exclude infectious diseases. Electrocardiography (ECG) and cardiac enzymes should be procured, to exclude arrhythmia and myocardial infarction (MI) [313]. Leukocytosis, increased transaminase-bilirubin levels, hypoglycemia and lactic acidosis can be seen in laboratory evaluation [316,317].

Neurolept malignant syndrome	Hypertensive encephalopathy
Malignant hyperthermia	Alcohol withdrawal
Phaeochromocytoma	Benzodiazepine / barbiturate withdrawal
Hypoglycemia	Opioid withdrawal
Hypoxia	Heat stroke
Sepsis	Encephalitis / meningitis

Table 5. Differential Diagnosis of Thyroid Storm

5.2. Management

The patient should be managed in an intensive care unit. ABCDEs (i.e. airway; breathing; circulation; disability, i.e. conscious level; and examination) should be provided as soon as possible. Precipitant factors such as infection, trauma, MI, DKA, and other underlying processes should be managed as per standard care [313].

General supportive care

First of all haemodynamic stability should be provided. Supportive care includes cooling measures, intravenous (IV) fluid-electrolyte replacement and nutritional support. In order to control profound pyrexia cooling blankets and acetaminophen can be used. Salicylates should be avoided (increase the concentration of circulating free thyroid hormones). Tachyarrhythmias, which cause haemodynamic instability should be managed with cardioversion by defibrillation. Otherwise, tachyarrhythmias can be managed with appropriate anti-arrhythmic therapy. Diuretics, ACE inhibitors and digitalis can be used carefully for heart failure. Based on arterial blood gas (ABG) analysis and other assessments; ventilatory support, either with non-invasive positive pressure ventilation (NIPPV) or intubated ventilation, could be performed. In patients with severe agitation, medical intervention could be difficult. Sedatives such as haloperidol or a benzodiazepine can be used in this situation. Phenobarbital increases peripheral metabolism and inactivation of FT3-FT4. Chlorpromazine has the additional benefit of reducing body temperature through effects on central thermoregulation. However, these agents should be monitored for respiratory side effects. Nutritional support is important. This includes vitamin (e.g. thiamine) and glucose replacement (as liver glycogen stores are depleted during a thyroid storm) [313].

Thyroid-specific therapy

Thyriod-specific therapy includes; decreasing thyroid hormone synthesis, prevention of thyroid hormone release and decreasing peripheral action of circulating thyroid hormones [318]. In the treatment of thyroid storm, the five B's should be kept in mind. This includes 'Bs':

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Block synthesis (i.e. antithyroid drugs); Block release (i.e. iodine); Block T4 into T3 conversion (i.e. highdose propylthiouracil [PTU], propranolol, corticosteroid and, rarely, amiodarone); Betablocker; and Block enterohepatic circulation (i.e. cholestyramine) [313].

Anti-thyroid drugs include PTU or carbimazole (or methimazole). PTU was preferred because of its more rapid onset of action, short half-life and inhibition of peripheral deiodinase enzyme-mediated conversion of T4 into T3. PTU could be administered orally or via a nasogastric (NG) tube, if the patient is not suitable for oral administration, both PTU and methimazole can be given as a rectal suppository or enema. PTU is administered with a loading dose of 600mg followed by a dose of 200-250 mg every 4-6 hours. Carbimazole (or methimazole) is administered at a dose of 20-30mg every 4-6 hours [318]. The major concern about PTU is hepatoxicity. In the thyroid storm management, there are not any comparative trials showing superiority of PTU over either carbimazole or methimazole. It's now recommended that using either carbimazole or methimazole in thyroid storm (unless there is a contra-indication such as pregnancy), and achieving T4 into T3 conversion inhibition just with beta-blockers and corticosteroids [319].

Iodine should be administered at least 1 hour after PTU or carbimazole (or methimazole) administration. In this way undesired tyrosine residue iodination and enrichment of thyroid hormone stores could be prevented. Iodine could be administered in various formulations (Table-6) [313].

In order to block the adrenergic effects of thyroid hormones betablockers should be administered immediately. A non-cardiac specific betablocker; propranolol can be used for this purpose. Propranolol has the advantages of being suitable for IV administration and of inhibition of peripheral T4-T3 conversion at high doses. Decompensated cardiac function, triggered with tachycardia, can be treated with beta-blockers. However, beta-blockers should be used with caution in patients with a history of heart failure. Cardioselective beta-blockers such as metoprolol or atenolol could be used in patients with asthma and chronic obstructive pulmonary disease, which are contra-indications for non-cardiac specific betablockers. If unfavorable cardiac effects are expected, a short-acting beta-blocker; esmolol, can be used as an alternative drug. Diltiazem, a calcium-channel blocker, can be used when there is absolute contra-indication for beta-blockers (Table-6) [313].

Thyroid hormones accelerate cortisol metabolism and may trigger an adrenal crisis. Thyroid crisis give rise to low plasma levels of ACTH and cortisol. Therefore, against a possible adrenal insufficiency, exogenous corticosteroid therapy should be administered [320]. Furthermore, corticosteroids inhibit peripheral conversion of T4 into T3 and have been shown to improve outcomes in patients with thyroid storm [318]. Hydrocortisone or an equivalent corticosteroid can be used for this purpose (Table-6). Then, the treatment should be withdrawn gradually, based on the required duration of steroid therapy.

Other possible treatment options are lithium carbonate, potassium perchlorate and cholestyramine. Lithium inhibits thyroid hormone release from the gland and reduces iodination of tyrosine residues. Lithium carbonate can be an alternative treatment option when there is a contraindication or previous toxicity history to thionamide therapy. The major concern about

lithium carbonate is it's toxicity. Potassium perchlorat inhibits iodide transport into the thyrocyte [313]. Erdogan et al. demonstrated that the combination of thionamides, corticosteroids and potassium perchlorat for a short period could be effective in the treatment of amiodarone-induced thyrotoxicosis [321]. The most important side effects of potassium perchlorat are aplastic anaemia and nephritic syndrome. To inhibit the enterohepatic circulation of thyroid hormones, a T4 and T3 binding resin, cholestyramine can be used [322].

Emerging treatments

In spite of all treatment approaches, clinical improvement could not be obtained. In this situation, different treatment approaches can be tried in order to remove thyroid hormones from the circulation.

Plasmapheresis should be considered as a treatment option, especially when patients have failed or cannot tolerate conventional therapy. Plasmapheresis leads to amelioration of symptoms and a significant decline in thyroid hormone levels, providing a window to treat definitively with thyroidectomy [323,324]. In each session only small amounts of thyroid hormones can be removed from the circulation, therefore plasmapharesis can be repeated. Koball et al. reported a case of thyrotoxic crisis treated with plasmapheresis and single pass albumin dialysis. Thyroxine can be bound by albumin and removed by extracorporeal single-pass albumin dialysis (SPAD). The patient underwent two sessions of plasmapheresis without clinical response. After four SPAD treatments clinical status of the patient improved. According to this report SPAD represents a safe and efficient alternative to plasmapheresis [325].

Charcoal haemoperfusion has also been demonstrated to be effective in thyrotoxic states [326].

6. Thyrotoxic hypokalaemic periodic paralysis

Hyperthyroidism can be related with muscular disorders such as acute and chronic thyrotoxic myopathies, exophthalmic ophthalmoplegia, myasthenia gravis, and periodic paralysis [327]. The association between thyrotoxicosis and periodic paralysis was first described by Rosenfeld in 1902. Thyrotoxic hypokalaemic periodic paralysis (THPP) is a rare condition which occurs in 2% of patients with thyrotoxicosis. THPP is generally sporadic, but autosomal recessive or autosomal dominant cases have been reported and may be associated with certain HLA haplotypes [HLA-Bw46 / B5 / DRw8 / CW7] [328-330]. THPP has been reported in many ethnic groups such as Asian populations and Caucasians [331]. THPP appears almost exclusively (85%) in young men between the ages of 20-39 [327].

Many aetiological factors that can lead to hyperthyroidism may be associated with THPP. It has been reported that the most important aetiologic factor is Graves' disease according to large case series [332,333]. Other possible aetiological factors are subacute thyroiditis, silent thyroiditis [334], autonomously functioning thyroid nodules [335], thyrotropin-secreting pituitary adenomas [336,337], ingestion of excessive thyroxine [338], thyroxine-containing herbal and dietary supplements [339], iodine induced thyrotoxicosis with inadvertent use of iodine or with drugs containing iodine such as iodinate contrast agents or amiodarone

Medication	Dose	Notes
Inhibition of hormone synthesis		
Propylthiouracil (PTU)	600mg loading dose, followed by 200-250mg PO q4-6h	Additional inhibition of peripheraldeiodination However, recent warning from FDA regarding severe liver toxicity with PTU makes either carbimazole or methimazole first-choice thionamide
Carbimazole (or methimazole)	20-30mg PO q4-6h	
Inhibition of hormone release		
Potassium Iodide	5 drops PO q6-8h	Administer at least 1 hour after thionamide
Lugol's Solution	5-10 drops PO q6-8h	Administer at least 1 hour after thionamide
Iapanoic Acid	1000mg IV q8h for 24 h, followed by 500mg bd	Administer at least 1 hour after thionamide, infrequently available
Inhibition of peripheral effects of excess thyroid hormone		
Propranolol	1-2 mg/min IV q15min up to max 10mg 40-80mg PO q4-6h	IV dose initially if haemodynamically unstable
Esmolol	50 mg/kg/min IV -may increase by 50 mg/kg/min q4min as required to a max of 300 mg/kg/min.	Short acting
Metoprolol	100mg PO q6h	Cardioselective; use if known airways disease
Diltiazem	60-90mg PO q6-8h	Use if beta-blockers contraindicated IV formulation available
Supplementary management		
Hydrocortisone	100mg IV q6h	
Dexamethasone	2mg IV q6h	Care if significant hepatic dysfunction
Acetaminophen	1 g PO q6h	
Additional therapies		
Lithium Carbonate	Carbonate 300mg PO q8h	Monitor for toxicity
Potassium perchlorate	1 g PO od	Associated with aplastic anaemia
Cholestyramine	4 g PO q6-12h	and nephritic syndrome

PO, oral; IV, intravenous; q4-6h, every 4_6 hours; q6h, every 6 hours; q8h, every 8 hours; q4min, every 4 minutes; q15min, every 15 minutes;od, once daily; bd, twice daily.

(Data adapted from reference 313)

Table 6. Medical Management of Thyroid Storm

[340,341], interferon-alpha-induced thyrotoxicosis [342] and radioactive iodine therapy induced radiation thyroiditis [343]. Many precipitating factors can trigger THPP attacks (Table-7) [344-346].

Carbohydrate-rich meal	Cold
Strenuous exercise	Alcohol
Awakening in the middle of sleep	Glucocorticoids
Emotional stres	Injection of medicine
Radioactive iodine treatment	Upper respiratory tract infection
Menses	Trauma
Epinephrine	Insulin

Table 7. Precipitating factors

The pathophysiology of THPP is not certain. However, it can be explained by some mechanisms (Figure-5). A quick shift of potassium from the extracellular compartment to the intracellular compartment causes hypokalemia. This especially occurs in the muscles. Excess thyroid hormone and insulin levels, increased sensitivity of beta-receptors to catecholamines in thyrotoxicosis causes an increase in sodium/potassium-adenosine triphosphatase (Na/K-ATPase) pump activity [347,348]. This mechanism explains insulin and epinephrine induced paralytic attacks. Factors related with an increased insulin and epinephrine levels, such as carbohydrate rich meals, emotional stress, cold, trauma and infection trigger THPP. During exercise K releases from the skeletal muscles, but in the resting process K again returns to the intracellular compartment. Because of this transport of the potassium, periodic and paralytic attacks usually occur during resting time [349].

6.1. Clinical features

THPP attacks mostly occur in the late night or early morning and last from a few hours up to several days. Prodromal symptoms such as aches, cramps and stiffness can be seen [334]. The typical motor involvement in THPP begins from the lower limbs and ascends to the upper limbs. The muscles affected may be asymmetrical. The severity of attacks range from mild weakness to flaccid paralysis. Clinical improvement starts from the most recently affected muscles. Sensory function is not affected and deterioration of mental functions has never been seen [327]. Paralysis of respiratory, bulbar, and ocular muscles has been rarely reported in severe attacks of THPP. Respiratory muscle involvement can be fatal [350]. Deep tendon reflexes are markedly diminished or absent. Patients completely recover between the attacks [348].

6.2. Laboratory features

The cardinal laboratory finding in THPP is hypokalaemia. But normokalaemic TPP have been reported in some cases [351,352]. Severe hypokalaemia may trigger life-threatening arrhythmias and the severity of paralysis correlates with the degree of hypokalemia but not with the

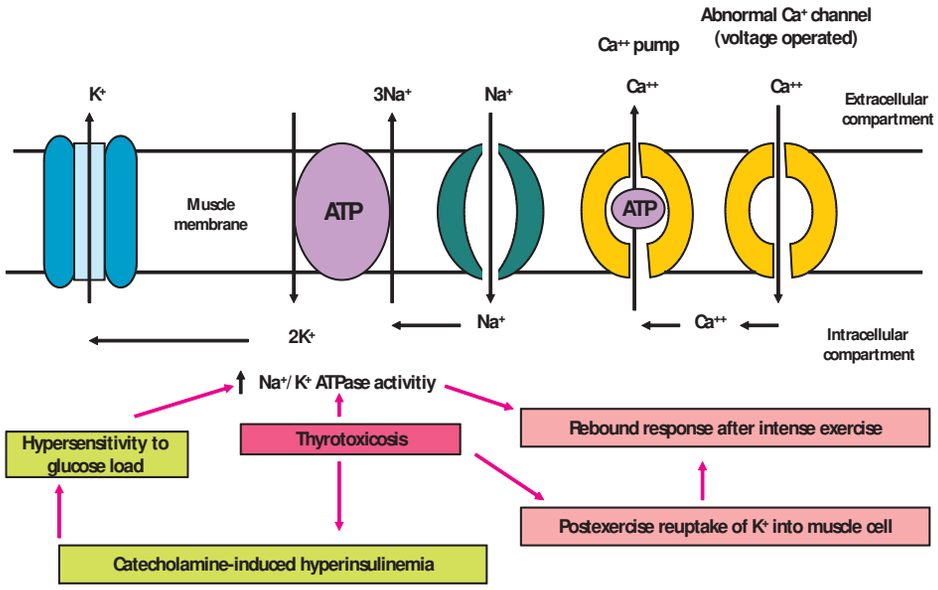

Figure 5. Pathophysiology of THPP

thyroid hormone level. Therefore the degree of hypokalaemia is important [353,354]. Hypophosphataemia and hypomagnesaemia could be obtained in THPP [332]. Hypokalemia can cause vasoconstriction in muscle arterioles and may lead to ischemic changes in sarcolemma. Thus hypokalaemia causes rhabdomyolysis [355]. Besides hypokalaemia, hypophosphataemia [356] and hyperthyroidism alone may cause rhabdomyolysis [357]. As a result of rhabdomyolysis, serum creatine phosphokinase (CPK) level increases [332,358]. ECG changes in THPP vary from nondiagnostic to those showing typical features of hypokalaemia and serious ventricular arrhythmias. Other possible ECG changes include rapid heart rate, high QRS voltage, and first-degree atrioventricular block [359,360].

6.3. Management

In cases of acute attacks of THPP immediate restoration and close monitoring of serum potassium is important. Potassium replacement can be done in two ways; oral or intravenous. Intravenous potassium has significant superiority to the oral route in the improvement of the clinical findings and it is the major choice if the patient shows signs of cardiac dysrhythmia, respiratory distress or is unable to take oral medications. Potassium replacement should not exceed 90 mEq/24h because of the possibility of rebound hyperkalemia [327,344,361]. A non-selective beta-blocker, propranolol, increases serum potassium and phosphate concentrations and ameliorates paralysis [362].

THPP does not disappear completely unless patients become euthyroid. Thus, the management of hyperthyroidism is the mainstay of therapy. Permanent treatment is so important and could be done by antithyroid drugs, radioiodine therapy or surgery [348]. Although glucocorticoids (GCs) have been used to treat hyperthyroidism, they have detrimental effects on insulin sensitivity. Thus GCs can mimic this physiologic process and induce attacks. Physicians

should be aware of the risk of triggering THPP when using high-dose GCs in the thyrotoxic phase [363]. To prevent recurrence of attacks, precipitating factors should be avoided.

The use of propranolol is important during early treatment with anti-thyroid drugs or after radioactive iodine when the euthyroid status is not yet achieved. Propranolol also reduces the frequency and severity of attacks. If the patient's serum potassium level is between normal ranges, prophylactic potassium supplementation is not effective to prevent the attacks. Acetazolamide may worsen the attacks in THPP and should be avoided [364,365].

7. Thyrotoxicosis related psychosis and convulsion

7.1. Hyperthyroidism and central nervous system

The brain, particularly the limbic system (amygdala and hippocampus), has a large number of Tri-iodothyronine (T3) receptors. These receptors affect a variety of functions such as emotion, behavior, and long term memory [366]. Excess thyroid hormones affect neurotransmitters such as serotonin, dopamine, or second messengers. This could be a possible explanation for the relation between neuropsychiatric symptoms and hyperthyroidism [367]. Evidence suggests that the modulation of the beta-adrenergic receptor response to catecholamines in the central nervous system by thyroid hormones in thyrotoxic patients, may contribute to psychotic behavior [368].

As a result, people with thyroid dysfunction could be presented with a wide variety of neuropsychiatric symptoms such as anxiety, irritability, unstable mood, fatigue, insomnia, dementia, confusion state, depression, thyrotoxic crisis, seizures, pyramidal signs, chorea, attention deficit-hyperactivity disorder, sleepwalking (somnambulism)and Hashimoto's encephalopathy. “Apathetic thyrotoxicosis” is an unusual presentation of hyperthyroidism, characterised by depression, psychomotor slowing and apathy and occurring mostly in the elderly [369-371].

7.2. Psychosis

More than 150 years ago, von Basedow first described a psychotic illness, probably mania, in a patient with exophthalmic goitre [372]. More recent case reports have emphasised depressive [373], manic [374], paranoid [375] and schizophreniform features [372]. But psychotic reactions as the presenting feature of thyrotoxicosis is extremely rare, it was reported in 1% of cases and most patients who develop psychosis have been previously diagnosed with mania and/or delirium [376]. The occurrence of psychosis depends on the severity and duration of thyroid disease and the underlying predisposition of the individual to psychiatric instability [377].

Most of the cases caused by thyrotoxicosis or hyperthyroidism have been described in patients with Graves’ disease or toxic multinodular goiter. Therefore, transient thyroiditis or factitious thyrotoxicosis can be related with neuropsychiatric symptoms, including organic psychosis [378]. Only one case each of postpartum thyroiditis [379] and subacute thyroiditis [377] have

been reported related with psychosis. The relations between thyroid autoimmunity and anxiety disorders have been reported [380].

But it should be noted that psychiatric disorders can trigger hyperthyroxinemia [381]. Differential diagnosis between the two conditions is important. In such cases the TSH level is usually in the upper "normal" range and free thyroxine elevation is modest and transient and is usually seen within 1 week. This entity has not been established clearly, but may be considered a form of non-thyroidal illness [382].

7.3. Management

Treatment of hyperthyroidism by standard anti-thyroid drugs (propylthiouracil, methimazole, carbimazole) results with improvement in mental and cognitive symptoms. Psychiatric improvements parallel with improvements in endocrine symptoms. Trzepacz et a.l also showed that a similar improvement both in psychiatric and endocrine symptoms by two weeks of propranolol treatment could be obtained [383,384].

Because of their slow onset of action and potential toxicity, psychotropic drugs (lithium, benzodiazepines, antidepressants and antipsychotics) are not recommended as the primary treatment option for neuropsychiatric symptoms caused by hyperthyroidism. Dopamine receptor blockade with an antipsychotic such as haloperidol can be used in patients with severe neuropsychiatric symptoms. If there is an exhibited psychiatric disease before hyperthyroidism, β-adrenoceptor antagonists may not be effective and neuropsychiatric symptoms may remain after euthyroidism has been achieved, in which case psychotropic drug treatment should be given. Selective serotonin reuptake inhibitors, lithium and benzodiazepines can be used for the treatment of neuropsychiatric symptoms [366].

If therapy fails with the above-mentioned options, more radical approaches such as radioactive iodine ablation and thyroidectomy should be considered [377,385].

7.4. Convulsion

Seizures in hyperthyroidism have rarely been reported in medical literature. Most of the cases were related with Graves' hyperthyroidism [386-388]. Other aetiologic factors were massive levothyroxine ingestion [389], L-thyroxine treatment for hypothyroidism [390,391], subclinical hyperthyroidism [392] and Hashimoto's encephalopathy (HE) [393,394]. The pathophysiology of HE is not clear but increased antithyroid antibodies in all affected patients supports an autoimmune etiology. Generally, patients in medical literaure were euthyroid or hypothyroid. But Sakurai et al reported a case of HE associated with Basedow's disease presented with hyperthyroidism. Another possible aetiologic factor for seizures in hyperthyroidism may be superior sagittal sinus (SSS) thrombosis. Hyperthyroidism may cause hypercoagulabilty, venous stasis and could be related with thrombosis. All cases of seizures in SSS thrombosis in medical literature were known cases of hyperthyroidism [395-397].

The certain incidence of seizures in hyperthyroidism is still unknown. Song et al. recently informed a 0.2% prevelance in a retrospective study [398]. Seizures were seen more frequent

in women than in men, but no differences in the pattern of clinical seizures or electroencephalography (EEG) were demonstrated between the two gender [399]. Most of the reports are for generations of childhood and young adults.

Hyperthroidism can exacerbate seizures and paroxysmal EEG abnormalities in patients with a diagnosis of epilepsy [390,400] or focal/generalized seizures only during thyrotoxicosis in patients without established epilepsy [401]. The mechanisms of seizure induction by thyroid hormones are not clear, but there are some possible explanations. Thyroid hormones may influence the activity of sodium potassium adenosine–triphosphatase, leading to severely altered concentrations of sodium in cerebral cells. In this way thyroid hormones trigger seizures by lowering the seizure threshold [402-405].

To confirm the diagnosis patients should be evaluated for the other causes of seizures. Any epileptic focus or organic lesion should not be obtained with EEG, CT or MRI. Hypoglycemia, hypoxemia, serum electrolyte imbalance, acid-base imbalance or possible central nervous system infections should be excluded [406]. Hyperthyroidism should be confirmed by low serum thyroid-stimulating hormone (TSH) and high concentrations of T4, T3, or both. EEG can be used as another diagnostic tool. Severity of hyperthyroidism correlates with EEG parameters [399]. Generally EEG abnormalities regress after a euthyroid state achieved. Thus EEG can be used to assess response to treatment [406]. The reversibility of EEG findings demontrates that seizures in hyperthyroidism are functional, not organic [407]. But EEG may not be positive in all cases of hyperthyroidism with seizures, and also positive EEGs in all cases of hyperthyroidism may not manifest clinical seizures [399].

7.5. Management

Treatment of hyperthyroidism with standard medical approaches (propylthiouracil, lugols iodine, propanolol and dexamethasone with additional vitamin B complex) have been shown to be effective in patients with seizures. Anti-epileptic drugs may have been useful when standard medical approaches were not adequate to control seizures. Thus, various anti-epileptic drugs (carbamazepine, phenytoin, sodium valproate, diazepam, or clonazepam) were used to treat seizures in the acute phase [399,408]. HE responds to glucocorticoids, immunosuppressive therapy and plasmapheresis which supports the autoimmune etiology. Seizure exacerbations usually remit when patients become euthyroid with treatment [409,410].

8. Thyrotoxicosis related diabetes mellitus

Glucose metabolism disorders can be seen in thyroid disorders, especially in hyperthyroidism. Hyperthyroid patients have a higher risk of developing diabetes mellitus. The pathogenesis is complex and there is lack of data about prevalence and severity in the literature [411].

8.1. Epidemiology

In young individuals with an autoimmune thyroid disease (as Graves' disease) it is common to develop type 1 diabetes. It is due to the alteration of the immune system which leads to a

pathological reaction against self-antigens. In fact other autoimmune diseases like celiac disease can also occur. Thyroid auto-immunity is common in type 1 diabetic patients, with up to 27% of them having detectable titers of anti-thyroid peroxidase antibodies [412]. A prevalence study by Greco et al. confirmed the frequent association between Graves' disease and type 1 diabetes. Graves' disease often preceded diagnosis of type 1 diabetes, particularly in female subjects with a high age at diabetes onset [413].

In older patients, hyperthyroidism can be associated with type 2 diabetes. The pathogenetic mechanism can be explained by insulin resistance and metabolic derangement [414]. A study showed that patients on treatment for hyperthyroid Graves' disease were almost twice as likely to develop type 2 diabetes than the general population, although they were less likely to be overweight and were less likely to have family history. This suggests an association between Graves' disease and type 2 diabetes [415].

8.2. Genetic predisposition

Studies have been performed for HLA-DR3, HLA-DR4 CTLA-4, and PTPN22. These studies suggest that abnormalities in antigen presentation and T cell activation might play a significant role in the shared genetic etiology of type 1 diabetes and auto-immune thyroid disease [416].

8.3. Hyperthyroidism and glucose homeostasis

The effect of hyperthyroidism on glucose homeostasis is complex [417]. Hyperthyroidism stimulates increased metabolism in many tissues, leading to an increased demand for glucose [418]. Altough having insulin resistance, as long as pancreatic beta cell functions remain normal, overt diabetes does not develop in a hyperthyroidism.

Gastric emptying and intestinal absorption

It has been suggested that rapid gastric emptying and increased rates of intestinal absorption of glucose could be responsible for altered glucose tolerance in hyperthyroidism [419]. In contrast to this, recent studies found that gastric emptying has been decreased [420,421] or unchanged [422,423] in hyperthyroidism.

Liver

Hyperthyroidism can cause insulin resistance with direct and indirect effects on the liver. The direct effect is to increase basal hepatic glucose output by promoting gluconeogenesis and glycogenolysis [424]. A sympathetic pathway from the hypothalamic paraventricular nucleus to the liver has been proposed as a central pathway for modulation of hepatic glucose metabolism by thyroid hormone, which forms the indirect effect [425].

Peripheral tissues

Glucose uptake in peripheral tissues especially in the skeletal muscle have been found to be increased in hyperthyroisdism [426-429]. This increased uptake is mainly related with an increase in insulin-stimulated glucose oxidation rates [430-433]. Furthermore, reduced glycogenogenesis and insulin-stimulated nonoxidative glucose elimination results with

intracellular glucose being redirected towards glycolysis and lactate formation [428,429,434]. The release of lactate from peripheral tissues back to the liver contributes to the Cori cycle where more hepatic glucose is being produced [434-436]. In the adipose tissue, lipolysis increases in the fasting state. This results with an increased production of glycerol and nonesterified fatty acids (NEFA). Increased glycerol generated by lipolysis and increased amino acids generated by proteolysis are used for gluconeogenesis. NEFA stimulate gluconeogenesis and provide substrate to other tissues such as muscle, for oxidation [437].

Cytokines

There is an interaction between thyroid hormones and adipose tissue derived cytokines. Effects of thyroid hormones on production rates and plasma levels of these cytokines could be used to explain mechanisms of insulin resistance in hyperthyroidism. Adipose tissue derived cytokines are adiponectin, leptin, interleukin-6, tumor necrosis factor-α, resistin and visfatin. There are conflicting reports about the role of these cytokines to insulin resistance in hyperthyroidism [418].

Insulin and glucagon secretion

Decreased [438-442], normal, or even increased [437,443] levels of plasma insulin have been reported in hyperthyroidism. There are conflicting reports about insulin secretion in hyperthyroidism. But it is more consistent that insulin degradation increases. Hyperthyroidism augments renal clearance of insulin [428,444,445]. Another important pathologic change induced by long-term hyperthyroidism has been shown to be irreversible pancreatic damage [446-448]. Secretion and metabolic clearance rates of glucagon have been found increased in hyperthyroidism [449]. Increased levels of growth hormone and catecholamines that accompany hyperthyroidism may further contribute to insulin resistance. Interorgan communication in hyperthyroidism are shown in Figure-6 [418].

8.4. Subclinical hyperthyroidism and glucose homeostasis

Subclinical hyperthyroidism could be endogenous and exogenous. Both of them have also been associated with insulin resistance in some studies [450,451]. But there are conflicting reports in the literaure about insulin resistance in exogenous subclinical hyperthyroidism. Yavuz et al. have reported reduced insulin sentivity in these patients [452,453]. In contrast to this Heemstra et al. have reported that insulin sensitivty was not altered [454]. According to its cronicity and higher T3 levels endogenous subclinical hyperthyroidism may have a larger impact on glucose homeostasis when compared to exogenous subclinical hyperthyroidism [451].

8.5. Impact of hyperthyroidism on diabetes

In some young women with Type 1 diabetes, glucose control may fluctuate following childbirth due to post-partum thyroiditis, when a state of hyperthyroidism is followed by hypothyroidism. Routine screening of TSH is recommended in such patients 6-8 weeks following delivery [455]. Thyrotoxicosis and diabetic ketoacidosis can occur simultaneously. In this

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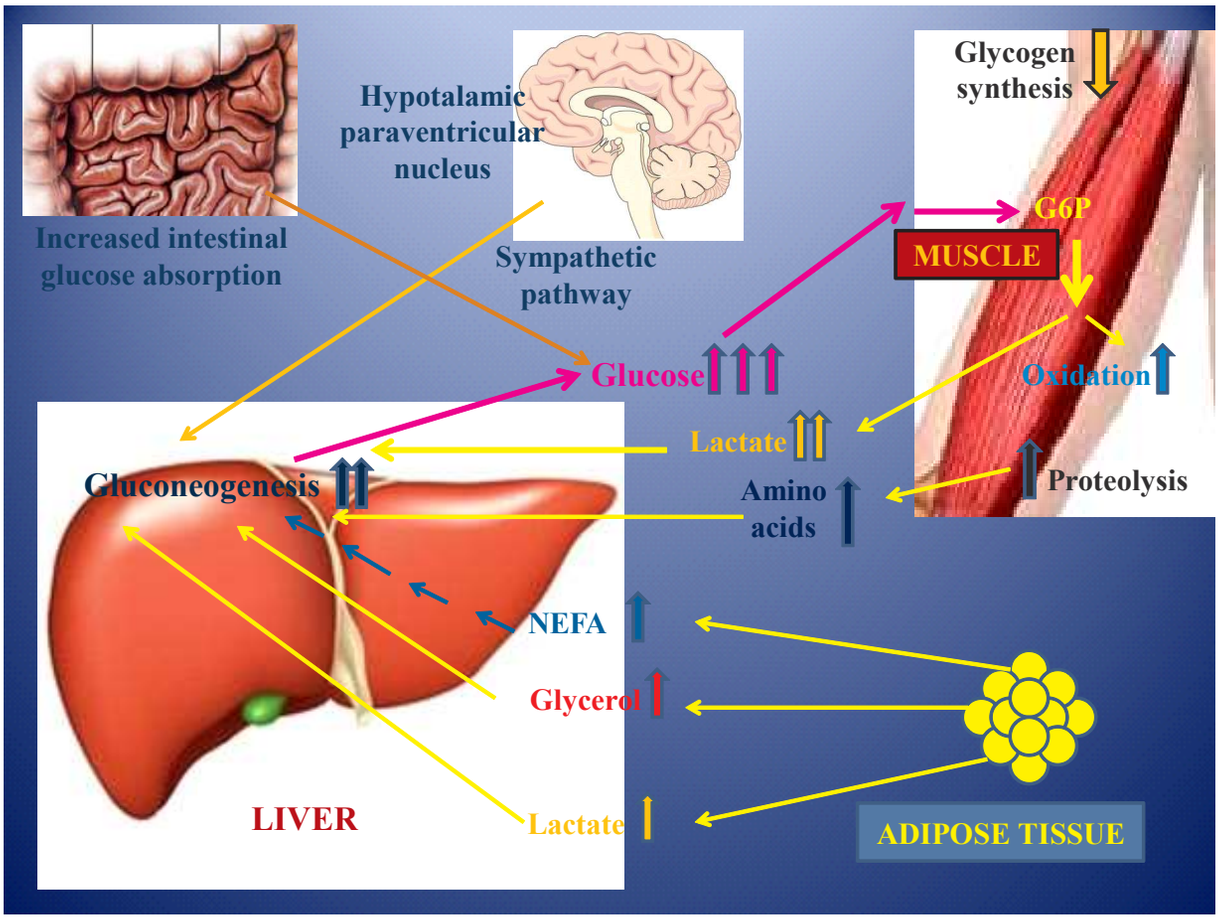

(Data adapred from reference 418)

Figure 6. Interorgan Communications in Hyperthyroidism

instance the combination could be fulminant and potentially life threatening. The first goal of treatment is to maintain electrolyte balance to avoid cardiac arrest [456].

As far as hyperthyroidism affects glucose homeostasis and causes insulin resistance, the patients need more insulin administration for glycemic control. Moon et al. reported a case of hyperglycemic hyperosmolar state (HHS) associated with Graves' hyperthyroidism. HHS rarely associates with Graves' hyperthyroidism but this unusual relation should be considered [457].

9. Conclusion

In conclusion all types of thyrotoxicosis may induce severe systemic complications which may affect morbidity, even mortality of the disease. Prompt and effective treatment of the complications and proggresing to euthyroidism is important for the management.

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