Endokrynologia Polska
DOI: 10.5603/EP.a2018.0031
Tom/Volume 69; Numer/Number 3/2018
ISSN 0423–104X

Thyroid hormones and obesity: a known but poorly understood relationship

Hormony tarczycy i otyłość: znana, lecz słabo rozpoznana relacja

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Abstract

Thyroid hormones (TH) are involved in a wide variety of biological processes, including neurodevelopment, regulation of intermediary metabolism, and energy expenditure. TH actively participate in basal energy expenditure and adaptive thermogenesis, and for this reason body weight can be affected during dysthyroidism. Obesity is a non-transmissible, chronic, inflammatory, metabolic disease that implies a positive energy balance. The adipose tissue produces a series of hormones and adipocytokines such as leptin, which can influence the thyroid status at different levels. There is evidence showing that thyroid dysfunction could predispose to obesity; conversely, there is also evidence suggesting that obesity induces thyroidal alterations. The aim of this review is to describe the relation between the thyroidal system and obesity; in addition, we present a hypothetical model highlighting the importance of TH peripheral deiodination and its role in the establishment of a positive energy balance. We conclude that the relation between the thyroid system and obesity and overweight is complex and involves multiple levels of interaction. In addition, the assessment of the obese patient should consider an evaluation of the thyroidal function in order to achieve a better and personalised treatment for these patients. **(Endokrynol Pol 2018; 69 (3): 292–303)**

Key words: *thyroid hormone metabolism, obesity, iodothyronine deiodinases, thermogenesis, energy balance*

Streszczenie

Hormony tarczycy (*thyroid hormones*, TH) są zaangażowane w wiele różnych procesów biologicznych, wliczając rozwój układu nerwowego, regulację metabolizmu pośredniego oraz zużycie energii. Aktywnie uczestniczą w podstawowym zużyciu energii i termogenezie adaptacyjnej i z tego względu mogą mieć wpływ na masę ciała w przebiegu chorób tarczycy. Otyłość to niezakaźna, przewlekła, zapalna choroba metaboliczna, która implikuje dodatni bilans energetyczny. Tkanka tłuszczowa produkuje szereg hormonów i adipocytokin, takich jak leptyna, które mogą wpływać na stan tarczycy na różnych poziomach. Istnieją dowody na to, że dysfunkcja tarczycy może predysponować do otyłości i odwrotnie, istnieją dowody sugerujące, że otyłość powoduje zmiany dotyczące tarczycy. Celem tej pracy było opisanie związku między układem tarczycy a otyłością. Ponadto w pracy zaprezentowano hipotetyczny model podkreślający znaczenie obwodowej dejodynacji hormonów tarczycy i jego rolę w ustanowieniu dodatniego bilansu energetycznego. Podsumowując, możemy stwierdzić, że relacja między układem tarczycy a otyłością i nadwagą jest złożona i obejmuje wiele poziomów interakcji. Ponadto, poddając ocenie otyłego pacjenta, powinno się rozważyć ocenę funkcji tarczycy, aby uzyskać lepsze i spersonalizowane efekty leczenia. **(Endokrynol Pol 2018; 69 (3): 292–303)**

Key words: *metabolizm hormonów tarczycy, otyłość, jodotyroninowe dejodynazy, termogeneza, bilans energetyczny*

Abbreviations

TH: thyroid hormones
T4: thyroxine
T3: triiodothyronine
TSH: thyrotropin
TRH: thyrotropin-releasing hormone
TR: thyroid hormone receptor
HPT axis: hypothalamic-pituitary-thyroid axis
NR: nuclear receptor
Ds: iodothyronine deiodinases
D1: iodothyronine deiodinase type 1
D2: iodothyronine deiodinase type 2
UCP1: uncoupling protein type 1
ASNS: autonomic sympathetic nervous system
BMI: body mass index

Introduction

Thyroid hormones (TH) participate in the regulation of most of the cellular processes, like growth and development, intermediary metabolism, and neurodevelopment, among others. TH are key regulators of

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energy balance, and this is reflected in the associated alterations in patients with hypo- and hyperthyroidism. TH metabolism is complex and depends on the peripheral deiodination of the pro-hormone T4 to T3, which is the main bioactive hormone [1]. On the other hand, obesity is the most prevalent metabolic disease worldwide and it is a major health issue considering the associated comorbidities like hypertension, type 2 diabetes mellitus, dyslipidaemia, and cancer, among others [2]. Obesity is a disease with multiple alterations at the endocrine and immune levels, where hormones like leptin and adipocytokines play a significant role.

TH metabolic effects are strongly related to the mechanisms regulating body weight balance and body fat mass, by stimulating thermogenesis, lipid catabolism, and heat production [3]. One of the main target tissues of TH are adipocytes; therefore, obesity is strongly related to TH metabolism. In this context, there are several studies suggesting that a thyroidal dysfunction could predispose to obesity. Conversely, there is also evidence showing that obesity could lead to a thyroidal dysfunction. Considering this information, this review analyses the relation and mechanisms involved between thyroidal physiology and obesity.

Thyroid hormones

Thyroid gland

The thyroid gland is one of the body's largest endocrine organs, and one of the most richly vascularised tissues with the greatest blood flow in the human body. This is probably a reflection of the metabolic and functional relevance of this tissue, an exclusive site of production of TH, which participate in the morphogenesis and functional maturation of virtually all tissues of the body, being crucial in the central and peripheral nervous system [1].

The basic functional units of the thyroid gland are the thyroid follicles — spherical structures composed of a simple cubic epithelium of specialised cells called thyrocytes. This spherical arrangement defines a central follicular cavity where the thyroid colloid is stored [4]. Significant amounts of iodine, an essential component of TH, are found within the thyroid colloid. The intraglandular deposit of TH is dependent on the thyroid functional status and dietary intake of iodine, and it is considered that this hormonal store is sufficient to protect the organism for an approximate period of up to three months, in a scenario of sudden cessation in the intake of iodine [1, 4]. The thyroid can concentrate iodine on average 40 times more compared to the levels found in plasma, making it the main body store of the halogen in the body [1].

Structure of TH

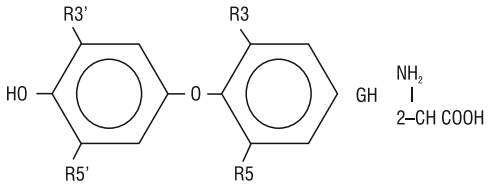
TH are essential during critical periods of the development and differentiation of a large number of organs and systems, and participate in processes such as body growth, neurodevelopment, differentiation, and thermogenesis [4–6]. Also, during adulthood TH are one of the main endocrine regulators of energy expenditure [1, 6].

TH are formed by two rings derived from the amino acid tyrosine (Figure 1) and are synthesised in the thyroid gland, through the iodination of the tyrosine residues present in the structure of the glycoprotein thyroglobulin, which acts as a template in the process of hormone synthesis [1, 5, 6].

TH synthesis is regulated by the hypothalamic-pituitary-thyroid axis (HPT axis) through complex interactions that include the thyrotropin-releasing hormone (TRH) secreted by the paraventricular nucleus of the hypothalamus, and the thyroid-stimulating hormone (TSH) secreted by the pituitary thyrotrophic cells [4, 7]. The increase in TH circulating concentrations inhibits TRH and TSH production and release, an effect known as negative feedback. In contrast, a decrease in TH circulating levels eliminates the inhibitory signals, reactivating TRH and TSH synthesis and release, and consequently the production of TH by the thyrocytes [7].

TH receptors

TH induces its biological effects through receptor-mediated genomic mechanisms, which belong to the nuclear receptor superfamily (NR). NR are ligand-dependent transcription factors that are functionally divided into six structural domains called A to F (Figure 2A) [8]. The A/B domain is susceptible to post-translational modifications, while the C domain allows interaction with DNA. The D domain possesses the "hinge" function, and the E domain is the binding site of the ligand and co-regulatory proteins. The F domain corresponds to a variable region at the C-terminal end involved in receptor activation. The C domain binds to DNA through a zinc finger structural motif, which recognises specific hexanucleotide sequences termed thyroid hormone responsive elements. The binding of TH to the receptor induces conformational changes in the protein that favour the interaction with coactivating proteins or corepressors, which modulates the transcriptional effect of TH [8]. T4 is considered a prohormone because it is 3-4 times less potent than T3, considered the main bioactive TH, and because most of the circulating T3 is generated at the peripheral level by enzymatic deiodination of T4 (its circulating levels are approximately 40 times higher than T3) [5].



Common name	Symbol	Substituents				Systematic name
		R_3	R_3	R_5	R_5	
Thyroxine	T_4	I	I	I	I	3,3´,5,5´-Tetra-iodo-L-thyronine
Triiodothyronine	T_3	I	I	I	H	3,3´,5,-Tri-iodo-L-thyronine
Reverse Triiodothyronine	rT_3	I	I	H	I	3,3´,5´-Tri-iodo-L-thyronine
3,5'-diiodothyronine	3,5-T_2	I	H	I	H	3,5-Di-iodo-L-thyronine
3,3'-diiodothyronine	3,3´-T_2	I	I	H	H	3,3´-Di-iodo-L-thyronine

Figure 1. *Chemical structure and nomenclature of the main TH. Upper part shows TH basic chemical structure composed by two rings of the amino acid tyrosine. The inner ring retains the amino and carboxyl groups (β-alanine chain), and the outer ring is bound to the inner one by an ether type bond. The figure shows the nomenclature used in relation to the substituents present in the 3, 5 and 3', 5' positions of the inner and outer rings; respectively. Where: I — iodine; H — hydrogen. Modified from Solís-S et al., 2011 [6]*

Rycina 1. *Struktura chemiczna i nazewnictwo głównych hormonów tarczycy. Górna część przedstawia podstawową strukturę chemiczną hormonów tarczycy, złożoną z dwóch pierścieni aminokwasu tyrozyny. Pierścień wewnętrzny zachowuje grupy aminową i karboksylową (łańcuch β-alaniny), natomiast zewnętrzny jest połączony z pierścieniem wewnętrznym wiązaniem eterowym. Na rycinie przedstawiono nazewnictwo używane w odniesieniu do podstawników obecnych w pozycjach 3, 5 i 3', 5' odpowiednio zewnętrznego i wewnętrznego pierścienia, gdzie: I — jod; H — wodór. Zmodyfikowano z Solís-S i wsp., 2011 [6]*

The *THRA* and *THRB* genes are located in the human chromosomes 17 and 3, respectively, and codify for the major TH receptors isoforms (TR): TRα1, TRβ1, and TRβ2 (Figure 2B) [9]. Each of these isoforms binds to T3 with similar affinity and mediates the genomic effects of TH [10, 11]. The TRβ1 isoform predominates systemically, with greater expression in hepatic tissue, brain, retina, inner ear, kidney, and adipose tissue [8, 12]. The TRβ1 isoform is also widely distributed in all tissues, especially heart, where its expression is responsible for changes in heart rate and frequency, as well as in brain and skeletal muscle [8]. TRβ2 expression is limited to the anterior region of the pituitary and hypothalamus, where it acts as the major regulator of the negative feedback of the HPT axis [8]. The expression of TR and that of multiple TH-dependent genes is regulated by T3 in a specific tissue manner (Table I) [13, 14]. Therefore, an area of recent interest is the study of selective agonists of the different TR subtypes with distinct potential therapeutic actions [15].

TH deiodination

As previously mentioned, T4 circulating levels are higher than those of T3, because the thyroid gland secretes mainly T4 and much less T3, in an approximate ratio of 6 to 1. However, it is considered that on average 80% of the circulating T3 comes directly from the enzymatic deiodination of T4 at the peripheral level. The deiodination is catalysed by a group of isoenzymes generically known as iodothyronine deiodinases (Ds). Three isotypes of Ds are known: D1, D2, and D3, which are integral membrane enzymes with punctual differences between them, such as their subcellular localisation, preferred substrates, and generated products — which explains their functional differences [5, 6]. Ds regulate the bioavailability of active/inactive TH at the peripheral level and are currently considered an extension of the HPT axis (Figure 2C).

TH, leptin, and weight regulation

The basal metabolic rate has long been used as an indicator of thyroid status [3]. The thyroid profile is also one of the most requested paraclinical exams in medical practice, especially due to the insistence of patients entering the clinic attributing the cause of its weight gain due to a thyroid malfunction [4]. One of the main regulators of appetite and weight gain is leptin, a protein hormone secreted by adipocytes, whose circulating concentration increases in relation to body fat mass. Among other tissues, leptin acts in the hypothalamus, where it regulates food intake and energy expenditure [16]. Interestingly, TSH synthesis by thyrotropes has been reported to increase due to the exogenous administration of leptin in a murine model [17]. The action of leptin is carried out mainly in the arcuate nucleus of the hypothalamus, but also through other regions of the brain such as the brain stem, the fourth ventricle, and the vagal dorsal complex, all innervating

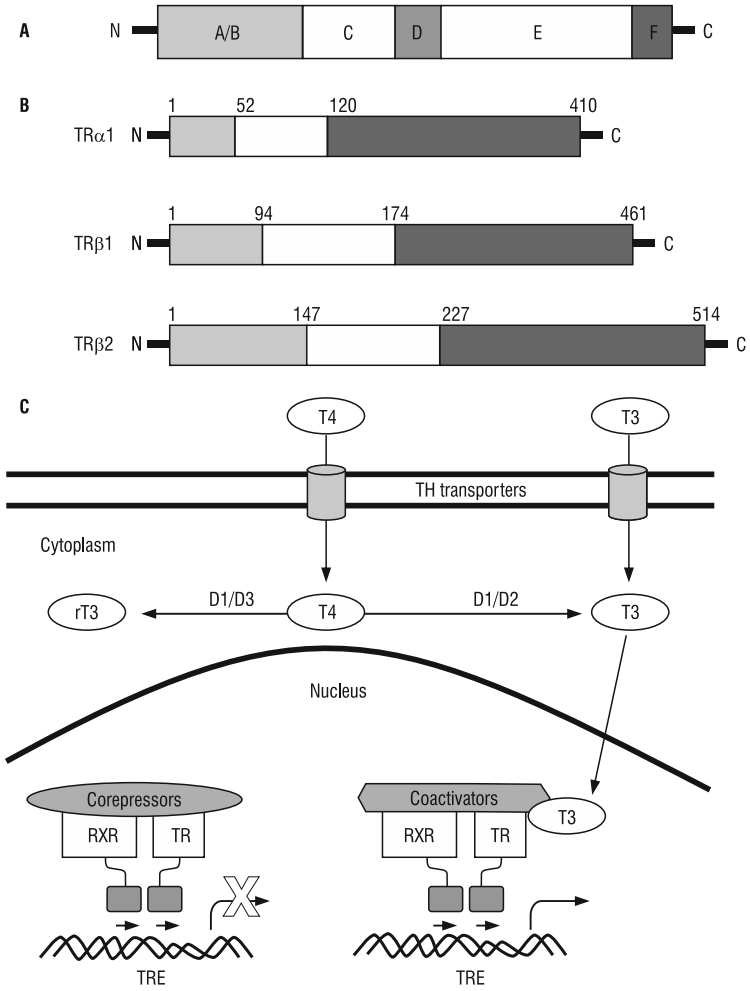


Figure 2. *Structure of TH receptors (TR) and associated genomic mechanisms.* ***Panel A****: General scheme of nuclear receptors. The A/B domain is a hypervariable domain with transactivation functions, the C domain is the DNA binding region, the D domain contains the hinge. The E domain binds the ligand and has dimerisation sequences, and the F domain is a hypervariable transactivation domain. The amino (N) and carboxyl (C) terminal end of the protein are also shown.* ***Panel B:*** *Schematic representation of the main TH receptors. The TR have a high homology in the C domain (blank region) and D/E (grey region) domains. The A/B domain (dotted region) at the N-terminal end is variable in length. Numbers indicate the length in number of amino acids.* ***Panel C:*** *Simplified mechanism of TH action. TH enter the cell through membrane-specific transporters. The circulating T4 is intracellularly transformed by deiodinase type 2 (D2) to the active form T3. Deiodinase type 3 (D3) transforms T4 into the inactive form rT3. Deiodinase type 1 (D1) can either activate or inactivate T4. At the nuclear level, in the absence of the hormone; the complex formed by the heterodimer: retinoic acid receptor (RXR) and TR (RXR-TR), binds to TH-response elements located in the DNA (TRE). The RXR-TR complex recruit corepressors proteins that will inhibit gene transcription. In the presence of T3, the binding of the ligand induces conformational modifications of the TR, which favours the displacement of corepressors and the recruitment of coactivators, which promote transcriptional machinery binding to DNA and the expression of the target genes. Modified from Cheng et al. 2010 [12] and Brent, 2012 [22]*

Rycina 2. *Struktura receptorów hormonów tarczycy (thyroid hormone receptors; TR) i powiązane z nimi mechanizmy genomowe.* ***Panel A:*** *Ogólny schemat receptorów jądrowych. Domena A/B jest domeną hiperzmienną z funkcją transaktywacyjną, domena C jest regionem wiążącym DNA, domena D zawiera zawias. Domena E wiąże ligand i umożliwia dimeryzację, a domena F jest domeną hiperzmienną z funkcją transaktywacyjną. Na rycinie przedstawiono również koniec aminowy (N) i karboksylowy (C) białka.* ***Panel B:*** *Schematyczne przedstawienie głównych receptorów hormonów tarczycy. Receptory hormonów tarczycy wykazują wysoką homologię w obrębie domeny C (pusty obszar) i domen D/E (obszar w kolorze szarym). Domena A/B (obszar wykropkowany) na końcu aminowym N ma zmienną długość. Liczby wskazują długość w ilości aminokwasów.* ***Panel C:*** *Uproszczony mechanizm działania hormonów tarczycy. Hormony tarczycy dostają się do komórki dzięki specyficznym błonowym transporterom. Krążący T4 jest przekształcany wewnątrzkomórkowo przez dejodynazę typu 2 (D2) do postaci aktywnej T3. Dejodynaza typu 3 (D3) przekształca T4 w nieaktywną postać rT3. Dejodynaza typu 1 (D1) może aktywować lub dezaktywować T4. Na poziomie jądrowym, w przypadku braku hormonu, kompleks utworzony przez heterodimer: receptor kwasu retinowego (retinoic acid receptor; RXR) i receptor hormonów tarczycy (RXR-TR) wiąże się ze specyficznymi dla hormonów tarczycy elementami odpowiedzi umiejscowionymi w DNA (thyroid hormone response elements, TRE). Kompleks RXR-TR rekrutuje białka hamujące, które zahamują transkrypcję genów. Wiązanie ligandu w obecności T3 indukuje zmiany konformacyjne receptorów hormonów tarczycy, co sprzyja przemieszczaniu się białek hamujących oraz rekrutowaniu koaktywatorów, które wspierają transkrypcyjny mechanizm wiązania z DNA oraz ekspresję genów docelowych. Zmodyfikowano z Cheng i wsp., 2010 [12] i Brent, 2012 [22]*

Table I. *TH effects in mammals*
Tabela I. *Działanie hormonów tarczycy u ssaków*

FUNCTION	EFFECT	REGULATED GENES
Thermogenesis	↑ glycolysis and oxygen consumption and synthesis of uncoupling proteins (UCP) in BAT	↑ UCP1, 2 and 3; Na/K ATPase (α and β subunits)
Vitamins	Participate in vitamin A synthesis ↑ demand of other B complex components ↓ thiamine phosphorylation	——
Growth and cellular differentiation	↑ somatic growth, maturation of the nervous system, and epiphyseal ossification	↑ GH
Central nervous system	Essentials in development and neuronal growth. Modulate the speed of excitation and conduction and behaviour patterns.	↑ β5-tubulin; NGF; TrkA; RORα; CAMK-IV; PCP-2; COX-1; laminin; RC3; etc. ↓ tenascin C; NCAM; L1; SWAP; p75LNGFR; TOM M70A; α1 y β2 tubulin; etc.
Carbohydrates	↑ absorption & glucose oxidation, glycogenolysis and insulin degradation	↑ PEPCK; G6P; GLUT4
Heart	Inotropic & chronotropic effect, synergism with catecholamines	↑ α-myosin (heavy chain); SERCA; β adrenergic receptors ↓ β-myosin (heavy chain)
Lipids	↑ synthesis, degradation and excretion of cholesterol and bile acids Modify the catecholamines response	↑ malic enzyme; S14 protein; carbonyl reductase; FATP
Haematopoiesis	Participate in haemoglobin synthesis	↑ globin chain (α and β subunits)
Proteins	Anabolism/catabolism	——
Muscle	↓ conversion of creatine to phosphocreatine	↑ MBP ↓ actin; creatine kinase
Hydroelectrolytic metabolism	↑ glomerular filtration rate & sodium extracellular diuresis	↑ Na/K ATPase (α and β subunits); Na^+/H^+ interchanger
Hypothalamus/Pituitary	Regulate TRH, TSH, GH, FSH, LH, and PRL synthesis and secretion	↑ GH ↓ TRH; TSH (α and β subunits); PRL
Reproductive system	GONADS: needed for differentiation	——
	MAMMARY GLAND: essentials for the functional differentiation of the glandular primordium. Participate in the galactopoietic complex	
Digestive system	Modulate the gastrointestinal transit speed, increase vitamin B12 and folate absorption	↑ Na/K ATPase (α & β subunits); alkaline phosphatase ↓ lactase

Where: ↑ — increase or stimulation; ↓ — decrease or inhibition; TSH — thyroid-stimulating hormone; GH — growth hormone; FSH — follicle-stimulating hormone; LH — luteinizing hormone; PRL — prolactin; UCP — uncoupling protein; NGF — neural growth factor; TrkA — tropomyosin receptor kinase A; RORα — orphan nuclear receptor alpha; CAMK-IV — calcium/calmodulin-dependent protein kinase IV; PCP-2 — Purkinje cells type 2 protein; COX-1 — type 1 cyclooxygenase; RC3 — neurogranin; NCAM — neural cell adhesion molecule; SWAP — suppressor-of-White-APricot splicing regulator; p75LNGFR — low affinity nerve growth factor receptor; TOM M70A — translocase of outer mitochondrial membrane 70; SERCA — sarco/endoplasmic reticulum Ca2+-ATPase; PEPCK — phosphoenolpyruvate carboxykinase; G6P — glucose-6-phosphatase; MBP — myosin binding protein; FATP — fatty-acid transport protein
*Modified from Solis-S et al., 2006 [4]

the paraventricular nucleus through multi or monosynaptic projections [16].

It is generally accepted that a positive energy balance (obese subjects) presents increased TSH and free T3 concentrations [18]. On the other hand, a negative energy balance in obese and thin humans inhibits the activity of the HPT, and gonadal and hypothalamus-pituitary-somatotrope axis, while stimulating the adrenal axis [19]. An example of this relation can be found in anorexia nervosa, where some clinical manifestations of hypothyroidism such as bradycardia and hypothermia are present [19]. Thus, during periods of

starvation, serum leptin levels decrease, as do TH, TSH, and TRH concentrations [16]. In addition, it has been reported that TH increase the expression of leptin in adipocytes *in vitro* [20].

TH and intermediate metabolism

Basal metabolism or energy expenditure at rest is regulated by TH and constitutes approximately two thirds (66%) of total daily energy expenditure [21–23]. In the absence of TH, basal energy expenditure would be reduced by more than 30%. The autonomic sympathetic nervous system (ASNS) and TH are the two main factors that directly influence energy expenditure at rest and glucose and lipid metabolism [1, 23].

T3 stimulates oxygen consumption in tissues by regulating proteins necessary for the synthesis and degradation of macronutrients, muscle contraction, and maintenance of transmembrane ionic gradients [8, 24]. It also modifies the function of mitochondria by affecting the composition of the membrane lipid and its protein components [8, 24]. The adipose tissue constitutes the main energetic store of the organism, and based on its histological and functional characteristics two main cell types of adipocytes are distinguished: white and brown. The main function of white adipose tissue (WAT) in humans is the storage, synthesis, and mobilisation of triglycerides. The main function of brown adipose tissue (BAT) is adaptive thermogenesis, a function that has recently undergone a metabolic rebirth by identifying its presence in adults [25]. Both in WAT and BAT, TH promote lipid mobilisation (lipolysis) and thermogenesis [12, 25].

TH and thermogenesis

In humans, energy expenditure has several components, which are generally divided into: obligatory thermogenesis or basal metabolism, food-related thermogenesis, thermogenesis related to physical activity, and facultative or adaptive thermogenesis [21, 26]. Characteristically, for the most part these processes involve TH as regulators. Basal metabolism refers to the energy used by a resting organism due to essential metabolic activities [21]. Thermogenesis associated with diet represents 10% of daily energy expenditure and occurs due to digestion, absorption, distribution, and storage of nutrients. Thermogenesis associated with physical activity represents from 50% of total energy expenditure in high performance athletes and up to 10% in sedentary individuals. Facultative thermogenesis occurs in response to cold exposure or a hypercaloric diet, and accounts for 10–15% of total energy expenditure [27].

The ASNS, when exposed to lower temperature, increases the content of noradrenaline in BAT and, in synergism with T3, promotes the expression of an important protein for thermogenesis that is expressed exclusively in brown adipose tissue, the uncoupling protein type 1 (UCP1) [22, 24, 25]. UCP1 acts as a regulator in the transport of protons in the mitochondria, promoting proton leakage from the intermembranal space to the mitochondrial matrix. This leak decreases the proton gradient generated between these two mitochondrial structures. In this way instead of synthesising ATP, the energy dissipates as heat [26].

TH regulate the activity of BAT by endocrine and paracrine mechanisms. In this regard, both systemic and central nervous system administration of T3 in experimental animals has been shown to increase ASNS activity, which induces thermogenesis in BAT as well as weight loss. Likewise, the inhibition of TH receptors in the hypothalamus prevents the activation of thermogenesis and consequently leads to weight gain [26–28].

Adrenergic signalling in adipocytes and cardiomyocytes plays a very important role in thermogenesis by supplying fatty acids from lipolysis, which are transported to BAT through increased blood flow [24, 29]. Interestingly, there is also an increase in the expression of the enzyme D2 in BAT, favouring the conversion of T4 to T3, thus enhancing thermogenesis [22, 24, 26]. This increase in D2 activity is due to stimulation of the ASNS by TH. In this way, the thermogenic response induced by cold is altered in mice whose D2 expression in BAT is suppressed. Likewise, the expression of UCP1 is abolished in mice that do not express the TR 1 isoform in BAT [5, 26]. It has also been reported that genetically modified rodents that do not express the UCP1 protein lose more than 10°C body temperature when exposed lower temperatures [27]. The effect of the alteration in adaptive thermogenesis can be evidenced by the characteristic cold intolerance presented by patients with hypothyroidism.

Obesity

Obesity Epidemic

Obesity is a chronic, low-grade inflammatory and non-transmissible disease that affects practically all ages and is relevant in most countries [30]. The worldwide prevalence of obesity in adults was 13% [2]. In Latin America, the prevalence of obesity in adults was 23.4%, in the most populated countries of the region, Argentina, Brazil, and Mexico, the prevalence of obesity was 29.4, 19.5, and 32.8%, respectively. On the other hand, the global prevalence of obesity in children older than five years was 6.7% in 2010 [31]. In Mexico, data from 2016 showed a prevalence of obesity of 15.3% in children between five and 11 years old [32].

Obesity is the result of an imbalance between energy intake and expenditure. Energy expenditure may

be reduced by lack of physical activity, by a reduction in basal metabolism, by a decrease in thermogenesis, or by the combination of one or more of these factors [21, 33, 34].

Comorbidities in patients with obesity may be due to extra body weight on the musculoskeletal system or by increased secretion of free fatty acids, peptides, and adipocytokines produced by adipocytes [35]. As complications, the following alterations may be present concomitantly or separately: depression, biliary lithiasis, hepatic steatosis, dyslipidaemia, arterial hypertension, coagulopathies, endothelial dysfunction, thyroid alterations, type 2 diabetes mellitus, polycystic ovarian syndrome and hypogonadism, breast, oesophagus, pancreas, and colon neoplasms, sleep apnoea, and social stigma [31, 36, 37].

Obesity as an inflammatory disease

Obesity is recognised as a systemic condition of chronic low-grade inflammation, characterised by elevation of proinflammatory cytokines and activation of its signalling pathways in various organs, and by accumulation of leukocytes in adipose tissue, liver, and other organs [29, 38]. Adipose tissue secretes adipocytokines such as leptin, adiponectin, resistin, tumour necrosis factor alpha (TNF-α), and interleukin type 6 (IL-6) and type 1beta (IL1-β); capable of modifying the regulation, metabolism, and secretion of various hormones [29, 39].

When a positive energy balance is established, there is an increase in the synthesis and storage of fatty acids in the form of triglycerides in adipocytes. When WAT approaches the limit of its storage capacity, a toxic accumulation of lipids (endotoxaemia) occurs in non-adipose tissue, promoting proinflammatory mechanisms. At the same time, hypertrophic adipocytes undergo necrosis, due to the restriction in the blood flow caused by hypertrophy, causing an infiltration of leukocytes in white adipose tissue. This type of inflammation has been termed metabolic inflammation or metainflammation [29].

The metainflammation may extend to the central nervous system; in the hypothalamic inflammation, the TNF-α, IL-6, and IL-1β proteins are involved, promoting a state of alteration in the processes that regulates energy balance, favouring the development of obesity [29, 38]. In hypothalamic inflammation, there is resistance to leptin, which contributes to the adipose tissue gain by the loss of anorexigenic mechanisms, as well as alterations in the secretion of TRH by hypothalamic neurons.

Thyroid dysfunction and obesity

TH participate in both expenditure and energy consumption [26]. In this way, the dysthyroid states are associated with weight changes and changes in thermogenesis and basal metabolism. In hypothyroidism, a modest weight gain occurs, decreasing thermogenesis and basal energy expenditure; contrary events occur in hyperthyroidism [35].

Positive correlations have been found between TSH levels and body mass index (BMI), suggesting that changes in body weight are associated with thyroid dysfunction [36, 40–42]. These associations have been reported in premenopausal women, children, euthyroid adults with obesity, and in patients with morbid obesity, excluding causes such as iodine deficiency and autoimmune thyroiditis [35]. However, several studies have found variable results regarding TSH and TH levels in obesity, with both positive and negative associations or without any relation [43–47]. In this sense, there is still controversy between the relationship of thyroid function and BMI, although it is generally recognised that in obesity there is an increase in TSH and free T3 [41].

Serum levels of leptin have been studied in hypothyroid patients reporting both high and low concentrations compared with euthyroid patients [16, 48]. Variations are likely to be due to a lack of control of variables such as BMI and TH replacement therapy [49]. In conditions where there is endogenous obesity, such as Prader-Willi syndrome (PWS), some features such as short stature, central obesity, and changes in muscle and bone mass, which are characteristic of hypothyroidism, are also included. In this sense, approximately one-third of patients with PWS have hypothyroidism. The abnormalities presented suggest alterations at the level of the hypothalamic-pituitary axis, causing secondary hypothyroidism. In this context, obesity is partially a consequence of thyroid disorders [50]. Likewise, a high prevalence of approximately 20% of hypothyroidism and subclinical hypothyroidism has been found in individuals with morbid obesity, a number that doubles in relation to what is observed in the general population [51]. Another association that is found between obesity and the thyroid system is the risk of neoplasias. In women, there is a 16% increase in the development of differentiated thyroid carcinoma for every 5 kg/m^2 increase in BMI [52]. In this sense, it has been reported that small variations in TSH levels, caused by minimal changes in T4 dosage during replacement therapy in hypothyroid patients, are associated with significant changes in resting energy expenditure. These observations support the clinical evidence that hypothyroidism represents a risk factor for the development of overweight and obesity [51, 53].

In primary hypothyroidism, altered metabolic functions involved in energy expenditure may be the primary event, with an ensuing increase in BMI.

Subsequently, adipose tissue increases and TSH levels rise concomitantly with leptin concentrations [51].

In addition, TSH receptors have been found in preadipocytes and adipocytes, and this signalling pathway has been implicated in adipogenesis processes, suggesting that TSH itself may promote adiposity [36, 54]. These connections establish a new hypothalamic-pituitary-adipose tissue axis [55, 56]. Under this scenario, TH deficiency (hypothyroidism) with the consequent increase in TSH could promote weight gain [57, 58].

It is considered that alterations in the regulation of TSH secretion may explain the elevated TSH levels in patients with obesity. In this regard, D2 activity, the main deiodinase at the pituitary level, is key for TSH secretion under T3 regulation (negative feedback), and it has been observed that in obese patients D2 expression is decreased. Thus, the recovery of the HPT axis in these patients should be the key step in order to restore energy expenditure [51]. Other authors suggest that in patients with obesity there may be some degree of TH resistance due to a reduction in the TR expression [26].

In addition, due to the participation of UCPs in thermogenesis in different tissues, it is considered that the levels of expression and the degree of activity of UCPs could have a direct effect in energy expenditure and a different predisposition to the accumulation of adipose tissue [26]. Facultative thermogenesis, mediated by ASNS and T3 within BAT, is diminished in obesity models [5]. Notably, simple nucleotide polymorphisms associated with obesity have been described in the promoter of the gene encoding UCP1 [59]. Likewise, TR isoform potentiates the adrenergic effect in WAT for the production of free fatty acids (lipolysis) as an energy substrate for the generation of heat in BAT. In this reagard, it has been observed that in animal models where TR is mutated there is accumulation of visceral fat [6].

Another condition associated with obesity is the so-called endoplasmic reticulum stress, which occurs when there is an accumulation of malformed proteins in the lumen of such organelle [5, 60]. It has been found that D2 activity is rapidly lost in cells that have a stressed endoplasmic reticulum [60]. This loss of enzymatic activity is accompanied by a state of relative cellular hypothyroidism due to the reduction in the cellular production of T3 from T4 [5, 60]. In addition, there has been an association between a polymorphism of nucleotide in the gene coding for D2 with the presence of central obesity, arterial hypertension, and diabetes mellitus type 2 [5].

Obesity has an influence on the HPT axis feedback mechanisms, as shown by the elevation of TSH in obese patients, in the absence of thyroid disease [36]. Hyperthyrotropinaemia associated with obesity could be mediated by a number of factors, for example the increase in leptin derived from hypertrophic adipose tissue [21]. In this respect, positive correlations between leptin and TSH levels support this mechanism [56, 58].

Leptin stimulates the expression of TRH in the arcuate nucleus of the hypothalamus, generating a lower expression of hypothalamic TRs, which affects the negative feedback system, thus generating disruption in the system [55]. As mentioned previously, high levels of leptin have been found in adults and children with obesity. Likewise, the development of secondary hypothyroidism has been reported in subjects with leptin deficiency or resistance [18, 61]. Leptin also regulates central and peripheral Ds activity, affecting deiodination (and therefore the bioactivity) of T4 and T3 [62].

In hyperleptinaemia states, there is an increase in TSH, which stimulates the activity of thyroid and extrathyroidal D1, increasing free T3 generation and the subsequent decrease in free T4 serum levels [19]. In this condition, there is also an increase in rT3 serum levels, due to deiodination in peripheral tissues such as liver and kidney [62, 63]. At the pituitary level, it has been found that the administration of leptin inhibits the activity of D2, which decreases T3 formation, increasing TSH levels. Thus, it has been proposed that in BAT rT3 inhibits D2 post-translationally, which decreases the intracellular generation of T3 [64]. This in turn could decrease both basal metabolism and facultative thermogenesis.

In animal models it has been observed that TSH stimulates the secretion of leptin through a direct effect on the adipocytes, probably through the TSH receptors expressed in this tissue [38, 57, 64].

Figure 3 shows a hypothetical model based in the previously discussed information. This model shows the possible interaction between the thyroid system and obesity, it also shows the processes involved that maintain the state of obesity, such as adipogenesis and positive energy balance.

It has been shown that the thyroid gland function and volume increased in relation to body weight and adipocyte mass in premenopausal euthyroid women. In addition, a ≥ 10% body weight reduction in obese women was found to decrease thyroid volume and circulating TSH concentrations [65]. This could be due to a decrease in leptin levels due to the reduction of WAT, which would subsequently decrease TSH and thyroid volume concentrations [56].

A prospective study in euthyroid patients evaluated thyroid function with changes in body weight as a risk factor predictor for obesity. At six years of follow-up, people who were not obese at the beginning of the study but who were obese at the end of the study showed a significant increase in free T4 and free T3 levels, compared to those who did not develop obesity

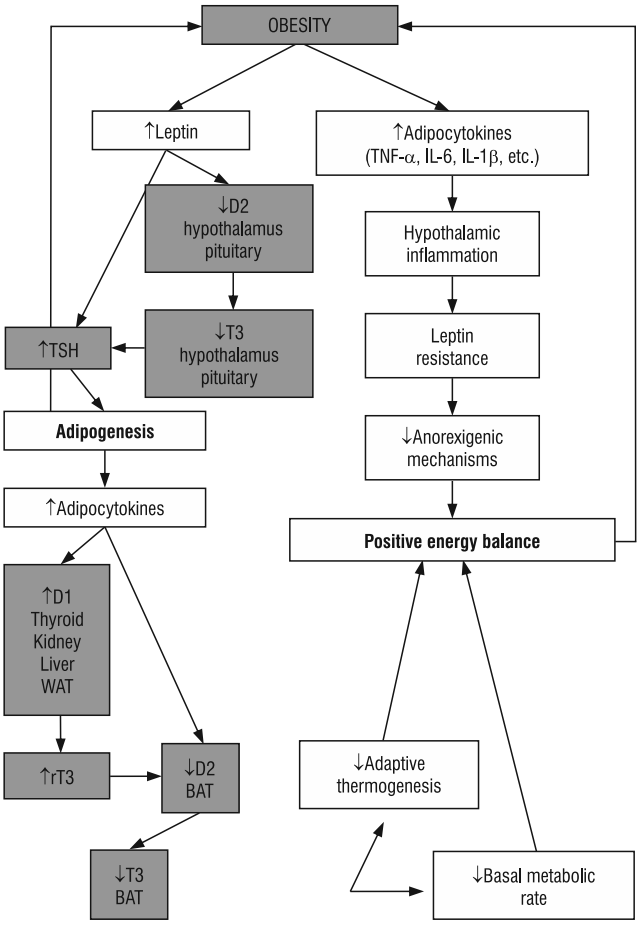


Figure 3. *Hypothetical model of the relation between the thyroidal system and obesity. The mechanisms of the thyroidal system are shown in grey. In this model, both the adipogenesis and the positive energy balance favour and/or maintain obesity. Where: TNF-α, tumour necrosis factor alpha; IL-6, interleukin 6; IL-1β, interleukin one beta; D2, deiodinase type 2; T3, triiodothyronine, TSH, thyrotropin; D1, deiodinase type 1; WAT, white adipose tissue; rT3, reverse triiodothyronine; BAT, brown adipose tissue. The non-continuous line shows the effect exerted through the autonomic sympathetic nervous system in BAT*

Rycina 3. *Hipotetyczny model zależności między układem tarczycy a otyłością. Mechanizmy układu tarczycy przedstawiono kolorem szarym. W modelu tym, zarówno adipogeneza, jak i dodatni bilans energetyczny sprzyjają i/lub utrzymują otyłość. TNF-α — czynnik martwicy nowotworów alfa; IL-6 — interleukina 6; IL-1β — interleukina 1β; D2 — dejodynaza typu 2; T3 — trójjodotyronina; TSH — tyreotropina; D1— dejodynaza typu 1; WAT — biała tkanka tłuszczowa; rT3 — odwrotna trójjodotyronina; BAT — brunatna tkanka tłuszczowa. Linia nieciągła przedstawia działanie wywierane przez współczulny autonomiczny układ nerwowy w brunatnej tkance tłuszczowej*

during the follow-up [58]. These results suggest that elevated TH levels in obese patients are a consequence of weight gain rather than the cause of this increase.

The pathogenesis of decreased TH levels in obesity has not yet been elucidated, but it is likely that excess visceral fat releases cytokines and adipocytokines that promote inflammatory mechanisms that interfere with the HPT axis. In this context, alterations of the HPT axis would be the consequence of the metainflammation in states of obesity [36]. On the other hand, the role of autoimmunity has become important given the effect of leptin as a peripheral determinant of immune function, including an increase in the activity of Th1 helper lymphocytes, which are associated with the pro-inflammatory response [35, 66, 67].

Levels of anti-thyroperoxidase antibodies, considered as a marker of autoimmune thyroid disease, have been found to be elevated in a group of obese patients. In this sense, leptin levels have also been positively related to anti-thyroid antibody titres and to TSH levels [67]. This suggests that obesity increases the susceptibility of developing autoimmune thyroid disease, probably through the contribution of leptin in the immune system [67–69].

Thyroid volume increases with obesity, and associations exist between thyroid volume and the presence of

autoantibodies [69]. Autoimmune thyroid diseases are twice as prevalent in people with obesity compared to non-obese people, and slightly more than half of obese patients with elevated TSH levels have positive titres of anti-thyroid antibodies [67, 70].

Anti-thyroid antibodies may interfere with TH normal synthesis, thus explaining the decrease in circulating TH observed in obesity. However, the reversibility of TSH circulating levels in some obese patients after weight reduction implies that the alterations derived from thyroid autoimmunity are not always responsible for the elevated TSH levels [68].

Obesity: a cause or consequence of thyroid disorders?

Based on information from the publications that have studied the associations between thyroid function and BMI, the different results support the existence of two different scenarios. The first one includes alterations in thyroid function as a cause of weight gain, while the second considers alterations in thyroid function as a consequence of obesity [35, 58].

In the first scenario, hypothyroidism is the initial event, with a reduction in basal metabolic expenditure, resulting in a positive energy balance associated with weight gain. On the other hand, during a decrease in TH, the expression of orexigenic peptides decreases, favouring a reduction in food consumption [19], thus constituting a mechanism that addresses the reduction of basal energy expenditure to prevent a weight increase in hypothyroidism. Because of this, usually there is only a moderate weight gain in the hypothyroid patient. A higher weight gain is directly related to the degree of hypothyroidism, with higher weight gain due to a greater severity of thyroid dysfunction. Although there is a reduction in caloric intake, the positive energy balance predominates because of the large decrease in basal energy expenditure [19].

In the second scenario, obesity could be positively associated with fluctuations in TH circulating levels and the degree of adiposity. The response to the excess of adipose tissue is an increase in TH levels, through increased secretion of TSH promoted by the increase in leptin circulating concentrations generated by the adipocytes [51]. Subsequently, with the maintenance or increase of adipose tissue, there is a greater degree of metainflammation. This causes hypothalamic inflammation and alterations in TRH and TSH secretion, and interferes with leptin signalling, losing its stimulatory effect on the TRH hypothalamic synthesis. These mechanisms would then reduce the amounts of circulating TH. As previously mentioned, hyperleptinaemia could also condition an acquired thyroid dysfunction, through autoimmune phenomena.

Therefore, in the second scenario the reduction in TH levels may be due to the phenomena triggered by metabolic inflammation, autoimmune events against the enzymes necessary for TH synthesis, or a combination of both. The final effects of the second scenario, where obesity is the cause of thyroid disorders, converge towards the first scenario, at the point where TH levels are reduced, promoting a positive energy balance in obesity.

The variation in the results involving TSH or TH determinations in obese patients is possibly due to the different degrees and time of evolution of obesity presented by individuals at the time of measurement [52]. These variables could be equivalent to the severity of hypothalamic inflammation or autoimmunity that condition thyroid failure.

Conclusions

Because obesity and hypothyroidism are common diseases, the possibility of thyroid dysfunction in obese patients should be ruled out. Patients with obesity are at increased risk of developing thyroid failure, through metainflammation and/or autoimmunity.

The presence of elevated TSH circulating concentrations in individuals with obesity does not strictly imply a hypothyroid state, but they may be due to adaptive mechanisms in the face of the increased adipose tissue. In these situations, it is necessary to investigate several aspects that condition variations in TSH levels, such as the presence of alterations in the TH circulating levels and its associated treatment, thyroid autoimmunity markers, iodine intake, or drugs that interact negatively with the synthesis of TH. In addition, the enzymatic deiodination of TH at the peripheral level is a key step in the process of regulating the energy balance.

A further benefit on the reduction of adipose tissue in obese patients would be the reversibility of alterations observed in thyroid function. Likewise, weight loss favours significant reductions in circulating concentrations of leptin and TSH. In summary, the relation between the thyroid system and obesity and overweight is complex and involves multiple levels of interaction.

Perspectives

The development of future thyromimetic drugs seeks the selective stimulation of TR, which would allow the generation of certain types of effects without the secondary complications characteristically associated with the stimulation of the other receptor subtypes. Also, another field of intense study at the present time is the analysis of the factors that induce adipocytes to differentiate in BAT, as well as the knowledge of the

factors that stimulate the expression of the UCP proteins. This would allow better and personalised treatment in obese patients.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflicts of interest
The authors declare none.

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