# Thyroid, Obesity and Metabolism

## Exploring Links Between Thyroid Function, Obesity, Metabolism and Lifestyle

Livio Luzi
*Editor*

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# Contents

**Part I Thyroid**

**1 Iodine Deficiency and Thyroid Function** . . . . . 3
Antonella Olivieri, Simona De Angelis, Mariacarla Moleti, and Francesco Vermiglio

**2 Classification of Thyroid Diseases** . . . . . 21
Sabrina Corbetta

**3 Techniques to Study Thyroid Function and Morphology** . . . . . 37
Francesca Serpi, Salvatore Gitto, Giovanni Mauri, and Luca Maria Sconfienza

**4 Overt Hyperthyroidism and Subclinical Hyperthyroidism: Who and How to Treat** . . . . . 53
Renato Cozzi

**5 Minimally Invasive Treatments of Benign Thyroid Nodules: Techniques and Results** . . . . . 61
F. Ferrari, L. M. Sconfienza, L. Nicosia, and G. Mauri

**Part II Obesity**

**6 Obesity: Classification and Diagnosis** . . . . . 73
Anna Ferrulli

**7 Complications of Obesity** . . . . . 95
Caterina Conte

**8 Techniques to Study Metabolism** . . . . . 117
Roberto Codella

**9 Obesity: Medical and Surgical Treatment** . . . . . 131
Daniele Tassinari, Alessandro Giovanelli, and Carmela Asteria

**Part III Thyroid, Obesity and Metabolism**

**10 Thyroid and Obesity** . . . . . 179
Vincenzo De Geronimo

**11 Thyroid Dysfunction and Metabolism: Diagnosis and Follow-Up** . . . 191
Livio Luzi, Stefano Massarini, Ileana Terruzzi, Anna Ferrulli, and Claudio Cusini

**12 Muscle Tissue in Hypothyroidism and Hyperthyroidism** . . . . . 209
Ileana Terruzzi

**13 Thyroid Function and Effects on Cardiovascular System** . . . . . 221
Cesare C. F. Berra and Mariluce Barrasso

**14 Obesity, Adipokines and Thyroid Dysfunction** . . . . . 241
Cristina Parrino

**15 Adipokines and Thyroid Malignancies** . . . . . 253
Carla Colombo and Laura Fugazzola

**Part IV Clinical Cases**

**16 Clinical Cases** . . . . . 263
Claudio Cusini

# Part I
# Thyroid

# Chapter 1
# Iodine Deficiency and Thyroid Function


**Antonella Olivieri, Simona De Angelis, Mariacarla Moleti, and Francesco Vermiglio**

## 1.1 Introduction

Iodine deficiency has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency disorders (IDD). These result from inadequate thyroid hormone production due to insufficient iodine intake and represent a global health threat to individuals and societies. Iodine deficiency during pregnancy and breast feeding adversely affects the development of the child. Adults living in iodine-deficient regions show a high risk of goiter, thyroid nodules, and hyperthyroidism. Subclinical hyperthyroidism is a common and frequently undiagnosed IDD and is associated with an increased risk of mortality and coronary heart disease [1–3]. In this chapter, the most important aspects concerning the effects of iodine deficiency exposure during all phases of life are discussed.

## 1.2 Iodine Absorption and Metabolism

Iodine is an essential dietary nutrient for humans and, as its water-soluble iodide ion ($I^-$), is a key component of the chemical structure of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), comprising 65% and 59% of their respective weights. The availability of iodide depends on iodine intake. Overall, the natural

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iodine content of many foods is low, whereas foods from marine origin have a higher iodine content [4]. Nevertheless, sea salt has negligible amounts, because iodide in seawater is sublimated into the atmosphere as volatile organic iodine [5]. Iodine is ingested in several chemical forms. Iodide ($I^-$) is rapidly and nearly completely absorbed in the stomach and duodenum. Iodate ($IO^-$), widely used in salt iodization, is reduced in the gut and absorbed as iodide. In healthy adults, the absorption of iodide is greater than 90% [6].

Iodine is rapidly cleared from the circulation mainly by the thyroid gland and kidney. The urine contains the fraction of the serum iodine pool that is not concentrated by the thyroid gland. Typically, urine contains more than 90% of all ingested iodine and only 1–2% is excreted in feces and in sweat [7]. While renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. In conditions of adequate iodine supply, no more than 10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80% [8, 9]. The salivary glands, gastric mucosa, small intestine, and choroid plexus take up small amount of iodine. The lactating mammary gland also concentrates iodine to provide iodide into the milk for thyroid hormone biosynthesis by the nursing newborn [10, 11]. Under normal circumstances, plasma iodine has a half-life of approximately 10 h, but this time is shortened if the thyroid is overactive, as in iodine deficiency or hyperthyroidism. In iodine-sufficient areas, the adult thyroid traps about 60 μg of iodine per day to balance losses and maintain thyroid hormone synthesis [12].

The $Na^+/I^-$ symporter (NIS) is the plasma membrane glycoprotein that mediates active $I^-$ transport into the thyroid and other tissues. NIS transfers iodide into the thyroid at a concentration gradient 20–50 times that of plasma [13] and mediates the uptake of iodide into the thyroid follicular cells using the electrochemical gradient generated by the $Na^+/K^+$ ATPase [14–16]. Iodide efflux into the follicular lumen is mediated in part by pendrin (SLC26A4), which is a coupled electroneutral iodide/chloride, iodide/bicarbonate, and chloride/bicarbonate exchanger [17–19]. At the intraluminal side, iodide is oxidized, a reaction that requires hydrogen peroxide ($H_2O_2$) and is mediated by thyroid peroxidase (TPO), which is located at the apical surface of the thyrocyte [20].

TPO and hydrogen peroxide oxidize iodide and attach it to tyrosyl residues on thyroglobulin (Tg), to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), the precursors of thyroid hormones. TPO then catalyzes the coupling of the phenyl groups of the iodotyrosines through a di-ether bridge to form the thyroid hormones [21]. In the thyroid, mature Tg, containing 0.1–1.0% of its weight as iodine, is stored extracellularly in the luminal colloid of the thyroid follicle [21, 22]. After endocytosis, endosomal and lysosomal proteases digest Tg and release T4 and T3 into the circulation where the half-life of T4 and T3 is 5–8 days and 1.5–3 days, respectively. Degradation of T4 and T3 in the periphery releases iodine that enters the plasma iodine pool and can be taken up by the thyroid or excreted by the kidney.

### 1.2.1 Iodine Requirements and Tolerable Upper Levels

Since iodine cannot be stored for long periods by the body, tiny amounts are needed regularly. Iodine turnover, thyroidal radioiodine uptake, and balance studies in euthyroid adults have suggested that the average daily requirement for iodine is 91–96 μg/day [12, 23, 24]. Therefore, according to the U.S. Institute of Medicine (IOM), the estimated average requirement (EAR) for iodine for men and nonpregnant, nonlactating women has been set at 95 μg/day [25]. EAR represents the daily iodine intake that meets the requirement of half of the healthy individuals in a particular life stage. The corresponding Recommended Dietary Allowance (RDA), calculated as the EAR plus twice the coefficient of variation in the population (rounded to the nearest 50 μg) is 150 μg/day [25]. RDA corresponds to the WHO recommendation for adequate daily iodine intake (AI) of 150 μg/day for men, nonpregnant, nonlactating women [26]. In other words, international groups have made recommendations which are fairly similar. Iodine Global Network (IGN, formerly ICCIDD), WHO, and UNICEF recommend the following daily amounts: age 0–5 years: 90 μg/day; age 6–12 years: 120 μg/day; older than 12 years: 150 μg/day; pregnant and lactating women: 250 μg/day.

The Food and Nutrition Board, Institute of Medicine also set the tolerable upper limits of the daily iodine intake as 1.1 mg (1100 μg) for adults, with proportionately lower levels for younger age groups [25], while lower are the tolerable upper limits set by WHO [27] (Table 1.1).

### 1.2.2 Thyroidal Adaptation to Iodine Deficiency

The body of a healthy adult contains 10–20 mg of iodine, of which 70–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid may fall to <10 mg. Specifically, thyroidal adaptation to low iodine intake (50–100 μg/day) is mediated by an increased secretion of thyroid stimulating hormone (TSH) which

**Table 1.1** Tolerable upper intake level for iodine

| | Upper tolerable levels (μg/day) | |
|---|---|---|
| Life-stage group | European Commission Scientific Committee on Food | U.S. Institute of Medicine |
| 1–3 years | 200 | 200 |
| 4–6 years | 250 | 300 |
| 7–10 years | 300 | 300 |
| 11–14 years | 450 | 300 |
| 15–17 years | 500 | 900 |
| Adult | 600 | 1100 |
| Pregnant and lactating women | 600 | 1100 |

**Table 1.2** Thyroidal adaptation to iodine deficiency

| Daily iodine intake | Mechanisms of adaptation | Iodine content in the thyroid | Synthesis of thyroid hormones |
|---|---|---|---|
| 50–100 μg/day | ↑ TSH | Still in the normal limits (10–20 mg) | Preferential synthesis and release of T3 |
| | ↑ $I^-$ uptake by the thyroid | | |
| | ↑ Tg breakdown | | |
| | ↓ UIC | | |
| <50 μg/day | ↑ TSH | Below the normal limits (<10 mg) | Reduced synthesis of thyroid hormones |
| | ↑ $I^-$ uptake by the thyroid | | |
| | ↑ Tg breakdown | | |
| | ↓ UIC | | |

increases iodine uptake by the thyroid through stimulation of NIS expression. As a greater fraction of circulating iodide is cleared by the thyroid, there is a progressive reduction in renal iodide excretion. TSH also stimulates breakdown of Tg and preferential synthesis and release of T3 into the blood [28]. Below 50 μg/day, despite a high fractional clearance of plasma inorganic iodine by the thyroid, absolute iodine intake falls, the iodine content of the thyroid is depleted, and many individuals develop goiter (Table 1.2) [9, 29].

The effects of iodine deficiency on the development of goiter and thyroid hypofunction are extremely variable among populations and individuals, even in endemic areas. Dietary, environmental, and/or genetic factors may account for this variability [30–33]. Initially, goiter is characterized by diffuse, homogeneous enlargement, but nodules often develop over time. Many thyroid nodules derive from a somatic mutation and are of monoclonal origin [34]. Although iodine deficiency produces diffuse goiter in all age groups, it is also associated with a high occurrence of multinodular toxic goiter, mainly in women older than 50 years [35].

## 1.3 Iodine Deficiency in Pregnancy and Fetal Brain

Iodine requirements during pregnancy are substantially increased compared to the nonpregnant state because of changes in maternal thyroid economy that occur as pregnancy establishes [36]. Three events are mainly responsible for a trend toward a reduction in maternal iodide pool during pregnancy: (1) an increased iodide consumption; (2) an increased renal clearance of iodide; and (3) transfers of iodine from mother to fetus [37].

Maternal T4 production during pregnancy is roughly estimated to exceed by 50% of the normal hormone synthesis in the nonpregnant population, which implies that additional 50–100 μg of iodine/day is needed to cope with the increased functional demands imposed by pregnancy.

Early in pregnancy, iodide losses are augmented because of an increase in renal blood flow and glomerular filtration. In addition, the placenta transfers iodine from the maternal circulation to the fetal placental unit, which is estimated at about 50–75 μg/day toward the end of gestation, but it is likely more minimal in the first trimester. Overall considered, these factors are responsible for an additional dose of iodine needed to provide an adequate substrate for both maternal and fetal needs that is quantified in around 150 μg/day [36]. In accordance, recommended iodine intake in pregnancy based on a technical consultation on behalf of the WHO is 250 μg/day [38], roughly corresponding to a urinary iodine excretion of 185 μg/L [39]. This goal is reasonably achievable through universal salt iodization (USI), provided that this measure has been in effect for at least 2 years, and iodized salt is consumed by more than 90% of households. By contrast, in countries where a USI program is lacking, daily iodine intake is assumed to be insufficient to meet the increased requirements for pregnancy, and both women of child-bearing age and pregnant women should be given a daily iodine supplementation in order to start pregnancy with enough iodine stored in their thyroid [38].

An iodine intake below the threshold of 250 μg/day is considered insufficient, and both the mother and fetus are simultaneously exposed to the potentially severe consequences of iodine deficiency. These include different degrees of both maternal and fetal thyroid failures, which in turn may compromise pregnancy outcome and affect fetal neuro-intellectual outcome [40].

### *1.3.1 Maternal Thyroid Adaptation to Iodine Deficiency*

The first biochemical alteration occurring when gestational iodine intake is not sufficient to maintain the intrathyroidal iodine pool is a decrease in maternal T4 production, which soon becomes inappropriately low relative to the increasing thyroxine-binding globulin (TBG) concentrations. This event leads to the progressive desaturation of TBG by T4, which ultimately results in steadily declining free T4 concentrations [37]. Conversely, circulating T3 remains within the normal range, or is even slightly over the upper limit, because of a switch toward a preferential secretion of T3 over T4. This mechanism of adaptation to iodine deficiency is mainly aimed to save iodine and is reflected by an elevated total T3-to-T4 molar ratio, along with TSH concentrations that are maintained within the normal range [41]. As a result, the women are clinically maintained euthyroid by T3, even when T4 is reduced (isolated hypothyroxinemia). Notably, this mechanism, though beneficial to the mother, does not prevent the fetus to be exposed to insufficient maternal thyroid hormone, as it is primarily T4 that crosses the placenta and is delivered to the fetus [40]. If iodine supply persists to be insufficient, also the compensatory mechanism of preferential T3 secretion fails, because of the inability of the maternal iodine pool to guarantee even T3 maternal euthyroidism. Finally, this leads to overt hypothyroidism, due to reduction in total and free T3 concentrations and subsequent increase in serum TSH [42, 43].

As a result of maternal thyroid stimulation by TSH, an enlargement of the maternal thyroid may lead to a transient gestational goiter, which is an additional adaptive mechanism to this condition and is paralleled by progressive increase in serum Tg over the course of pregnancy [37].

### *1.3.2 Fetal Consequences of Maternal Iodine Deficiency*

Unlike the mother, a fetus cannot rely on preferential thyroidal secretion of T3 to face the insufficiency of iodine, because this autoregulatory mechanism only becomes fully operative after birth. Consequently, an insufficient iodine supply to the fetus can result in a reduction in both T4 and T3 production by the fetal thyroid, and clinical and biochemical fetal hypothyroidism occur. In addition, fetal goiter may develop because of sustained TSH stimulation on fetal thyroid in conditions of low iodine intake during pregnancy [40].

The most severe consequences of gestational iodine deficiency are due to inadequate thyroid hormone supply for fetal neurodevelopment [40]. Prior to the onset of fetal thyroid function, the only source of thyroid hormone for the developing brain is the mother, whereas from weeks 16 to 20 post-conception onward both the mother and fetus cooperate to make-up the fetal thyroid hormone pool [40, 44]. Thus, any impairment of maternal and fetal thyroid function—occurring either independently or concomitantly—can result in brain damages and neuro-intellectual disorders in the offspring.

Thyroid hormone influences all stages of brain development by acting through specific gestational time windows during which early and late phases of brain development occur. In particular, early gestation neurogenesis and neuronal migration are under the control of thyroid hormone from the mother, which is the unique source of thyroid hormone at that time. Conversely, neuronal and glial cell differentiation, myelination, and synaptogenesis, which occur from the second trimester of gestation onward, result from a cooperation of both maternal and fetal thyroid hormone contribution [44].

Thyroid hormone actions on the brain are mostly due to the interaction of the biologically active T3 with its specific nuclear receptors and the regulation of related gene expression [45]. In the brain, only a small part of T3 derives from circulation, the vast majority of this hormone being generated from local 5′-deiodination of T4 by type 2 deiodinase (D2) within the astrocytes [46]. Both T4 and T3 cross the blood–brain barrier by means of specific transmembrane transporters, such as the organic anion transporter polypeptide 1c1 (OATP1c1) and the monocarboxylate transporter 8 (MCT8) [47, 48]. Mutations of the latter have been reported to be responsible for the Allan–Herndon–Dudley syndrome, a rare disease characterized by severe mental retardation and neurological impairment due to deficient thyroid hormone transport to the brain [49]. The role of thyroid hormone on brain development is also demonstrated by the evidence of variable degrees of brain damage occurring in patients affected with resistance to thyroid hormone syndromes [50].

Apart from the above rare conditions involving thyroid hormone transport and action, maternal and fetal thyroid insufficiency due to iodine deficiency still remains the leading cause of preventable brain damage. The spectrum of iodine-deficiency neurological damages encompasses several clinical manifestations, from endemic cretinism, which is the most severe manifestation of iodine deficiency, to subtle cognitive deficits, observed in association with even mild to moderate iodine deficiency in pregnancy [51, 52].

Cretinism is characterized by mental retardation in combination with: (1) predominant defects of hearing and speech and characteristic disorders of stance and gait of varying degree (neurological cretinism); or (2) predominant hypothyroidism and growth retardation (myxedematous cretinism); or (3) a combination of the two above syndromes (mixed cretinism) observed in some areas [53]. Cretinism has been typically reported to occur in severely iodine-deficient regions (i.e., median UIC < 20 μg/L in school-age children) and is related to both maternal and fetal hypothyroidism occurring from early gestation onward [40]. Indeed, pivotal intervention studies carried out in populations with high levels of endemic cretinism clearly showed that iodine supplementation before or early in pregnancy is associated with a sharp reduction in the incidence of the condition [9]. Even mild to moderate iodine deficiency (median UIC values of 20–99 μg/L in school-age children) may be associated with altered child neurobehavioral development, likely because of a reduced maternal thyroid hormone availability during early phases of brain development [52].

### *1.3.3 Iodine Supplementation During Pregnancy*

Overall, evidence has been provided that strongly suggests that maternal iodine supplementation started well in advance of conception improves maternal thyroid function and is effective in preventing early maternal thyroid failure [54]. By contrast, no significant changes in maternal thyroid parameters have been reported with iodine supplementation started during pregnancy. Nonetheless, the evidence of a significantly lower thyroid volume and a reduction in neonatal serum thyroglobulin and TSH concentrations in the newborns of iodine supplemented mothers compared with non-supplemented controls is suggestive of improved fetal iodine status with gestational iodine supplementation [9, 55].

With regard to the effects of prenatal iodine supplementation on child neurodevelopment, findings of both observational and intervention studies in mild to moderate iodine deficiency are mixed [56, 57], with some reporting no benefits on child neurobehavioral development [58, 59] and others showing a possible improvement in psychomotor development with prenatal supplementation [60, 61]. Possible explanations for these conflicting results include the use of different tests to measure developmental domains, differences in study inclusion criteria, and, not least, the timing of iodine supplementation during gestation. In this regard, a recent meta-analysis of individual participant data from three prospective population-based

European birth cohorts showed that a lower maternal urinary iodine during pregnancy was associated with lower verbal IQ score in children, but this effect was evident up to the 14th week of gestation only [62]. This finding suggests that, in order to guarantee optimal fetal brain supply of thyroid hormone, iodine supplementation in women with mild to moderate iodine deficiency should be started not later than the first trimester to be effective on child neurodevelopment.

### *1.3.4 Iodine and Lactating Mothers*

Since the mammary gland during lactation is able to concentrate iodine, iodine supply to the newborn via the breast milk may be maintained even in the face of maternal iodine deficiency [63, 64]. This explains why, in areas of iodine deficiency, breast milk iodine concentrations are often greater than expected based on the UIC of the lactating mother [65, 66]. However, there is no consensus on what an adequate breast milk iodine concentration is, and WHO has not made a recommendation on this issue because available studies aimed at evaluating breast milk iodine concentration in iodine-sufficient areas have been conducted in nonrepresentative too small samples [39].

Regarding median UIC in lactating women that indicates adequate iodine nutrition, it is important to underline that, although the iodine requirement is high in lactating women (250 μg/L according to WHO recommendation), after accounting for iodine losses into breast milk, the median UIC that indicates adequate iodine nutrition is the same as that of nonpregnant, nonlactating women (≥100 μg/L) [26].

## 1.4 Iodine Deficiency in Infancy and Childhood

The WHO recommends an iodine intake of 90 μg/day in early infancy, indicating that a median UIC of at least 100 μg/L in infants is sufficient [26]. These recommendations are currently debated because, assuming a urine volume of 300–500 ml/day, such a daily iodine intake would provide a higher UIC cutoff of 180 μg/L. Iodine balance studies by Delange [67] showed that the average iodine retention of full-term infants was 6.7 μg/kg/day. With an average of fetal weight of 3 kg, the mean retention of a fully developed fetus would be approximately 22 μg/day. These data are consistent with a more recent study in which UIC was measured in a representative national sample of healthy, full-term, iodine-sufficient, euthyroid, breast feeding Swiss infants in the first week after birth [68]. A median UIC of 77 μg/L was found. Therefore, assuming a urine volume of 300–500 ml/day, extrapolating from this median UIC suggests that the mean daily iodine intake in iodine-sufficient Swiss newborns in the first week of life is 30–50 μg/day. These findings suggest that further studies are necessary to establish optimal UIC reference range for iodine-sufficient newborns and to facilitate the use of UIC as an indicator of iodine status in this age group.

Currently, the only indicator used to assess iodine status in newborns is neonatal TSH [69, 70], which is used in many countries for routine newborn screening of congenital hypothyroidism [26]. Since the newborn thyroid has limited iodine stores, even mild deficiency during pregnancy will compromise neonatal secretion of both T4 and T3, with a consequent increased pituitary TSH secretion [71]. It has also been demonstrated that newborn TSH, obtained with the use of a sensitive assay on samples collected 3–4 days after birth, is a sensitive indicator of even marginal iodine nutrition in pregnancy [72].

Besides elevated TSH levels, both transient and permanent forms of congenital hypothyroidism are more frequently observed in iodine-deficient than in iodine-sufficient areas [73, 74]. It has also been demonstrated that, after the correction of iodine deficiency, the time needed to observe a decrease in the incidence of permanent congenital hypothyroidism is about a decade under a condition of iodine sufficiency. This time may be explained by the need to achieve a long-lasting adequate iodine status in the population before observing an effect on the incidence of the disease [74]. In this regard, it has been shown that sustained salt iodization can maintain adequate iodine status in all population groups, even in pregnant women despite their higher requirements [39].

During childhood, iodine deficiency has been linked to reduced intellectual and motor performance [75, 76]. It has been reported that mild iodine deficiency impairs cognition in children, and moderate to severe iodine deficiency in a population reduces the intelligence quotient by 10–15 points [9]. In this regard, it is important to underline that in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion [77].

Iodine status may influence growth through its effects on the thyroid axis, as demonstrated by the fact that administration of T4 to hypothyroid children increases their growth. Thyroid hormone promotes GH secretion and modulates the effects of GH at its receptor. In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-I and IGFBP-3 concentrations [78]. In addition, iodine repletion in iodine-deficient children was found to be associated with increase in IGF-I and IGFBP-3 concentrations and improved somatic growth [79, 80].

As iodine intake falls, secretion of TSH increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. If this adaptation is successful and the iodine deficiency is not too severe, the person may escape with only an enlarged thyroid and no other apparent damage from the iodine deficiency. Goiters in children are usually small, soft, and diffuse, but over time, thyroid follicles may fuse and become encapsulated, a condition termed nodular goiter.

Chronic iodine deficiency increases the TSH concentration and may also produce a thyroid hormone pattern consistent with subclinical hypothyroidism [80]. In children, subclinical hypothyroidism may be associated with a more atherogenic lipid profile [81]. An uncontrolled study reported iodine treatment of goitrous German adolescents decreased plasma cholesterol concentrations [82]. Another study reported that iodine treatment of moderately iodine-deficient children with elevated TSH concentrations due to iodine deficiency improves their lipid profile and reduces their insulin (C-peptide) levels compared with control [83]. This

previously unrecognized benefit of iodine prophylaxis may be important because iodine deficiency remains common in many countries with increasing rates of obesity and cardiovascular disease.

## 1.5 Iodine Deficiency in Adults and Elderly

The consequences of iodine deficiency have been so far regarded as conditions mostly involving specific subset of population such as fetuses, newborns, pregnant women, and lactating mothers, for whom a definitely large number of clinical and biochemical data are now available in the literature. Basically, this is due to the fact that iodine deficiency during pregnancy and lactation is known to irreversibly affect brain development and explains why studies on iodine deficiency are mainly targeted to pregnant and lactating women. Conversely, in the elderly and adults, data on dietary iodine status are still relatively limited.

Few observational studies aimed at verifying the status of iodine nutrition over the course of life in the general population from different geographic areas overall demonstrated a significant decline in daily iodine intake later in life [84–87]. Explanations for this trend include a reduction in milk consumption, particularly evident among females, a reduction in salt consumption, and a major condition of global undernourishment in the elderly [88].

The importance of the population iodine intake and of related different thyroid abnormalities in elderly subjects was studied in several reports from over the world. Either uni- or multi-nodular goiter is the more common consequence of iodine deficiency at all ages, even in mild to moderate iodine-deficient areas. In fact, the reduction in thyroid hormone synthesis due to inadequate iodine availability triggers TSH-driven goiter growth and nodularity, which, at least initially, is accompanied by biochemical euthyroidism. In long-standing multi-nodular goiter, because of the persistently increased thyroid cell replication rate, somatic point mutations of the TSH receptor (TSHR) may occur, which result in a constitutive activation of the TSHR and the development of autonomously functioning thyroid nodules [89, 90]. This finally leads to hyperthyroidism, either subclinical or overt, with related cardiac risks of atrial fibrillation, embolism, and congestive cardiac failure [91]. Indeed, thyroid hormones play a central role on heart function, through both genomic and nongenomic effects. Thyroid hormone excess results in deep changes of both cardiac function and cardiovascular hemodynamics, with increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction. All these events may precipitate a “high output heart failure” and arrhythmia such as atrial fibrillation with related risk of embolic complications, especially in the elderly [91]. The relationship between iodine deficiency and hyperthyroidism due to multinodular goiter is evident from studies carried out in both iodine-deficient and iodine-sufficient areas, showing higher prevalence of hyperthyroidism (subclinical or overt) in the former and higher prevalence of hypothyroidism in iodine-sufficient populations [1]. Notably, after implementation of iodine prophylaxis programs, the

incidence of hyperthyroidism may transiently increase, as a consequence of iodine-induced thyrotoxicosis in elderly subjects with preexisting autonomously functioning nodule(s).

While long-term effects of iodine deficiency in early life on neurodevelopment are well acknowledged, little evidence is presently available regarding the impact of iodine deficiency occurring in elderly on brain function. Pioneering researches involving adults residing in areas with severe iodine deficiency showed that correction of iodine deficiency by means of iodized oil injections dramatically reverted the state of lethargy observed in endemic populations in these villages, likely because of a restoration of brain thyroid hormone levels [92]. In fact, thyroid hormones are required for brain function throughout life, and both hypo- and hyperthyroidism occurring in adults can manifest with a wide range of mood disorders and cognitive decline. Typically, these changes regress with euthyroidism restoration, thus indicating that, contrary to what is observed in early life, thyroid hormone alterations of adult onset are not associated with permanent brain damages [93]. Nonetheless, some evidence has been recently provided suggesting a link between low iodine intake in older adults and inner brain atrophy as evaluated by brain structural magnetic resonance imaging scans [94]. Further studies specifically addressing the relationship between long-lasting iodine deficiency, structural brain abnormalities, and cognitive abilities would be useful, for specific preventive strategies be adopted also in elderly people.

In conclusion, the elderly is a rapidly growing segment of the population. It is a high public health priority to ensure older adults having sufficient iodine intake to maintain optimal thyroid function and reduce the burden on health care resources. Recommendations to monitoring iodine nutritional status in elderly should be reinforced and iodine deficiency corrected with the same attention already reserved to other population subsets.

## 1.6 Prevention of Iodine Deficiency Disorders

Iodine deficiency disorders (IDD) still represent a global health threat to individuals and societies. To eradicate IDD, the WHO recommended USI as the preferred strategy [95]. Over the years, voluntary or mandatory programs of salt iodization have been implemented in many countries. Salt is considered an appropriate vehicle for fortification with iodine, for the following reasons: (1) it is widely consumed by virtually all population groups in all countries; (2) in many countries, salt production is limited to a few centers, facilitating quality control; (3) the technology needed for salt iodization is well established, inexpensive, and relatively easy to transfer to countries around the world; (4) addition of iodate or iodide to salt does not affect the taste or smell of the salt or foods containing iodized salt; (5) iodine (mainly from iodate) remains in processed foods that contain salt; and (6) iodization is inexpensive (the cost of salt iodization per year is estimated at US$0.02–0.05 per individual covered, and

even less for established salt-iodization programs) [96]. Additionally, the concentration of iodine in salt can easily be adjusted to meet policies aimed at reducing the consumption of salt in order to prevent cardiovascular disease. The WHO recommends combining strategies of salt/sodium reduction with parallel salt iodization programs [97]. To make both prevention programs effective, iodine prophylaxis programs should be adapted to the actual salt intake of the population by increasing iodine concentration of iodized salt, when necessary, and by promoting the use of iodized salt in processed food production.

Every year, the IGN, which is a nonprofit, nongovernment organization for the sustainable elimination of iodine deficiency worldwide (www.ign.org), releases a global scorecard of iodine nutrition in populations based on median urinary iodine concentration in school-age children as a proxy for the general population. Based on the most recent scorecard [98, 99], 115 countries are classified as having optimal iodine nutrition, while 23 countries are still classified as iodine deficient (in Europe: Finland, Germany, and Norway). It is worth to note that the iodine intake in several countries formerly classified as optimal has declined, including Cambodia, Nicaragua, Tajikistan, and Germany, which reflects the risk of program backsliding and the need for vigilance and continuous monitoring. The scorecard also indicates that the iodine intake is classified as excessive in 14 countries, which reinforces the need for measures to reduce the excessive iodine exposure in these countries.

### *1.6.1 Monitoring of Iodine Prophylaxis Programs*

Achieving optimal iodine nutrition at the population level is necessary but maintaining it through careful monitoring is equally important. Assessing iodine nutrition at the population level is usually done by (1) determining salt iodine levels, (2) estimating household coverage of adequately iodized salt, (3) measuring the urinary iodine concentration and estimating the prevalence of goiter in schoolchildren.

As mentioned in the first part of this chapter, most iodine absorbed in the body eventually appears in the urine. Therefore, urinary iodine excretion is a good marker of very recent dietary iodine intake. In individuals, urinary iodine excretion can vary somewhat from day to day and even within a given day. However, this variation tends to even out among populations. Conversely, goiter assessment by thyroid ultrasound in schoolchildren is an indicator of a long-lasting iodine intake in a population. In fact, it has been demonstrated that iodine prophylaxis is able to prevent the development of goiter in children born after the implementation of iodized salt and to control thyroid enlargement in older children, although it is less effective in reducing goiter size in children exposed to iodine deficiency in the first years of life [100]. However, the prevalence of goiter in monitoring iodine status in populations may be difficult to estimate because of the lack of consensus on international reference values for thyroid volume [101, 102].

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# Chapter 2
# Classification of Thyroid Diseases


**Sabrina Corbetta**

## 2.1 Introduction

Alterations of the circulating thyroid hormones levels, namely hypothyroidism and hyperthyroidism, are common conditions with potentially devastating health consequences that affect all populations worldwide [1]. Thyroid dysfunction is common, readily identifiable, and easily treatable. Nonetheless, if undiagnosed or untreated, it can have profound adverse effects. Despite an increase in thyroid disease awareness and the availability of sensitive laboratory assays for the measurement of thyroid hormones, cases of extreme thyroid dysfunction occasionally still occur. Hypothyroidism and hyperthyroidism commonly arise from pathological processes within the thyroid gland (primary thyroid disease), although in rare cases, they can arise from disorders of the hypothalamus or pituitary (central hypothyroidism) or from peripheral causes, such as struma ovarii, or functional thyroid cancer metastases. Iodine nutrition is a key determinant of thyroid disease risk; however, other factors, such as aging, smoking status, genetic susceptibility, ethnicity, endocrine disruptors, and the advent of novel therapeutics, including immune checkpoint inhibitors, also influence thyroid disease epidemiology [1]. Nodular thyroid disorders are prevalent in areas where iodine deficiency is common, while autoimmune thyroid (AIT) disorders, including Hashimoto thyroiditis and Graves' disease, occur more frequently in iodine-replete populations. Indeed, a number of other risk factors, including genetic and ethnic susceptibility, sex, smoking status, alcohol consumption, presence of other autoimmune conditions, syndromic conditions and exposure to therapeutic drugs, also influence thyroid disease epidemiology. In this general epidemiological setting, the incidence of thyroid cancer worldwide has

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increased significantly over the past three decades, due mostly to an increase in papillary thyroid cancer cases. Although most of these cancers are small and localized, population-based studies have documented a significant increase in thyroid cancers of all sizes and stages, in addition to incidence-based mortality for papillary thyroid cancer. Increasing incidence of thyroid cancer seems to be due in large part to increasing surveillance and overdiagnosis, but researchers agree that there is also a true increase in new cases of thyroid cancer [2]. The detection of thyroid dysfunction has been driven over the past two decades by the progressive lowering of treatment thresholds, together with increased thyroid function testing with sensitive assays, determining a higher prevalence of borderline or mild cases. The complex inverse association between the pituitary-derived TSH and T4 and T3 indicates TSH as the most sensitive marker of thyroid status. Accordingly, *overt hypothyroidism* is defined as TSH concentrations above the reference range and free T4 levels below the reference range, while *subclinical hypothyroidism* is defined as TSH levels above the reference range when levels of free T4 are within the population reference range (Table 2.1). Likewise, the reverse hormone pattern is applied in the definition of *overt* (low TSH and high free T4) and *subclinical hyperthyroidism* (low TSH and normal free T4) (Table 2.1). In the present chapter, the main clinical thyroid disorders will be presented focusing on epidemiological and clinical features (Table 2.1).

## 2.2 Hypothyroidism

Hypothyroidism is common throughout the world. Iodine deficiency and autoimmune disease (known as Hashimoto thyroiditis) are the prevalent causes of primary hypothyroidism [3]. In iodine-sufficient countries, the prevalence of hypothyroidism ranges from 1% to 2% [4, 5], rising to 7% in individuals aged more than 85 years [6]. Hypothyroidism is approximately ten times more prevalent in women than men. The prevalence of overt hypothyroidism in the general population ranges from between 0.2% and 5.3% in Europe [7, 8] and 0.3% and 3.7% in the USA [9].

### *2.2.1 Autoimmune Thyroiditis*

Hashimoto thyroiditis is the most frequent autoimmune thyroid (AIT) disorders. It causes a chronic inflammation of the thyroid tissue, and hypothyroidism occurs in about 20–30% of patients [10]. AIT incidence is about 0.3–1.5/1000 subjects/year, with a major frequency in women than in men (from 4 to 10 times). Hashimoto thyroiditis is considered to depend on a combination of genetic susceptibility and environmental risk factors, which determines the breakdown of immunological tolerance, with a resulting autoimmune attack to the thyroid itself. Lymphocytic infiltration, especially of T cells, and follicular destruction are the histological AIT hallmark, which can induce progressive thyroid atrophy and fibrosis.

**Table 2.1** Classification of thyroid diseases and associated thyroid hormone alterations

| | Hypothyroidism | Euthyroidism | Hyperthyroidism |
|---|---|---|---|
| *Hormonal patterns* | | | |
| TSH | ↑ | | ↓ |
| FT4 | N/↓ | | N/↑ |
| FT3 | N/↓ | | N/↑ |
| *Frequency (overt disease)* | 0.2–5.3% | | 0.1–1.3% |
| *Etiology* | | | |
| Congenital | | | |
| Thyroid dysgenesis | + | + | |
| Thyroid dyshormonogenesis | + | | |
| Acquired | | | |
| *Autoimmunity* | | | |
| Hashimoto thyroiditis | + | + | + |
| Postpartum thyroiditis | + | | + |
| Graves' disease | | | + |
| *Iodine status* | | | |
| Severe iodine deficiency | + | | |
| Mild to severe iodine excess | + | | |
| *Infections* | | | |
| Viral | + | | + |
| Postpartum (De Quervain syndrome) | | | |
| Bacterial | + | + | + |
| *Thyrocytes proliferation* | | | |
| Uninodular goiter | | + | + |
| Multinodular goiter | | + | + |
| Malignant neoplasia | | | |
| Papillary | | + | |
| Follicular | | + | + |
| Medullary | | + | |
| Anaplastic | | + | |
| *Iatrogenic* | | | |
| Radioiodine | + | | |
| Surgery | + | | |
| Drugs[a] | + | | + |
| *Secondary (central)* | | | |
| Hypothalamic failure/dysfunction | + | | |
| Pituitary macroadenoma and/or apoplexia | + | | |
| Resistance to TSH or TRH | + | | |
| Drug-induced[b] | + | | |
| Inappropriate TSH secretion[c] | | | + |
| *Extra-thyroidal* | | | |
| Consumptive hypothyroidism[d] | + | | |

(continued)

**Table 2.1** (continued)

| | Hypothyroidism | Euthyroidism | Hyperthyroidism |
|---|---|---|---|
| Tissue-specific due to genetic mutations[e] | + | | |
| Excess intake of thyroid hormone | | | + |
| Ectopic thyroid hormone secretion[f] | | | + |

*TSH* thyroid stimulating hormone, *FT4* free tiroxine, *FT3* free triiodiotirosine, *N* within normal range, *TRH* thyrotropin releasing hormone

[a]Amiodarone, lithium, monoclonal antibodies, sodium valproate (anti-epileptic), tyrosine kinase inhibitors and immune checkpoint inhibitors

[b]Dopamine, somatostatins

[c]TSH secreting pituitary adenoma or pituitary resistance to thyroid hormone

[d]It is a paraneoplastic syndrome, resulting from the aberrant uncontrolled expression of the type 3 deiodinase (D3) that can induce a severe form of hypothyroidism by inactivating T4 and T3 in defined tumor tissue

[e]*THRα, THRβ, MCT8/SLC16A2*

[f]Struma ovarii and functional thyroid cancer metastases

It is worth noting that there is an association between AIT disorders and other organ specific/systemic autoimmune disorders. It is not unusual to find patients with more than one immune-mediated endocrine disorder. As a result, polyglandular autoimmune syndromes (PAS), characterized by the failure of different endocrine glands, occur. Most of these patients showed Addison's disease, hypogonadism, Graves' disease, AIT, vitiligo, alopecia, pernicious anemia, and type 1 diabetes mellitus. In most cases (48%), the first manifestation of PAS was the type 1 diabetes–AIT disorders association [11].

Moreover, AIT is associated with papillary thyroid cancer and thyroid autoimmunity, and high TSH levels are considered independent risk factors for thyroid cancer [12]. Ten to 30% of patients with papillary thyroid cancer and AIT disorders show an aggressive form of the disease [13].

### *2.2.2 Subclinical Hypothyroidism*

Subclinical hypothyroidism exists when serum thyroid hormone levels are within the reference range, but serum TSH levels are elevated outside the reference range. In iodine-sufficient populations, subclinical hypothyroidism affects up to 10% of the population, being highly prevalent among women and elderly individuals [14]. However, it should be considered that (1) subclinical hypothyroidism frequently reverts to euthyroidism, and (2) TSH levels rise as people without thyroid disease age, making it likely that the prevalence of subclinical hypothyroidism has been overestimated. Subclinical hypothyroidism may be categorized as grade 1, when TSH levels are between the upper limit of the reference range and 9.9 mU/L, and as grade 2, when serum TSH levels are 10 mU/L or higher. Approximately 90% of patients with subclinical hypothyroidism have serum TSH levels lower than

10 mU/L. Autoimmune thyroiditis is the most common cause of mildly elevated serum TSH levels. Indeed, older individuals with mildly elevated serum TSH in the absence of thyroid disease are not at risk of increased morbidity and mortality. A number of clinical conditions unrelated to primary thyroid diseases, able to induce increase in TSH levels, should be considered; they include external radiotherapy to the neck, drugs (such as lithium), laboratory anomalies (heterophilic antibodies in the serum), untreated adrenal insufficiency, mutations in the TSH receptor gene, obesity, critical illness, circulating macroTSH (similar to macroprolactin, in which TSH is complexed to antithyrotropic IgG to form a high molecular weight complex with low biological activity) and thyroid lobectomy for benign or malignant thyroid nodules. In the last setting, permanent hypothyroidism, typically subclinical, can occur in up to 60% of patients after thyroid lobectomy and more than 1 year after surgery. In 60% of patients with grade 1 subclinical hypothyroidism, TSH declines to the normal range over 5 years [15, 16]. The annual rate of progression to overt disease is about 2–4% in such patients, depending on anti-thyroperoxidase (TPO) antibody status [16–19]. Grade 2 subclinical hypothyroidism is associated with increased rates of progression to overt hypothyroidism, especially in women and in patients with positive anti-TPO antibodies. Grade 1 subclinical hypothyroidism is rarely associated with hypothyroid and neuropsychiatric symptoms or alterations in mood or cognition. Cardiovascular abnormalities (left ventricular systolic and diastolic dysfunction and impaired vascular relaxation) have been described in patients with grade 1 and grade 2 subclinical hypothyroidism. Hypothyroidism is one of the most frequent secondary causes of dyslipidemia (elevated low-density lipoprotein [LDL] cholesterol and triglyceride levels), and screening for hypothyroidism is recommended for individuals with hypercholesterolemia. Metabolic alterations can develop in grade 2 subclinical hypothyroidism, mainly in patients with insulin resistance. A meta-analysis performed by the Thyroid Studies Collaboration, a consortium of cohort studies with data from more than 75,000 participants, showed that TSH levels of 10 mU/L or higher were associated with increased risk of heart failure, coronary heart disease events, and mortality from coronary heart disease compared with normal TSH values [20]. In addition, TSH values of 7.0–9.9 mU/L were associated with increased risk of fatal stroke and mortality from coronary heart disease. Association of subclinical hypothyroidism with dementia, kidney function decline, bone mineral density, and fracture risk has been investigated, though conclusive results is lacking [14].

### *2.2.3 Iodine-Induced Hypothyroidism*

Iodine-induced hypothyroidism is attributed to a failure of thyroid adaptive mechanisms to an acute iodide load, known as the Wolff–Chaikoff effect. Common sources of excess iodine include supplementation, diet, iodinated contrast agents, and medication. Further details have been provided in Chap. 1.

### 2.2.4 Drug-Induced Hypothyroidism

Several drugs can cause hypothyroidism. Here the drugs that are most frequently associated with hypothyroidism are briefly presented [1]:

1. *Lithium* therapy causes overt hypothyroidism in 5–15% of patients treated; the use of lithium increased the risk of hypothyroidism by more than twofold.
2. *Amiodarone*-induced hypothyroidism may be more common than amiodarone-induced thyrotoxicosis in iodine-sufficient areas, with amiodarone-induced hypothyroidism occurring in 6.9–22.0% of patients in iodine-sufficient areas and amiodarone-induced thyrotoxicosis occurring in between 2.0% and 12.1% of patients.
3. *Immune checkpoint inhibitors*, used both as single agents or in combination, have emerged as key treatments in managing advanced cancers, making the disease chronic. Immune checkpoint inhibitors are antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA4), such as ipilimumab; programmed cell death protein 1 (PD1), such as nivolumab and pembrolizumab; and anti-PD1 ligand molecules (PDL1 and PDL2), such as atezolizumab and durvalumab. These agents have been approved for a variety of cancers, including melanoma, non-small-cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancers. Immune checkpoint inhibitors reactivate the immune system against cancer cells but can also induce autoimmune adverse effects that particularly affect the hypothalamic–pituitary–thyroid axis. Patients taking immune checkpoint inhibitors can develop primary or secondary hypothyroidism and primary hyperthyroidism. Secondary hypothyroidism is more common in patients treated with anti-CTLA4 antibodies, whereas primary hypothyroidism is observed more frequently in patients taking anti-PD1 and anti-PDL1 monoclonal antibodies. Hypothyroidism has been reported to occur in 1.5–6.8% of patients on ipilimumab, 9.0–10.8% of patients on nivolumab, and 5.5–9.6% of patients on durvalumab. In combination therapy with nivolumab and ipilimumab, hypothyroidism occurs even more frequently in 4–27% of cases.
4. *Alemtuzumab*, a novel treatment for multiple sclerosis, has also been associated with a high prevalence of hypothyroidism.
5. *Tyrosine kinase inhibitors* can result in an increased risk of hypothyroidism with 27% of treated patients requiring levothyroxine replacement during their treatment.

### 2.2.5 Congenital Hypothyroidism

Primary congenital hypothyroidism (CH) is the most common preventable cause of mental retardation and is associated with 12-fold increased risk of multiple neonatal malformations that may cause additional disease complications [21–23]. A tendency toward an increased CH detection has been described in several

socio-economically advanced countries, and it has been related to improved outcome of CH more frequently allowing transmission of heritable defects, endocrine disrupting chemicals, and the lower threshold of neonatal TSH screening [22–24]. With the introduction of the neonatal screening of congenital hypothyroidism, the incidence is 1:1500–1:2000. CH occurs due to defective thyroid gland development or hormone biosynthetic function and is traditionally sub-classified as thyroid dysgenesis or dyshormonogenesis [25, 26]. Thyroid dysgenesis refers to a spectrum of aberrant thyroid gland development, most commonly involving thyroid ectopy, an abnormally situated and mostly small thyroid gland. Complete absence of the thyroid gland (athyreosis) occurs in 20–30% of cases with thyroid dysgenesis, while a small minority exhibit a normally located though hypoplastic thyroid gland. Dyshormonogenesis refers to failure of thyroid hormone production by a normally located, sometimes enlarged goitrous thyroid gland in which the molecular pathway for thyroid hormone biosynthesis is disrupted. Thyroid dysgenesis is generally considered to be a sporadic disease for which the underlying etiology is usually not clear. Genetic causes involve genes mediating thyroid differentiation, migration, and growth. However, in less than 5% of cases with thyroid dysgenesis, a loss-of-function mutation in a known thyroid dysgenesis-associated gene can be detected, namely *TSHR* (TSH receptor), *NKX2.1/TTF1*, *PAX8*, *FOXE1/TTF2*, *GLIS3*. Additional genes associated with thyroid dysgenesis include *NKX2.5*, *JAG1*, *CDCA8*, and *NTN1*/Netrin 1. Recent evidence suggests the existence of hypomorphic alleles of these candidate genes, whose combination can explain a significant portion of congenital hypothyroid cases [25]. The oligogenic involvement should be considered as a solid hypothesis for the genetic etiology of congenital hypothyroidism: variants with a modest functional impairment can produce a negligible effect on thyroid function when expressed alone, but the sum of minor alleles, even acting at different levels (thyroid morphogenesis or hormonogenesis), can justify the birth of a child with congenital hypothyroidism in families with a history of minor thyroid defects or without any previously recognized thyroid disease [25]. In contrast, the majority of individuals with dyshormonogenesis harbor mutations in genes encoding known components of the thyroid hormone biosynthesis machinery, including *TG* (thyroglobulin), *TPO* (thyroperoxidase), *SLC26A4* (pendrin), *SLC5A5* (sodium/iodide symporter), *DUOX2* (dual oxidase 2), *DUOXA2* (dual oxidase maturation factor 2), *IYD* (iodotyrosine deiodinase).

### *2.2.6 Central Hypothyroidism*

Central hypothyroidism is characterized by a defect in thyroid hormone secretion, resulting from the insufficient stimulation of a healthy thyroid gland by TSH. It can be a consequence of an anatomic or a functional disorder of the pituitary gland and/or the hypothalamus [27]. Central hypothyroidism can be congenital, caused by genetic defects, or acquired, resulting from lesions such as tumors, traumas, or cerebrovascular accidents that affect the hypothalamic–pituitary axis. Central

hypothyroidism may present as an isolated defect of pituitary function, while in most patients it occurs in combination with other pituitary hormone deficiencies. The global prevalence of central hypothyroidism ranges from 1 in 20,000 to 1 in 80,000 individuals in the general population, representing a rare cause of hypothyroidism (1 out of 1000 patients with hypothyroidism). Central hypothyroidism affects patients of all ages and both sexes equally. Defects in TSH secretion can be quantitative (due to reduced TSH reserve), qualitative (sustained by reduced bioactivity of the released TSH molecules), or both. In the congenital forms of central hypothyroidism the defect is usually quantitative. By contrast, the defect is frequently both quantitative and qualitative in acquired central hypothyroidism. The secretion of bioinactive TSH can occur following hypothalamic–pituitary tumors or injuries sustained during a breech delivery, external radiation for head tumors and Sheehan syndrome. The clinical features of central hypothyroidism depend on the etiology, the severity of the hypothalamic–pituitary impairment, the extent and severity of associated hormone deficiencies, and the age of the patient at the time of disease onset. Congenital central hypothyroidism is clinically more severe than the acquired forms. The symptoms and signs of central hypothyroidism, which include fatigue, depression, cold intolerance, hoarseness, dry skin, constipation, bradycardia, and hyporeflexia, are usually the same but milder than those of primary hypothyroidism, and goiter is seldom present. In the presence of combined pituitary deficiencies, other endocrine manifestations, for example, growth failure, delayed puberty, adrenal insufficiency and diabetes insipidus, lead the patients to seek medical attention before their hypothyroidism manifests. Patients with congenital central hypothyroidism present with various syndromic and complex clinical features depending on the genes involved.

## 2.3 Hyperthyroidism

The prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world [1]. Graves' disease is the most common cause of hyperthyroidism in iodine-replete populations. Other common causes include toxic multinodular goiter and autonomously functioning thyroid adenoma [28]. Less common causes of hyperthyroidism are thyroiditis, pituitary TSH secreting adenoma, and drug-induced hyperthyroidism. In iodine-sufficient countries, Graves' disease accounts for 70–80% of patients with hyperthyroidism, whereas in areas with iodine deficiency, Graves' disease constitutes about 50% of all cases of hyperthyroidism, with the other half attributable to nodular thyroid disease [29].

The clinical phenotype in hyperthyroidism also shows geographical variation. Moreover, compared with patients with nodular disease, patients with Graves' disease are younger, have higher thyroid hormone levels, and are more likely to present with overt hyperthyroidism than subclinical hyperthyroidism. Cardiovascular complications resulting from hyperthyroidism seem to be more prevalent in areas where toxic multinodular goiters are common, in part because patients with nodular

disease are typically older. Ethnicity does seem to influence the risk of developing certain disease complications. For example, Graves' ophthalmopathy is six times more common in white populations than in Asian populations. Furthermore, the rare but serious complication of hyperthyroidism, thyrotoxic periodic paralysis, is markedly more common in Asian men [1, 30].

### 2.3.1 Graves' Disease

Graves' disease is a systemic autoimmune disorder caused by thyroid stimulating autoantibodies directed against the TSH receptor on thyroid follicular cells that results in follicular cell hypertrophy, thyroid enlargement, increased synthesis of thyroid hormone, and hyperthyroidism. Ophthalmopathy and pretibial myxedema can also occur. Graves' ophthalmopathy occurs in 20–30% of patients, while pretibial myxedema is rarely observed. Graves' disease affects approximately 0.5% of the population and is the most common cause of hyperthyroidism, accounting for 50–80% of all cases [29]. Graves' disease predominantly affects women with a female to male ratio of 8:1, typically in their third to fifth decade of life. The clinical phenotype of Graves' disease, at least in Western countries, is becoming milder, presumably due to earlier diagnosis and treatment.

### 2.3.2 Toxic Nodular Disease

Toxic nodular goiter is the most frequent cause of thyrotoxicosis in elderly individuals, especially those in iodine-deficient areas. Solitary toxic nodules are more common in women than in men, with a likely male:female ratio of 1:5 [31]. In areas where low iodine intake is prevalent, the incidence of toxic multinodular goiter is significantly higher in areas with low iodine intake (18.0 cases/100,000/year) compared with high-iodine-intake areas (1.5 cases/100,000/year) [32]. The incidence of solitary toxic nodules is similarly higher in low-iodine-intake areas than in high-intake areas.

### 2.3.3 Thyroiditis

Thyroiditis is characterized by a self-limiting course of thyrotoxicosis, followed by hypothyroidism and then return to normal thyroid function. The condition is slightly more common in females than males (female:male ratio of 1.5:1), and permanent hypothyroidism occurs in 10–20% of cases overall [3]. Acute painful thyroiditis often presents following a respiratory tract infection, while painless thyroiditis can occur postpartum in up to 9% of otherwise healthy women [33].

### 2.3.4 Drug-Induced Hyperthyroidism

The iodine-rich compound amiodarone is widely prescribed as an anti-arrhythmic agent. Amiodarone-induced thyrotoxicosis is more common in iodine-deficient areas and appears to be more common in men with a male:female ratio of up to 3:1. Other drugs that cause thyrotoxicosis include interferon (IFN)-α, lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies, immune checkpoint inhibitors, and the humanized monoclonal antibodies used in the treatment of multiple sclerosis, alemtuzumab. Although these drugs can cause transient thyrotoxicosis through destructive thyroiditis, immune-modifying agents such as IFN-α, highly active antiretroviral therapies, and alemtuzumab can also induce Graves' disease through less well-defined immune reactivation mechanisms [34].

### 2.3.5 Iodine-Induced Hyperthyroidism

Iodine-induced hyperthyroidism, which is also known as the Jod–Basedow phenomenon, is more common in older persons with longstanding nodular goiter and in regions of chronic iodine deficiency where the populace is undergoing iodine supplementation [35]. Iodization programs temporarily increase the risk of iodine-induced hyperthyroidism; elderly individuals who might have coexisting cardiac disease and also those with limited access to health care are principally at risk [35]. Radiographic contrast agents can also cause iodine-induced hyperthyroidism. Individuals with preexisting multinodular goiter or those from iodine-deficient areas are at greatest risk of iodine-induced hyperthyroidism following the administration of a radiographic contrast agent [36].

### 2.3.6 Subclinical Hyperthyroidism

The prevalence of subclinical mild hyperthyroidism has been estimated ranging from 1% to 5% [37]. Data from the NHANES III study suggest a bimodal peak at age 20–39 years and at >80 years of age [38]. The NHANES III study also showed that women were more likely to have subclinical hyperthyroidism. The greatest risk factor for subclinical hyperthyroidism, aside from levothyroxine use, is iodine deficiency. The prevalence of subclinical hyperthyroidism increases from around 3% in iodine-sufficient areas to 6–10% in iodine-deficient areas, largely owing to toxic nodular goiters. Data on the risk of progression from subclinical to overt hyperthyroidism are limited. In a Scottish database including more than 2000 cases of subclinical hyperthyroidism, the most untreated patients did not progress to overt hyperthyroidism, and one-third of patients returned to normal thyroid status 7 years after initial diagnosis [39]. Other studies showed that patients with more severe grades of subclinical hyperthyroidism progressed more frequently to overt disease.

## 2.4 Thyroid Nodular Diseases

Thyroid nodules are defined as discrete lesions within the thyroid gland, distinct from surrounding thyroid parenchyma [40]. Thyroid nodules are common, being detected in up to 65% of the general population. Approximately 90% of thyroid nodules are benign and 95% are asymptomatic, remain so during follow-up, and can be safely managed with a surveillance program. The main goal of initial and long-term follow-up is identification of the small subgroup of nodules that harbor a clinically significant cancer (≈10%), cause compressive symptoms (≈5%), or progress to functional disease (≈5%) [41].

There is considerable heterogeneity between thyrocytes in the same follicle in terms of iodine retention, hormone synthesis, and mitotic response to proliferative stimuli [42]. These physiological variations cause differences in the hyperplastic nodules originating from these cells. TSH is the main mitotic factor. Elevation of serum TSH levels causes significant increases in thyroid volume, and even minimal elevations over an adequate amount of time are sufficient for goiter formation. Iodine deficiency is the leading cause of increases in TSH levels. Thus, the incidence of nodules is high in regions with endemic goiter due to iodine deficiency. Selenium deficiency also causes goiter and nodular goiter. Some chemicals (e.g., nitrate and perchlorate) can cause goiter by affecting iodine uptake or hormone synthesis. There is an increased incidence of thyroid nodules despite the use of iodine prophylaxis in many countries [43]. Other factors involved in the development of thyroid nodules include radiation, environment (nitrates, benzene, formaldehyde, pesticides, bisphenol A, polychlorinated biphenyl, polyhalogenated aromatic hydrocarbons, and polybrominated diphenyl ether), gene mutations (*RAS*, *PAX8/PPARγ*, *RET/PTC*, *BRAF*), metabolic syndrome, insulin resistance, and obesity [44].

One of the leading causes of nodule detection is the increased use and sensitivity of radiological imaging. Ultrasound can currently detect nodules as small as 1–2 mm, causing the incidence of nodules to increase to 60,000–70,000/100,000 adults in a population. This number was below 10,000 when palpation and scintigraphy were the only methods used for nodule evaluation. However, many studies have found that the incidence of nodular goiter is increased even when this factor is eliminated. The cancer rate of nodular goiter is around 5%. The rate does not differ between single nodules and multinodular goiter [1].

Risk factors for malignancy include childhood irradiation (mainly head and neck and whole body radiation), exposure to ionizing radiation from fallout in childhood or adolescence, family history of thyroid cancer or hereditary syndromes that include thyroid cancer [multiple endocrine neoplasia syndrome type 2 (MEN2A and 2B), family with ≥3 affected relatives, or genetic syndromes such as Cowden disease, familial adenomatous polyposis, Carney complex], rapid nodule growth, or hoarseness [41]. Family history plays a significant role in the development of thyroid cancer, and having first-degree relatives with not only medullary, but also papillary thyroid cancer strongly predicts the risk of developing the malignant thyroid disease. In contrast, benign thyroid disorders in family history do not lead to the development of thyroid cancer [45].

Thyroid cancer is the fifth most common cancer in women in the USA. The incidence continues to rise worldwide. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer [46, 47]. Although over 90% are small, nonpalpable, benign lesions that will never become clinically significant tumors, some patients have nonpalpable or palpable lesions that are malignant. Identification of malignant thyroid nodules is important, especially those that will cause morbidity if not diagnosed early. Thyroid cancers are distinct in follicular-derived thyroid cancers and neuroendocrine C-cell-derived thyroid cancers. The follicular-derived cancers include differentiated and anaplastic thyroid cancers. From a genetic point of view, most thyroid cancers harbor mutations along the mitogen-activated protein kinase (MAPK) cellular signaling pathway [46].

## *2.4.1 Follicular-Derived Thyroid Cancers*

### 2.4.1.1 Differentiated Thyroid Cancers

Differentiated thyroid cancer is the most common thyroid cancer, accounting for more than 95% of cases, and originates from thyroid follicular epithelial cells [48]. This category includes papillary thyroid cancer, follicular thyroid cancer, and Hurthle cell thyroid cancer. Poorly differentiated thyroid cancer is a more aggressive follicular-derived thyroid cancer than differentiated thyroid cancer. Papillary thyroid cancer is the most common subtype and carries the best overall prognosis. Metastases most commonly involve cervical lymph nodes and, less commonly, the lungs. Follicular thyroid cancer, Hurthle cell thyroid cancer, and poorly differentiated thyroid cancers are high-risk cancers that have a tendency to metastasize hematogenously to distant sites, in particular, to lung and bones.

### 2.4.1.2 Anaplastic Thyroid Cancers

Anaplastic thyroid cancer is a rare form of thyroid cancer (<1%) [48] that usually presents as a rapidly growing neck mass. Patients often develop hoarseness, dysphagia, and dyspnea. The most common site of distant metastatic disease is the lung, followed by bones and brain. Anaplastic thyroid cancer often arises from and can coexist with differentiated thyroid cancer, but can also occur de novo.

## *2.4.2 Neuroendocrine C-Cell-Derived Thyroid Cancer*

### 2.4.2.1 Medullary Thyroid Cancers

Medullary thyroid cancer accounts for 1–2% of all thyroid cancers and originates in the parafollicular neuroendocrine cells of the thyroid [48]. It most commonly presents as a solitary thyroid nodule in patients in the fourth to sixth decade of life. A

quarter of medullary thyroid cancer cases occur in patients with the inherited type 2A multiple endocrine neoplasia syndrome (MEN2A;OMIM#171400), type 2B multiple endocrine neoplasia syndrome (MEN2B;OMIM#162300), and familial medullary thyroid cancer (MTC;OMIM#155240).

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# Chapter 3
# Techniques to Study Thyroid Function and Morphology


**Francesca Serpi, Salvatore Gitto, Giovanni Mauri, and Luca Maria Sconfienza**

## 3.1 The Role of Ultrasound

Thyroid ultrasound with B-mode gray-scale and color Doppler is the most important imaging modality to study normal thyroid parenchyma and investigate the presence of diffuse or nodular thyroid disease by evaluating glandular size, echogenicity, echotexture, margins, and vascularity.

Ultrasound does not use ionizing radiations, is cheaper and quicker than other imaging modalities, and is widely available in clinical settings. Moreover, the superficial location of the thyroid makes high-resolution ultrasound the imaging modality of choice for the evaluation of diffuse and focal processes. Thyroid ultrasound is able to confirm the presence of a thyroid nodule when the physical examination is equivocal and to differentiate between thyroid nodules and cervical masses from other origins. Although thyroid nodules may be detected at computed tomography (CT) and magnetic resonance (MR) imaging (usually by chance), these modalities are not useful for nodule's characterization. Ultrasound has however some

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limitations, such as low contrast resolution, that may be overcome thanks to contrast-enhanced ultrasound (CEUS), and it is not panoramic, with only small field of view and impossibility to scan deep structures. Normal ultrasound examination is conducted with a high-resolution probe (12 MHz), which offers very high spatial resolution with lower penetration.

## 3.2 Normal Anatomy

The thyroid is a bilobed structure located within the lower neck and is draped anteriorly around the trachea. The left and right lobes are located immediately to the left and right of the trachea, respectively, and are connected anteriorly by a thin rim of thyroid tissue known as the isthmus. The internal carotid arteries and internal jugular veins are located posterolateral to the thyroid lobes, whereas the strap muscles of the neck are located anteriorly [1]. Esophagus is located on the left posterolateral corner, between thyroid gland and the trachea. Parathyroid glands are normally four symmetric small structures located posterior to thyroid lobules, two on each side.

The thyroid lobes are normally 4–6 cm in craniocaudal length, 1.5–2 cm in their anteroposterior, and 2–3 cm in transverse dimensions; the isthmus normally has an anteroposterior thickness of up to 3 mm [2]. Total volume, measured as length × width × depth × 0.523 for each thyroid lobe (the isthmus is omitted unless its thickness is over 3 mm), should be <12–18 mL in men, <10–15 mL in women [3].

At ultrasound, thyroid parenchymal echogenicity is described as isoechoic, hypoechoic, markedly hypoechoic, or hyperechoic compared to the echogenicity of the anterior strap musculature as an internal reference. The normal parenchyma is usually homogeneous and slightly hyperechoic due to its follicular composition. The outer surface is surrounded by a thin layer of connective tissue, which has heterogeneous thickness and composition and discontinuous distribution, consistent with a pseudocapsule rather than a true capsule. Normal thyroid vascularity with color Doppler flow should be fairly symmetric and evenly distributed [2].

## 3.3 Diffuse Thyroid Pathology

*The various causes of diffuse thyroid disease often have overlapping, nonspecific sonographic imaging features*. Diagnosis is not generally based on ultrasound evaluation but on presenting symptoms, laboratory analysis of thyroid function, immunology, and occasionally radioactive iodine uptake scans [3]. Ultrasound, on the other side, may be helpful in excluding focal thyroid disease and assessing the size of the thyroid gland. With diffuse thyroid diseases, the thyroid is often enlarged and can have increased or decreased parenchymal echogenicity and coarsened

echotexture with nodular (micro- or macrolobulated) margins. Diffuse thyroid disease presents with variable vascularity with color Doppler evaluation that can be normal, increased, or decreased. Among diffuse thyroid diseases, the most common are multinodular goiter, thyroiditis, and Basedow/Graves' disease.

**Multinodular goiter** or **struma diffusa** is a generalized enlargement of the thyroid and can be diffuse or nodular (Fig. 3.1) [3]. It may be within a range from simple diffuse nontoxic non-nodular thyroid enlargement to multinodular goiter in a euthyroid patient. The cause of simple goiter is multifactorial. Insufficient thyroid hormone input is the most frequent cause. In an attempt to maintain euthyroid state, follicular epithelium compensatory hypertrophy leads to polyclonal follicles alternating with scarring caused by hemorrhagic necrosis over the course of goiter growth. It appears as thyroid enlargement with focal or diffuse replacement of the thyroid parenchyma by strictly adjacent, sometimes, not distinctive, variable echo structure nodules containing variable amount of cystic degeneration, vascularization, and dystrophic calcifications, without or with minimal normal remaining parenchyma [3]. The main aim of ultrasound is to identify nodules that have malignant sonographic features to be submitted to ultrasound-guided fine needle aspiration (FNA) [3].

Vascularity at color Doppler is usually normal.

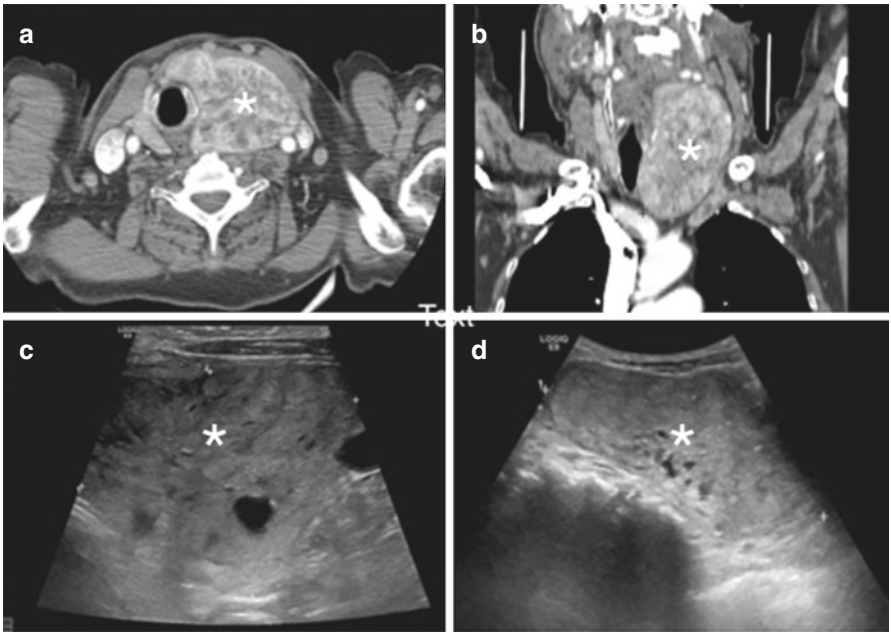


**Fig. 3.1** Nodular goiter. The thyroid gland is enlarged (asterisks) and a big left lobe nodule showing mediastinal extension is shown on axial (**a**) and coronal (**b**) CT scans, as well as axial (**c**) and longitudinal (**d**) US scans

**Thyroiditis** is an inflammatory condition affecting the total amount of thyroid gland, which reflects various etiologies (infection, autoimmune processes, medication, and ionizing radiation), clinical symptomatology, imaging findings, and treatment [2]. Thyroiditis is therefore a general term that encompasses several clinical disorders characterized by inflammation of the thyroid gland. The most common is Hashimoto thyroiditis.

*Chronic lymphocytic thyroiditis*, or *Hashimoto thyroiditis*, is the most common autoimmune disorder of the thyroid and the most common cause of hypothyroidism in iodine-sufficient areas [2]. It has a female predominance with 8–9:1 female to male ratio [3]. Patients develop antibodies targeting thyroglobulin (TG), thyroid peroxidase (TPO), an enzyme for thyroid hormonogenesis. The thyroid becomes infiltrated with lymphocytes, which leads to progressive replacement of follicular cells with eventual fibrosis and atrophy [2].

Sonographic appearances vary depending on the degree of gland involvement [2]. Initially, the parenchyma is heterogeneous and coarsened compared with normal thyroid [3]. Typical ultrasound appearance is characterized by a patchy heterogenous echotexture due to lymphocytic infiltration, which forms innumerable hypoechoic solid micro pseudonodules (from 1 to 7 mm in size), surrounded by echogenic rim of fibrosis, which gives the "giraffe skin" appearance (highly specific with a positive predictive value of 95%) [2, 3]. With the progression of the disease, thyroid parenchyma is progressively destroyed and develops echogenic linear bands of parenchymal fibrosis which can become confluent and thicker. The involvement can be asymmetric, with preference for the anterior part of the gland. Eventually the gland becomes atrophic with a hypoechoic appearance similar to that of strap muscles [3]. Color Doppler in Hashimoto's is variable with either normal or increased vascularity seen in the early disease [3].

Ultrasound can also identify an increased number of benign, hyperplastic lymph nodes in cervical levels II, III, and IV compared with patients without thyroid disease [2].

Final diagnosis is biochemical, made by detecting anti-thyroid antibodies, including anti-TPO and anti-TG antibodies [3].

Patients with chronic lymphocytic thyroiditis are at risk for developing primary thyroid lymphoma (usually a B-cell lymphoma), which represents less than 5% of all thyroid malignancies [2]. It should be suspected if an atrophic gland quickly enlarges or develops hypoechoic masses, particularly if associated to systemic symptoms [2].

*Subacute granulomatous thyroiditis*, or *De Quervain thyroiditis*, is a rare (3%–6% of all thyroid diseases), often self-limiting condition likely due to an immune response following a viral or upper respiratory tract infection [2]. Generally, appears 2 weeks after a viral upper respiratory tract infection and regresses spontaneously within 2–3 months [3]. The classic presentation is an acutely painful neck with tender glandular swelling and occasionally systemic symptoms, with elevation of inflammatory index at biochemistry analysis [2]. Thyroid function can be augmented in the acute phase, usually followed by a hypothyroid phase. It returns to euthyroid state after approximately 6–18 months [2, 3]. Ultrasound findings include an

increase in the size of the thyroid with ill-defined, moderate, or markedly patchy hypoechoic area, which tend to elongate along the long axis of the thyroid giving a pseudonodule appearance [2, 3]. In the subacute phase, the hypoechoic area increases in size in the ipsilateral thyroid lobe and may extend to the contralateral lobe. These ill-defined areas typically assumed a confluent appearance, known as "lava flow" [2, 3]. Hypoechoic appearance can also be seen in malignancy; however, other features of malignancy (e.g., calcifications and taller than wide shape) are absent. During recovery phase, thyroid parenchyma returns back to normal or atrophy may develop. Typically, enlarged and activated lymph nodes can be found as well.

Resolution at short-term follow-up and clinical response to anti-inflammatory therapy are highly diagnostic.

At color Doppler, the acute phase may demonstrate hypervascularity, whereas the subacute phase may reflect diffuse hypovascularity (which reflects interstitial edema), compared to the normal surrounding parenchyma [2].

*Acute thyroiditis* is a very rare disease, predominantly occurring in immunosuppressed patients, which may develop locally or hematogenically in septicemia [3]. It may also affect children and young adults with congenital fourth branchial pouch sinus tracts. Common local symptoms are sore throat, painful swelling, reddening of the skin, and lymph nodes enlargement. Fever may also be present [3]. US findings are not specific, thyroid gland is usually increased in volume with hypoechoic parenchyma due to inflammation. Although local inflammatory reaction is normally present, acute suppurative thyroiditis is uncommon due to the excellent lymphatic drainage, encapsulation, and high iodine content in the gland. However, the presence of focal fluid collection with bright echoes in it from gas can suggest an abscess [3]. Enlarged lymph nodes are usually present. Color Doppler shows normal or increased blood flow [3].

Other forms of thyroiditis include *drug-induced thyroiditis* such as amiodarone, interferon, and immunotherapy, with nonspecific sonographic features that overlap with other causes [2]. *Riedel thyroiditis* is a rare, local form of fibrosclerosis of the thyroid that presents in patients 30–50 years of age. Although etiology is unknown, it is likely due to an autoimmune process. It is most common in women and can be associated with mediastinal or retroperitoneal fibrosis (e.g., immunoglobulin G4–mediated diseases) [2, 3]. It results in an indolent hard swelling of the neck due to thyroid fibrosis and invasion of adjacent neck soft tissue structures with inflammatory cell infiltrates. At US scan, the gland is enlarged, hypoechoic, and coarsened with a pseudonodular appearance that has fibrotic bands and perithyroidal extension [2]. Color Doppler shows decreased vascular flow, which may improve with corticosteroid therapy [3].

**Graves' disease**, or **Basedow's disease**, is an autoimmune disorder, caused by thyroid receptors antibodies binding to TSH receptor (thyrotropin receptor) that results in epithelial hyperplasia and hyper-functioning of the thyroid [2, 3]. A positive family history is common. Biochemical evaluation typically shows increased thyroid hormones (fT4 and fT3) and decreased TSH. Ultrasound findings

are not specific; however, thyroid gland is characterized by diffuse enlargement with rounding of the normal angular outline and mild textural coarsening. The echogenicity is often decreased due to the increased blood flow, increased cellularity, and decreased colloid content [2]. Compared to Hashimoto's thyroiditis, the appearance of the thyroid in Graves' disease is less heterogeneous and the contour is lobulated. Color Doppler shows increased parenchymal vascularity and arteriovenous shunting creating a "thyroid inferno" appearance with a smooth or scalloped glandular contour [2].

## 3.4 Nodular Thyroid Pathology

Thyroid nodules are a common occurrence in the general population, with a prevalence of almost 50% [4]. The vast majority are benign and may be identified incidentally on chest computed tomography imaging or carotid ultrasound, or as part of a dedicated thyroid study for abnormal laboratory values or physical examination [2]. Approximately 60–70% of fine needle aspiration of thyroid nodules are reported to be benign, with the majority represented by benign follicular nodules (nodular goiter, adenomatoid or hyperplastic nodules, colloid nodules, nodules in Graves' disease, and macrofollicular subtype follicular adenoma), thyroiditis, and follicular adenoma [1]. Therefore, the first goal of initial sonographic assessment should be to distinguish between benign nodules that can be managed conservatively, and suspicious or malignant features, that require further management. Ultrasound-guided fine needle aspiration (FNA) plays a central role in this process, but its performance needs to be selective, since systematic FNA of all nodules, regardless of the size or appearance, is superfluous and may even lead to unnecessary diagnostic thyroid surgery [5].

Certain features of thyroid nodules on ultrasound are consistently predictive of malignancy but unfortunately none of them alone is sufficient to confirm or deny malignancy efficiently [5]. Therefore, the approach should be to combine several features to enhance the diagnostic value of ultrasound. This has prompted the development of standardized systems for reporting features, known as Thyroid Imaging and Reporting Data System (TIRADS), in an attempt to delineate sets of characteristics associated with specific risk levels for malignancy [5–8]. This comprises a thyroid ultrasound lexicon, a standardized report, definitions of benign and low-, intermediate-, and high-risk nodules with the estimated risks of malignancy in each category and indications for FNA.

The European guidelines (EU-TIRADS) delineate five risk categories, based on searching for echogenic features of high suspicion [5]. These are:

- ***Non-oval/round shape***, such as taller than wide shape (the ratio of the anteroposterior-to-transverse diameter of a nodule is >1).
- ***Irregular margins***, spiculated or microlobulated.

– ***Microcalcifications***, <1 mm, without posterior shadowing, corresponding to psammoma bodies.
– ***Markedly hypoechoic ecogenicity***, compared to normal surrounding thyroid parenchyma and muscles. The different patterns can be therefore described as anechoic (same echogenicity of fluid, with the absence of solid component), isoechoic (similar brightness to the surrounding thyroid parenchyma), hyperechoic (brighter appearance than the surrounding thyroid), mildly hypoechoic (refers to an appearance darker than the normal surrounding thyroid parenchyma, but less dark than the normal surrounding strap muscles), markedly hypoechoic (refers to an appearance of the nodule darer than surrounding strap muscles). In case the echogenicity of the surrounding thyroid tissue is decreased, such as in Hashimoto thyroiditis, the echogenicity of the solid component can be described relative to the normal submandibular salivary glands.

If at least one of these features is present, then the nodule is highly suspicious for malignancy (EU-TIRADS 5). If not, the nodule is subclassified according its echogenicity (Fig. 3.2):

– **EU-TIRADS 1**. No nodule is detectable at sonographic evaluation.
– **EU-TIRADS 2** (benign). Risk of malignancy close to 0%. Thyroid ultrasound should suffice to assert benignity without the need for FNA. This category includes purely cystic nodules (Fig. 3.3) and entirely spongiform nodules.

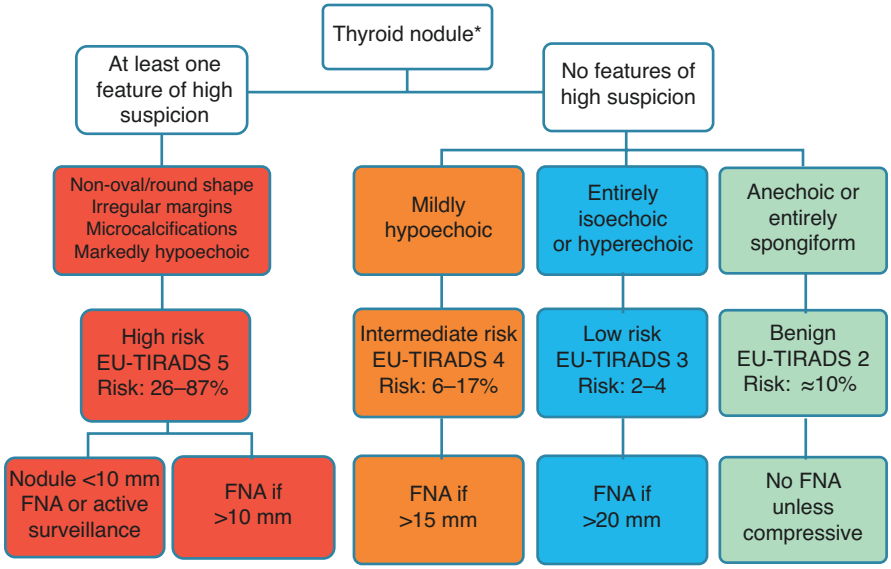


**Fig. 3.2** Algorithm of EU-TIRADS for malignancy risk stratification and fine needle aspiration (FNA) decision-making. From reference [5]

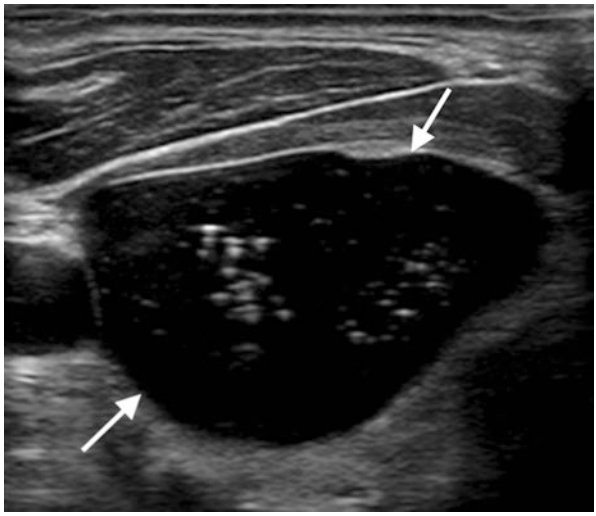

**Fig. 3.3** EU-TIRADS 2 nodule. A cystic nodule is depicted in the right thyroid lobe (arrows)

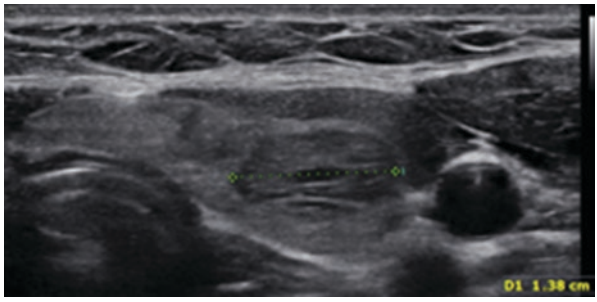

**Fig. 3.4** EU-TIRADS 3 nodule. In the left thyroid lobe, an oval-shaped, predominantly isoechoic nodule with peripheral halo is depicted (calipers). This nodule was further investigated with FNAB and classified as benign (TIR 2)

- **EU-TIRADS 3** (low risk). Risk of malignancy around 2–4%. FNA should usually be considered only for nodules >20 mm. The 20-mm threshold has been chosen based on the argument that distant metastases are rarely observed arising from follicular cancers <2 cm. Nodules in this category have usually oval shape, smooth margins, isoechoic or hyperechoic, without any feature of high risk (Figs. 3.4, 3.5, and 3.6).
- **EU-TIRADS 4** (intermediate risk). Risk of malignancy around 6–17%. FNA should usually be performed for nodules >15 mm. Nodules in this category have usually oval shape, smooth margins, mildly hypoechogenicity, without any feature of high risk (Fig. 3.7).
- **EU-TIRADS 5** (high risk). Risk of malignancy around 26–87%. Nodules with at least one of the high-risk features (Fig. 3.8). Nodules >10 mm should undergo FNA, unless a patient is inoperable or has a low life expectancy and negative FNA should be repeated within 3 months to reduce false-negative results. In nodules <10 mm, active surveillance is recommended if there are no abnormal lymph nodes and patient is compliant.

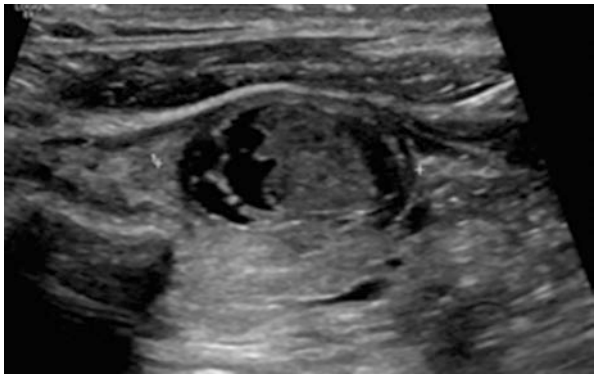

**Fig. 3.5** EU-TIRADS 3 nodule. An oval-shaped thyroid nodule with partially cystic and predominantly solid isoechoic echotexture is shown (calipers)

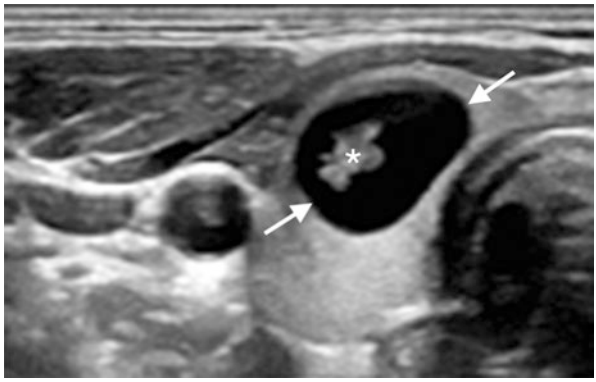


**Fig. 3.6** EU-TIRADS 3 nodule. An oval-shaped thyroid nodule predominantly cystic (arrows) and with central solid isoechoic tissue (asterisk) is shown

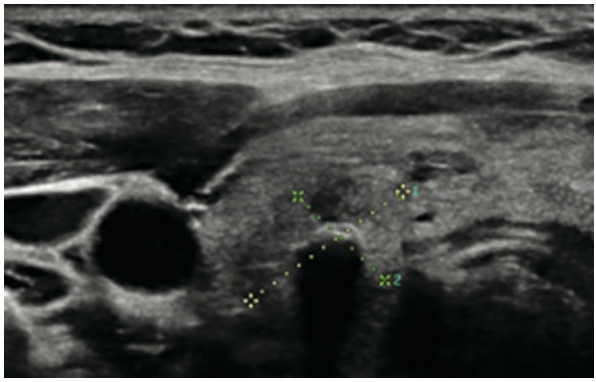

**Fig. 3.7** EU-TIRADS 4 nodule. An oval-shaped thyroid nodule with slightly hypoechoic echotexture relative to the adjacent parenchyma is shown in the right lobe (calipers). This nodule was investigated with FNAB and classified as suspicious for malignancy (TIR 4)

Moreover, several accessory ultrasound features can be used to refine the risk stratification assessment and modulate the indications for FNA:

– *Suspicious lymphadenopathy*. Ultrasound assessment of the lymph nodes is advised for all thyroid nodules but is mandatory for intermediate- and high-risk ones. In case of a suspicious lymph node (such as loss of fat center, cystic/

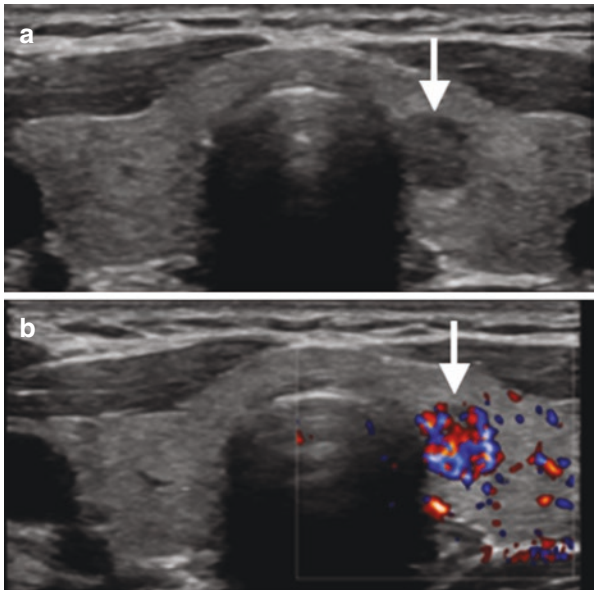


**Fig. 3.8** EU-TIRADS 5 nodule. A taller-than-wide markedly hypoechoic nodule with irregular margins is shown (arrows) in the left thyroid lobe on grayscale (**a**) and Doppler (**b**) US scans. This nodule was investigated with FNAB and classified as malignant (TIR 5)

necrotic area, calcifications), FNA of the lymph node and FNA of the most suspicious thyroid nodule(s) should be performed.

- *Extrathyroidal extension*. Capsular bulging, disruption, or abutment by the thyroid nodule are indicative of extrathyroidal extension and should be described in the report.
- *Macrocalcifications and hyperechoic spots*. Macrocalcifications (>1 mm) alone are not specific for malignancy. Rim (peripheral or curvilinear) or eggshell calcifications at the nodule margin may increase the malignancy risk if disrupted. True microcalcifications (<1 mm without posterior shadowing) should be differentiated from other echogenic spots, and such nodules must undergo FNA. Echogenic spots with comet-tail artifacts are suggestive of benignity (Fig. 3.9).
- *Halo*. It is thought to correspond either to the capsule of the nodule or to the surrounding capsular vessels, or even sometimes to the adjacent compressed parenchyma. A thin halo reduces the risk of malignancy, while a thick halo or absence of a halo increases it.
- *Vascularity*. Color Doppler is not recommended for ultrasound malignancy risk stratification (low PPV). It can be used instead to differentiate solid tissue from thick colloid, or to enhance the detection of the limits of a nodule in an isoechoic parenchyma.
- *Nodule growth*. It cannot accurately discriminate between benign and malignant lesions; therefore, routine determination of nodule growth by serial thyroid ultrasound assessments, in order to predict cancer, is not justified.

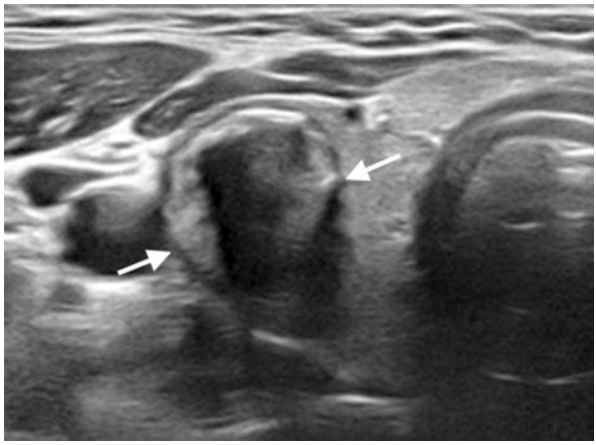

**Fig. 3.9** Calcified nodule. A thyroid nodule with macrocalcification causing posterior shadowing is shown in the right lobe (arrows)

**Table 3.1** Ultrasound management in multinodular disease (EU-TIRADS)

| Look for | Describe | FNA |
|---|---|---|
| High-risk nodules (EU-TIRADS 5) | Regardless their size | >10 mm (if negative, repeat FNA after 3 months) |
| Intermediate-risk nodules (EU-TIRADS 4) | >5 mm | >15 mm |
| Low-risk nodules (EU-TIRADS 3) | >10 mm | >20 mm |

In case of multinodular disease, at least the three most important features (according to the risk and size criteria) should be described in detail, as given in Table 3.1.

### *3.4.1 Hyperplastic Adenomatous Nodule*

Hyperplastic adenomatous nodules (also known as Plummer's adenoma) are benign autonomous thyroid adenoma, usually characterized by clinically symptomatic hyperthyroidism when they reach a cutoff diameter of 2.5 cm [4], although it can occur also with smaller nodules. They may be unifocal, multifocal, or disseminated. They usually grow very slowly. At US scan, they are usually hypoechoic and clearly delineated with a peripheral halo. Sometimes they may present cystic degeneration [4].

Color Doppler shows an increased peripheral and central blood flow, which may be an important indicator of functional activity (Fig. 3.10) [4].

Nuclear scintigraphy is usually positive, showing a "hot" nodule with markedly increased uptake, which may be helpful in ruling-out cancer (normally represented by "cold" nodules) [4].

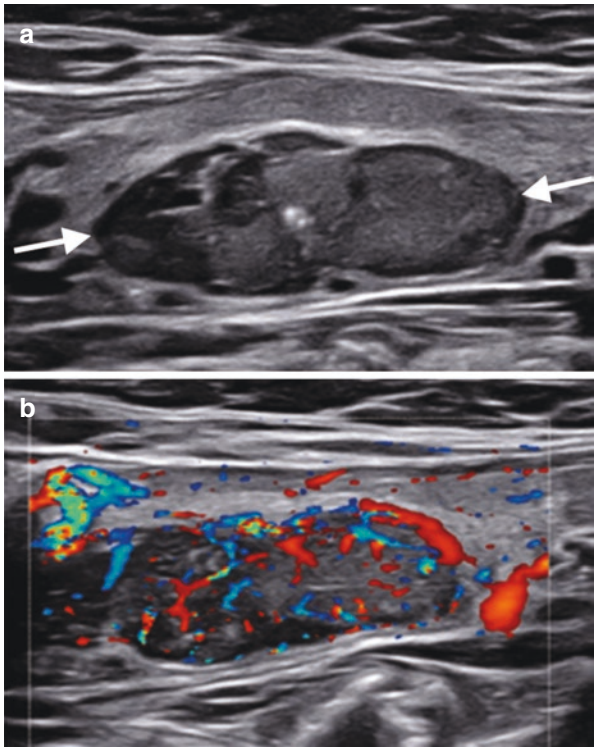


**Fig. 3.10** Plummer's adenoma. A hypoechoic nodule (**a**) with increased vascularity on Doppler imaging (**b**) is shown (arrows)

## 3.5 Sonoelastography

Changes in tissue stiffness are present in cancerous disease, fibrotic changes, or atherosclerosis. Ultrasound elastography provides stiffness information, which is complementary to grayscale findings, particularly in nodules with indeterminate US or cytologic characteristics [9].

By ultrasound elastography, the stiffness of a nodule is analyzed, either by measuring the amount of distortion that occurs when the nodule responds to an external pressure (strain elastography) or by measuring the speed of the shear wave produced by a US pulse (shear wave elastography [SWE], acoustic radiation force impulse). Strain elastography uses 3- to 5-point elasticity scales obtained from qualitative observations of colored pictures [10, 11].

Generally, more elastic lesions are more likely to be benign compared to less elastic lesions. However, there are important differences between manufactures, machines, techniques, and operators, and not all the results are comparable and therefore cannot be judged as a head-to-head comparison. Moreover, both strain elastography and SWE have many limitations and cannot reliably be applied to large nodules (>30 mm), nodules with macrocalcifications, cystic nodules, deeply located, and/or isthmic nodules and coalescent nodules [10, 11].

For these reasons, according to EU-TIRADS guidelines, elastography should not replace grayscale study, but it may be used as a complementary tool for assessing nodules for FNA, especially due to its high negative predicting value [5].

## 3.6 CEUS

Contrast-enhanced ultrasound (CEUS) is considered to be an effective technique to evaluate microvascularization, which is important because angiogenesis is the basis for neoplastic growth.

Second-generation contrast agents (SonoVue, Bracco Imaging, Milan, Italy) consists of sulfur hexafluoride microbubbles (2–10 μm), and it is injected intravenously as a small bolus from 1.2 to 4.8 mL followed by 5 mL saline flush. CEUS is performed using a high-frequency and low mechanical index (<0.10), as microbubbles burst at low ultrasound frequencies and at high mechanical index. The timer on the US machine is started during the CEUS process, and the images obtained during the next 2–3 min are digitally stored as raw data. Normally microbubbles last only 5–10 min in circulation [12].

CEUS evaluation has different applications in thyroid assessment, first of all CEUS is a promising noninvasive technique for the differential diagnosis of benign and malignant thyroid nodules (sensitivity 85–88%, specificity 88–90%) [12]. Hypoenhancement is considered to be a major CEUS pattern characteristic of malignant thyroid nodules, especially for thyroid tumors 10 mm or less in diameter. This finding is counterintuitive, because malignant tumors in other organs are well supplied by blood vessels. The main reason is that tumors grow with complex inner neovascularization; once the growth outweighs neovascularization, necrosis and embolus formation happens within the tumor, ultimately leading to hypoenhancement on CEUS [12]. Heterogeneous enhancement is another important CEUS pattern characteristic of malignant thyroid nodules, as blood vessels of malignant nodules are typically aberrant and tortuous. Moreover, most malignant nodules contain areas of fibrosis, calcification, or focal necrosis, which may explain the trend for heterogeneous enhancement. Wash in and wash out compared to surrounding parenchyma is another characteristic that needs further evaluation. Homogeneity and ring enhancement instead are the most two valuable CEUS indicators for predicting benignity [12].

Another potential role of CEUS is the ability to evaluate the ablated area compared to B-mode during or after percutaneous ultrasound-guided ablation techniques. CEUS, in fact, better enhances vascularized tissue, which helps to clarify boundaries between viable and nonviable tissue, during interventional procedures or after at follow up evaluation [13].

Finally, according to literature, CEUS may have a potential role in lymph nodes metastasis evaluation.

## 3.7 Parathyroid Glands and Lymphnodes

Four parathyroid glands are normally located posterior to the thyroid gland, two on each side (one superior and one inferior). Ectopic and supernumerary parathyroid glands can occur as well. The blood supply to the superior and inferior parathyroid glands comes from the inferior thyroidal artery in most patients, and tracing an enlarged inferior thyroidal branch is often of help in locating a parathyroid adenoma [4].

Parathyroid adenomas are typically uniformly hypoechoic relative to the thyroid gland and appear as well-circumscribed oval nodules. Large adenomas may assume a bilobed or lobulated configuration or develop internal cystic changes. When seen immediately adjacent to the thyroid, the curvilinear echogenic margin of the thyroid capsule should be appreciable and will help in localizing the nodule as external to the thyroid [4] Parathyroid adenomas are highly vascular lesions supplied by a prominent extrathyroidal feeding artery, usually the inferior thyroid artery. The feeding artery enters the adenoma at one pole along its long axis. The vascularity of an adenoma is peripheral in nature, encircling 90–270° of the gland; however, the internal vascular flow is variable [4]. Exophytic thyroid nodules can be mistaken for parathyroid lesions and rarely some parathyroid adenomas are located within the thyroid gland. If there is a suspicion for an intrathyroid parathyroid adenoma, samples from the FNA should also be sent for measurement of tissue parathyroid hormone levels, which will be diagnostic for parathyroid adenoma [4].

The ultrasound assessment of lymph nodes should comprehend bilateral laterocervical levels II, III, IV, V, and VI. Normal lymph nodes have oval shape with fatty center. Round shape, inner calcifications, loss of adipose center, markedly hypoechogenicity may reflect abnormal conditions and should be further investigated [4].

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# Chapter 4
# Overt Hyperthyroidism and Subclinical Hyperthyroidism: Who and How to Treat


**Renato Cozzi**

Several studies have shown an increased risk for cardiovascular disease in hyperthyroidism. Recent data issued from the Danish Civil Registration System and the Danish National Patient Registry obtained in 85,856 hyperthyroid patients were matched with 847,057 population-based controls and showed that the HR for mortality was highest in the first 3 months after the diagnosis of hyperthyroidism (HR 4.62, 95% CI: 4.40–4.85) and remained elevated during long-term follow-up (>3 years) (HR 1.35, 95% CI: 1.33–1.37). The risk for all examined cardiovascular events was increased with the highest risk in the first 3 months after hyperthyroidism diagnosis. The 3-month post-diagnosis risk was highest for atrial fibrillation (AF) and arterial embolism, but the risks of venous thromboembolism, acute myocardial infarction, nonischemic stroke, and percutaneous coronary intervention were also increased two- to threefold.

## 4.1 Hyperthyroidism

In hyperthyroid states, thyrotoxicosis without hyperthyroidism (i.e., clinical conditions with high plasma thyroid hormone levels, such as silent thyroiditis, postpartum thyroiditis, subacute thyroiditis, iatrogenic, factitia, without hyperthyroidism) has to be distinguished from thyrotoxicosis with hyperthyroidism (in which thyroid hormones in excess are directly synthetized by the thyroid gland).

The prevalence of hyperthyroidism in the USA is 1.2% of the population (0.5% overt, 0.7% subclinical). The commonest causes of thyrotoxicosis with hyperthyroidism are Graves' disease (GD), multinodular toxic goiter, toxic adenoma, and inappropriate TSH secretion (or TSHoma).

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### *4.1.1 Diagnosis*

The first step is the evaluation of the degree of thyrotoxicosis. TSH value has the highest sensitivity and specificity among the examinations of thyroid function and can be used to screen hyperthyroid patients from those who are not, but to establish the degree of hyperthyroidism FT4 as well as FT3 have to be assessed. Usually T3 and T4 hypersecretion is equimolar; in some patients, T3 hypersecretion is prevalent, and in these cases, the clinical picture is more severe (T3 toxicosis).

### *4.1.2 Treatment*

Therapeutic options are antithyroid drugs (ATD), surgery, and radioiodine. The preference of therapeutic strategy depends on clinical picture, endocrinologist's and patient's preference, geographical area.

#### 4.1.2.1 GD

ATD

The aim of ATD treatment is to restore patients rapidly to euthyroidism, by reducing thyroid hormone synthesis. The available drugs are thiamazole (methimazole), propylthiouracil (PTU), and carbimazole. They exert their effect similarly, by inhibiting the oxidation and organification of iodine, blocking TPO and the synthesis of T3 and T4 by inhibiting the coupling of iodine and tyrosine. Anti-inflammatory and immunosuppressive effects have been shown as adjunctive effects. PTU at the highest doses reduces the conversion of T4 to T3 in the peripheral tissues.

The first-choice antithyroid drug is thiamazole: it has a greater efficacy and a longer half-life (it can be administered once or twice daily, at variance with the shortest half-life of PTU, that has to be given three times daily). Its toxicity is low, in contrast to PTU fatal liver toxicity that may require acute liver transplantation. Contraindications in the use of thiamazole are at the first trimester of pregnancy, side effects in patients refusing surgery or radioiodine, and thyroid storm, in which the rapidity of the onset of action of PTU is preferred.

*ATD and Side Effects*

Agranulocytosis, liver toxicity, and vasculitis can be induces by ATD.

1. Agranulocytosis: The patient complains of fever and sore-ache, at the beginning of ATD treatment (first 2–3 months). It is more frequent with PTU (0.27%) than with thiamazole (0.11%) and in some cases (4%) may be fatal. Agranulocitosis has a crossed reactivity, so ATD cannot be switched between themselves; it may

be dose-related, and lowering the dosage or using the lowest dose may improve the clinical picture.
2. Liver toxicity is rare (0.03%). High transaminase levels have not to be confused with ATD-induced liver toxicity since transaminase levels are frequently increased in patients with hyperthyroidism, and this finding does not contraindicate the use of ATD. Thiamazole may induce a slight cholestatic hepatitis, whereas PTU may determine a fulminant liver necrosis, requiring liver transplantation. ATD has to be withdrawn if transaminase level becomes threefold higher than ULNR.
3. Vasculitis is rare and involves mainly Asian patients.

#### 4.1.2.2 Choice of Treatment

The choice of treatment depends on clinical presentation and thyroid physical examination.

ATD

ATD should be used in patients with high probability of remission (mild hyperthyroidism, small goiter, slight TRAb increase), during pregnancy, in older patients, in patients with comorbidities which lessen life expectancy, in patients who already underwent surgery or neck irradiation, or who have a mild Graves' ophthalmopathy (GO) or when a rapid control of hyperthyroidism is required. Their contraindication is the appearance of serious side effects.

Radioiodine

Radioiodine treatment is suggested in female patients desiring pregnancy in the next future, when comorbidities which determine an operatory risk increase are present, in patients already undergone to thyroid surgery or neck irradiation, in cases in which a skillful thyroid surgeon is missing, in ATD intolerance or contraindication, in those patients where ATD are unable to reach a stable control of hyperthyroidism, in its recurrences. Radioiodine is contraindicated during pregnancy or breast feeding, when pregnancy is planned at short term and in patients with poor therapeutic compliance.

Surgery

Surgery is indicated in patients with large goiter and severe hyperthyroidism, severe GO, female patients with active disease desiring to plan pregnancy at short term, in medical treatment resistance patients with amiodarone-induced thyrotoxicosis in

whom the persistence of severe hyperthyroidism may deteriorate clinical conditions (severe arrhythmias, intractable congestive heart failure) or according to patient's preference.

Overview

In Italy and in Europe, ATD are the most preferred option (nearly 80% of patients) followed by radioiodine (less than 20%) and surgery (the remaining). This strategy is at variance with the choices in the USA, where therapeutic options are equally subdivided between ATD (50%) and radioiodine (48%), whereas the percentage of surgically treated patients is close to zero. The reason of this different therapeutical behavior is that the prevalence of large goiters in the USA is lower, and the concern of causing permanent surgical complications (recurrent palsy, hypoparathyroidism) restrains the use of the surgical approach in the USA.

## 4.2 Multinodular Toxic Goiter (MTG): Toxic Adenoma

Therapeutic options include radioiodine or surgery. In some cases, a long-term ATD treatment is appropriate.

1. In MTG, radioiodine induces hyperthyroidism remission in 50–60% of cases after 3 months and in 80% at 6 months. In 20% of patients, a second radioiodine treatment is needed. The risk of developing hypothyroidism is 4% after 1 year, 16% after 5 years, and 64% after 24 years. Radioiodine relieves compressive symptoms in 46% of patients. In toxic adenoma, radioiodine normalizes thyroid function in 75% of patients after 3 months and in 89% after 12 months.
2. Surgery is indicated in large goiter with or without compressive symptoms, when thyroid tumor is suspected and when a rapid correction of hyperthyroidism is indicated. Euthyroidism must be restored by ATD before surgery. Total or near total thyroidectomy is indicated in MTG, whereas emithyroidectomy plus istmectomy is the choice in toxic adenoma.

## 4.3 Thyrotoxic Storm

Thyrotoxic storm is a severe complication of hyperthyroidism, and its diagnosis is clinical. Clinical picture includes fever, agitation, psychosis, tachycardia, arrhythmias, congestive heart failure, nausea, vomiting, diarrhea, jaundice, liver failure.

Its grading scale is evaluated by the Burch and Wartofsky score (Table 4.1).

Precipitating factors are abrupt withdrawal of ATD treatment, thyroidectomy or any other surgery without previous normalization of hyperthyroidism, intercurrent acute extra-thyroidal diseases, previous radioiodine treatment (actinic thyroiditis) without adequate ATD pretreatment.

**Table 4.1** Point scale for the diagnosis of thyroid storm

| Burch & Wartofsky Score | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Grading scale of thyroid storm severity* | | | | | | | | | | | |
| <25—unlikely to represent storm | | | | 25–44—suggests impending storm | | | | >45—highly suggestive of storm | | | |
| Temp | | CNS | | GI/liver | | HR | | Heart failure | | Precipitant | |
| 99–99.9 | 5 pts | Agitation | 10 pts | N/V/D | 10 pts | 99–109 | 5 pts | Pedal edema | 5 pts | Negative | 0 pts |
| 100–100.9 | 10 pts | Delirium | 20 pts | Jaundice | 20 pts | 110–119 | 10 pts | Rales | 10 pts | Positive | 10 pts |
| 101–101.9 | 15 pts | Seizure/ coma | 30 pts | | | 120–129 | 15 pts | Atrial Fib | 15 pts | | |
| 102–102.9 | 20 pts | | | | | 130–139 | 20 pts | | | | |
| 103–103.9 | 25 pts | | | | | >140 | 25 pts | | | | |
| >104.0 | 30 pts | | | | | | | | | | |

Scores totaled >45: thyroid storm; 25–44 impending storm; <25 storm unlikely

Treatment of thyrotoxic storm is based on PTU (its faster action and block of T4 toT3 conversion), propranolol, corticosteroids, potassium iodide, antipyretic drugs and cooling, hydration, nutritional support, and respiratory measurement in ICU.

## 4.4 Hyperthyroidism and GO

Fast normalization of hyperthyroidism and a stable control of hormonal levels are required. Risk factors such as smoking should be eliminated. In mild cases, ATD and methylprednisolone bolus treatment plus radioiodine are the choice options. In most severe cases, radioiodine is contraindicated and surgery has its main indication, obtaining rapidly a marked improvement of GO.

Therapeutic strategies for GO are variable throughout western endocrinologists: in Italy surgery and steroid boluses followed by radioiodine are the preferred options.

## 4.5 Amiodarone-Induced Thyrotoxicosis (AIT)

Patients treated with amiodarone may develop thyrotoxicosis. It occurs in 6% of patients in iodine-sufficient areas and up to 10% in areas with endemic lack of iodine. In some cases, the development of hyperthyroidism may occur in 12 months after amiodarone withdrawal. In AIT, amiodarone should be withdrawn and replaced by another antiarrhythmic agent. Amiodarone withdrawal may be followed by a

paradoxical increase of thyroid hormone levels, with worsening of hyperthyroidism. The pathogenesis of thyrotoxicosis depends on the high amount of iodine in amiodarone tablets (AIT type 1) and to its direct toxicity on follicular cells (AIT type 2), that causes a disruptive thyroiditis. In AIT type 1, high doses of ATD (plus sodium perchlorate) should be used, in type 2 only steroids. However, the distinction between type 1 and type 2 forms is not always so clear, so both ATD and steroids can be used together. In refractory forms, surgery is indicated.

## 4.6 Hyperthyroidism and Pregnancy

Diagnosis of hyperthyroidism requires the assessment of not only TSH but also FT3 and FT4, since in the first trimester of pregnancy, TSH is often below the range of normal value due to the high placental βHCG levels that directly stimulate thyroid function. As a consequence, values of thyroid hormones may be in the upper range of normal value or slightly elevated. TRAb is negative and clinical symptoms are missing. This clinical picture does not require any treatment and remits spontaneously after the third trimester. When hyperthyroidism is present before pregnancy, normalization of thyroid hormones has to be reached before pregnancy, and the therapeutical option depends on clinical presentation of hyperthyroidism. In most severe cases, a definite treatment (surgery or radioiodine) for hyperthyroidism should be pursued. In hyperthyroidism during pregnancy, ATD can be used, keeping in mind that both thiamazole and PTU possess a slight teratogenic effect (thiamazole > PTU). In the first trimester, ATD treatment must be shifted to PTU, in the second trimester, it can be shifted again to thiamazole. Treatment should pursue slightly elevated FT3 and FT4 levels using the minimal effective ATD dose, to avoid the development of goiter in fetus, and TSH remains suppressed. In most cases, hyperthyroidism spontaneously remits during pregnancy and recurs after delivery. During breast feeding, thiamazole is allowed.

After delivery, thyroid disfunctions develop in several patients (10% in the USA). Postpartum thyroiditis is an autoimmune disease that develops in the first trimester after delivery mainly in patients with high TPO titers. The typical form has a triphasic course, beginning with hyperthyroidism 1–6 months after delivery, followed by hypothyroidism and finally euthyroidism is restored. Many patients (43%) develop hypothyroidism without hyperthyroid phase, 32% develops thyrotoxicosis without reaching hypothyroidism. TRAb remains negative. Thyroid ultrasound may be diagnostic. Propranolol is the only treatment to be used in the hyperthyroid phase.

### *4.6.1 Subclinical Hyperthyroidism (SH)*

In this condition, TSH levels are below the normal range and FT3 and FT4 levels are normal. In the USA and in Europe, the prevalence of patients with TSH < 0.1 mU/ml not suffering from thyroid disease is close to 0.7% and with TSH < 0.4 mU/ml

is 1.8%. In 12 months, overt hyperthyroidism develops in 0.5–0.7% of these, whereas normal values are reached in 5–12%. The most frequent causes of SH are multinodular goiter, mainly in older patients, and Graves' disease in the younger, toxic adenoma and thyroiditis, in which SH is transient. SH is associated with an increase of cardiovascular risk, heart failure, and atrial fibrillation. SH may worsen the risk of fractures in osteoporotic women.

The normalization of TSH levels is recommended in patients with persistent SH older than 65 years, in those with cardiovascular risk factors or osteoporosis, in post-menopausal women, and in symptomatic patients. Treatment option should be issued considering basal thyroid disease, cardiovascular risk, comorbidities, the risk of thyroid neoplasm in large goiter, and the age of patients.

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# Chapter 5
# Minimally Invasive Treatments of Benign Thyroid Nodules: Techniques and Results


**F. Ferrari, L. M. Sconfienza, L. Nicosia, and G. Mauri**

## 5.1 Background

Benign thyroid nodules are frequently found incidentally in the general population, by palpation or clinical examination in 4–8% [1], by ultrasonography in 10–40% [2], and in 50% by autopsy [3].

In the majority of cases, thyroid nodules are benign and asymptomatic, no treatment is required and, according to current guidelines, should be only followed clinically [4].

However, when thyroid nodules grow in size, they can lead to the onset of symptoms (dysphagia, dysphonia) or some esthetic concerns. In these cases, a treatment may be necessary. Until recently, the first-line treatment for benign thyroid nodules has been surgery, even though it is invasive and with some drawbacks [5].

In order to spare thyroidectomy, more and more frequently, benign thyroid nodules are now treated by image-guided minimally invasive treatments.

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Image-guided ablation procedures have been used since the 1980s for ablation of many tumor types in different organ systems, have rapidly expanded in the 1990s, and are nowadays not only considered feasible but also recommended for several diseases [6, 7]. Since their born, these techniques have been introduced in the treatment guidelines for tumors of the liver [8], kidney [9], and bone, but also prostate, breast, and lung.

In the thyroid, the first thermoablative treatments were performed in the 2000s: Pacella et al. [10] used laser ablation (LA) in two volunteers with huge autonomously functioning nodules in 2000, and Kim et al. [11] used radiofrequency ablation (RFA) for ablating 35 benign cold thyroid nodules in 30 euthyroid patients in 2006 (Fig. 5.1).

In this chapter, an overview of the different available ablative techniques will be provided, with a particular focus on indications to treatment and clinical results.

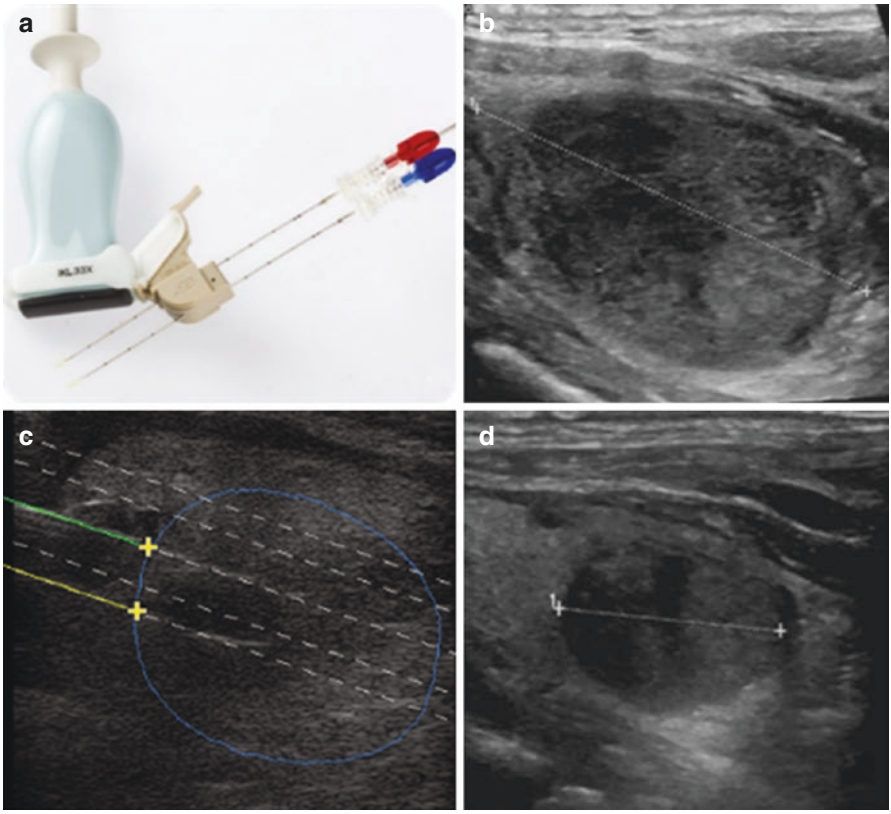


**Fig. 5.1** Laser ablation of benign thyroid nodule. (**a**) Optical fibers in ultrasound guidance device (21G), (**b**) benign thyroid nodule pretreatment, (**c**) placement of optical fibers using dedicated simulation software, (**d**) thyroid nodule reduction of 85% after 1 year from treatment

## 5.2 Indications

Already in 2009, the Korean Society of Thyroid Radiology (KSThR) had included some preliminary recommendations for thyroid RFA [12], focusing on indications and efficacy in the treatment of thyroid nodules.

Since then, with the emergence of new evidence from clinical trials, these recommendations have been progressively revised.

In a 2016 revision, the Korean Society of Radiology set the indication to local ablative thermal treatment as a first-line treatment for benign thyroid nodules that cause symptoms or esthetic concerns, as an alternative to surgery or radioiodine therapy [13].

The same recommendations for the use in clinical practice of minimally invasive thermoablation treatments have been achieved in Europe, with the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) on interventional ultrasound (INVUS)-guided procedures. More recently, in 2018, the Italian Minimally Invasive Treatment Thyroid (MITT) Group, based on literature review and consensus opinion of interdisciplinary experts, proposed thermoablation treatments as first-line treatments for solid nonfunctioning thyroid nodules that are benign at cytology when they become symptomatic and for nonfunctioning benign multinodular goiter only in patients who refuse or who cannot undergo surgery [14].

Recently, the guidelines have opened up the possibility to use thermoablative treatments also in autonomously functioning thyroid nodule (AFTN) in patients who refuse or cannot undergo traditional treatments with radioiodine or surgery or when the preservation of normal thyroid tissue function is a priority, and it is reasonable to expect at least 80% nodule volume ablation [15].

In any case, nodules need to be cytologically proven benign with at least two samples before being ablated. A single cytological sample can be considered adequate to confirm nodule benignity if the US appearance is at low risk of malignancy.

In 2020, the European Thyroid Association published a Clinical Practice Guideline for the use of image-guided ablation in benign thyroid nodules that offers a list of recommendations for a state-of-the-art use of thermal ablation in the management of benign thyroid lesions [16].

## 5.3 Techniques

The objective of thermal ablation is to induce irreversible cell injury and ultimately tumor apoptosis and coagulative necrosis by the application of high temperatures. Heat can be generated from a variety of sources, including radiofrequency (RF), microwave (MW), laser, high-intensity focused ultrasound (HIFU). The most commonly used techniques in the treatment of benign thyroid nodules are laser and radiofrequency.

RF ablation (RFA) is achieved by using 18–19G cooled electrodes, which from the nonisolated tips emit high-frequency alternating current into the surrounding tissue.

The tissue ions attempt to follow the change in direction of the alternating current, creating ionic agitation and then heating by friction to obtain thermal coagulation and denaturation of proteins.

Laser technology is based on the precise focal application of a laser light through optical fibers, from 1 to 4, with 0.3 mm in diameter, inserted by means of a 21G introducer needle, to achieve a local temperature increase and cell coagulative necrosis [17]. Several laser types have been evaluated and used for thermal ablation: the Nd:YAG laser (1064 nm), semiconductor diode laser (805 nm), and argon laser (488 and 514 nm).

The laser fiber, compared to the needle electrode of RFA (especially the umbrella-shaped one), is smaller and less traumatic, and so this technique hold the potential of allowing the treatment even in small nodules located in difficult or risky position for the RFA with minimal damage to adjacent structures [18, 19].

MW technology is based on the application of an electromagnetic wave (915–2450 MHz) through a 14–16G antenna placed directly into the target lesion. This wave causes oscillating electrical charge that, because of interaction with water molecules, causes the electrical charge of the molecules to flip back and forth. Movements of the water molecules produce temperature rise and thermal damage to the cells. Besides, it has been demonstrated that modern microwave ablation (MWA) devices are able to heat continuously at a faster rate to generate greater temperatures than RF ablation systems [20]. Increased heating rates and internal temperatures overcome vascular perfusion more effectively and generate a larger area of necrosis. MWA operates independently of any electrical current convection and is not limited by tissue impedance, due to water vaporization at high temperatures, or by the presence of adjacent high-flow vascular structures (heat-sink effects).

Finally, high-intensity focused ultrasound (HIFU) ablation is based on the application of US energy at high intensity, focused in a small volume where it determines a mechanical effect (cavitation) and an increase in temperature, with a consequent cell death.

The HIFU technique has the particularity of being the only true source of extracorporeal energy able to hit the lesion without damaging the overlying tissue.

All of these techniques are performed under local anesthesia and in some cases mild conscious sedation, in an outpatient setting.

Thanks to these characteristics, image-guided thermal ablations offer the possibility of being a minimally invasive treatment with low morbidity, low costs and time of intervention and postoperative hospitalization, and have also the ability to be feasible in patients who are not candidates for surgery due to the presence of comorbidities (advanced age, end-stage renal disease, etc.) or anatomical limitations.

## 5.4 Clinical Applications

In the multicenter prospective randomized trial conducted by Papini et al. [21], 200 nodules were randomized to percutaneous laser ablation (PLA) or follow-up.

Entry criteria were: solid thyroid nodule with volume of 6–17 mL, repeat benign cytological findings, normal thyroid function, no autoimmunity, and no thyroid gland treatment.

Nodule volume and local symptoms changes were evaluated at 1, 6, 12, 24, and 36 months, and it has been observed a progressive volume reduction after PLA until 12 months that remains stable until 3 years and a slow enlargement of untreated nodules in the absence of thyroid function changes.

The efficacy and safety of thermal ablative treatments, particularly of RFA, has also recently been confirmed by Jung et al.'s prospective multicenter study [22].

A total of 276 benign thyroid nodules, with a mean volume of 14.2 ± 13.2 mL, were ablated by trained radiologists using unified protocol: after 12 months, the mean volume reduction was 80.3%, even greater in the following months (36-month follow-up 89.2%), therapeutic success was obtained in 97.8% cases, mean symptom and cosmetic scores showed significant improvements ($p < 0.001$), and the rate of major complications (transient voice change, hyperthyroidism) was 1.0%.

In confirmation of the latter data, two multicenter studies have shown in particular that these treatments are well tolerated and the risk of major complications is very low.

In 2012 Baek et al. [23], in their retrospective multicentric analysis, evaluated clinical aspects and imaging features of complications encountered in 1459 patients underwent to treatment of benign thyroid nodules with radiofrequency (RF) ablation.

Forty-eight patients experienced complications (3.3%), of which 20 were major and 28 minor.

In particular major complications such as voice change, nodule rupture with or without abscess formation, hypothyroidism, or brachial plexus injury and minor complications such as hematoma, vomiting, or skin burn were considered.

The other multicenter study was performed in Italy in 2015 by Pacella et al. [24] on clinical records of 1534 consecutive laser-treated nodules.

In this study, the efficacy of the treatment, with a mean volume reduction of 72% ±11 (volume decrease from 27 ± 24 ml to 8 ± 8 ml ($p < 0.001$)) of the nodule treated, was confirmed. Seventeen complications (0.9%) were registered: eight patients (0.5%) with transitory voice changes and nine minor complications (0.5%) such as subcapsular or perithyroidal hematoma and skin burn.

Besides, 30.2% of patients experienced side effects, such as mild and moderate burning pain, with sensation of local heat, sometimes radiated; in all cases, these side effects lasted a few seconds and disappeared as soon as the laser was switched off.

Confirming their safety, it should be noted that ablative treatments are able to preserve the thyroid function without significant percentages of hypothyroidism [25].

There is still debate regarding which technique could achieve better results. In some studies, trying to compare directly the two techniques, no significant differences were seen, with some variability due to the experience of the operator performing the procedure. Thus, probably, when performed by operators with the same experience, laser and RFA can achieve the same clinical results [26].

Proper targeting of nodules in close proximity to vital structures such as neck vessels, trachea, and laryngeal nerve requires a good manual skill in placing the devices correctly in an anatomical region as small as the neck.

Mauri et al. [18] have, in fact, preliminarily demonstrated that RFA and PLA are similarly feasible, safe, and effective in treating benign thyroid nodules when performed by the same equipment.

Comparing the 59 patients who underwent RFA with the 31 patients who underwent PLA, no difference was found between the two techniques in time course of the relative volume reduction: in particular, it has been observed a % relative reduction at 6 and 12 months of 60 ± 15% and 70 ± 16% in PLA group and 64 ± 14% and 74 ± 14% in RFA group.

Technical success was always obtained, and no major complications occurred.

Though, it has been noticed that RFA is faster than PLA but requires significantly higher energy.

Then Pacella et al. [18], in a multicenter retrospective analysis with matched cohort composed of 138 patients from each group (RFA vs. PLA) selected after adjustment with propensity score matching, confirmed that PLA and RFA had nearly similar outcome, but PLA was slightly more effective than RFA in large nodules.

Mean percentage volume reduction was of −59 ± 18% and −63 ± 18% at 6 and 12 months, for small and medium nodules; in nodules >30 mL PLA, there was significantly higher percentage volume reduction at 6 and 12 months (−69 ± 19 vs. −50 ± 21, $p = 0.001$ and −73 ± 18 vs. −54 ± 23 8, $p = 0.001$) in the LA group than in the RFA group, respectively.

This could be explained by the difference execution technique: multiple optic fibers for PLA can be simultaneously inserted in the nodule and moved during the procedures with more "pull back" the bigger the nodule is, with a more homogeneous distribution of heat energy in the target area and thus with greater treatment efficacy. Moreover, with the trans-isthmic approach of RFA, it might be more difficult to treat the deeper part of large nodules, which can be conversely easily reached by a direct puncture of the nodule on its long axis like in PLA.

No differences in major complications rate was observed, but there was higher rate of hematoma in RFA group (4.5% vs. 0.9% in PLA group): in fact, the needle electrode of RFA (especially the umbrella-shaped one) is bigger and more traumatic compared to the laser fiber.

More recently, Bernardi et al. [27], in a multicenter retrospective study, have evaluated the rates of not only technique efficacy but also regrowth and retreatment

in 406 patients treated with either RFA or PLA, and followed for 5 years after initial treatment.

Both thermal ablation techniques result in a clinically significant and long-lasting volume reduction of benign thyroid nodules.

They confirmed that both RFA and LA have a good efficacy: a reduction of 50% after 1 year from the treatment was achieved in 85% of patients in the RFA group and in 63% of patients in the PLA group.

The risk of regrowth (20% in the RFA and 38% in the PLA group) and needing retreatment was lower after RFA (12% in the RFA and 24% in the LA group). The need for retreatment was associated with young age, large baseline volume, and treatment with low-energy delivery.

Given these percentage of efficacy and safety, it is clear that percutaneous ablative treatments have become more and more suitable today than surgery in the treatment of benign diseases.

Che et al. [28] have compared two groups of 200 patients with nodular goiters each treated with surgery or by radiofrequency ablation in terms of efficacy, safety, and cost-effectiveness during a 1-year follow-up (Fig. 5.2).

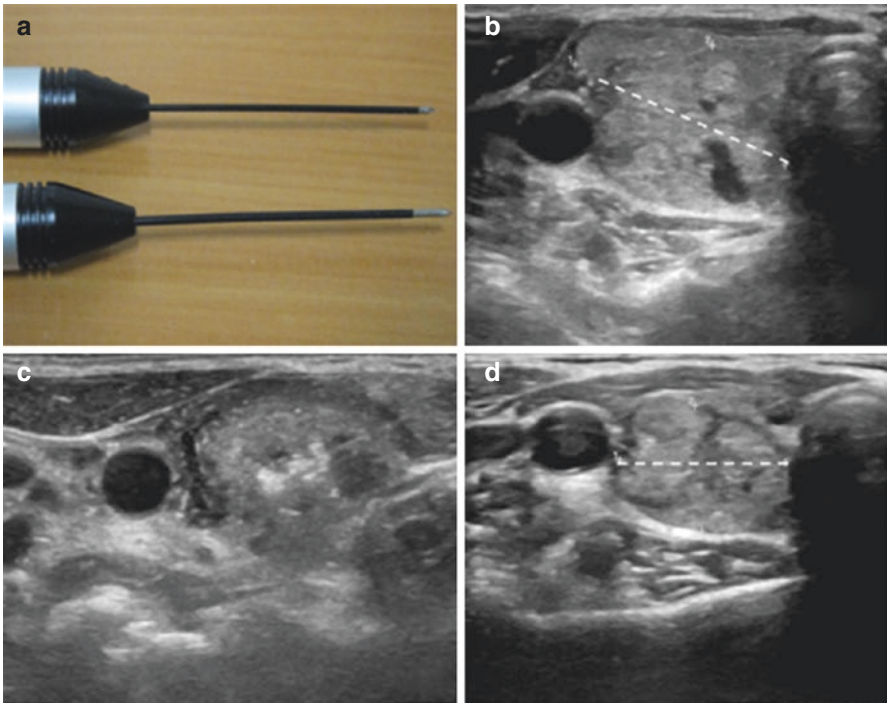


**Fig. 5.2** Radiofrequency ablation. (**a**) Internally cooled electrode (14G), (**b**) benign thyroid nodule pretreatment, (**c**) needle in the nodules during thermal ablation with gas production, (**d**) thyroid nodule reduction of 73% after 1 year from treatment

For equal effectiveness in nodule volume decreased, RFA had, versus surgery, minor rate of residual nodules (2.9% vs. 11.9%, $P = 0.004$), fewer complications (1.0% vs. 6.0%, $P = 0.002$), preservation of thyroid function, and fewer hospitalization days (2.1 vs. 6.6 days, $P = 0.001$), but the cost difference was not significant.

A different data emerges instead from the retrospective study of Bernardi et al. [29] in which 37 patients who underwent RFA were retrospectively compared to 74 patients surgically treated.

In this study, RFA has a significantly reduced cost than surgery (€1661.50 vs. €4556.30); besides, both RFA and surgery were safe, although RFA had less complications and pain was rare.

They had similar effectiveness, with no effect on thyroid function in euthyroid patients, but surgery had best results for the treatment of hot nodules: surgery had normalized TSH in 100% of the patients with hot nodules while hyperthyroidism was completely resolved only in 33% of patients underwent RFA.

This is consistent with what has already been reported by Deandrea et al. [30] and Faggiano et al. [31], who showed that hyperfunction was fully controlled respectively in 24% and 40% of patients with hot nodules at 6 and 12 months after RFA.

Therefore, due to its proven efficacy, safety, low incidence of complications, and good preservation of thyroid function, radiofrequency ablation should be considered a first-line treatment for benign thyroid nodules.

Less results are found in the literature regarding the use of MWA and HIFU in the treatment of thyroid nodules because of their recent introduction into clinical practice.

Korkusuz et al. [32] compared volume reduction of 118 benign thyroid nodules 3 months after RFA, MWA, or HIFU. MWA and HIFU showed results comparable to RFA in reducing nodule volume and were equally effective and safe, without major complications.

The effectiveness and safety of ultrasound-guided microwave ablation in the treatment of benign thyroid nodules is also confirmed by Liu et al. [33] in their study based on 435 patients' experience.

Despite the limited number of studies, Lang and Wu [34] made a review about the HIFU treatment in benign thyroid nodules in 2017. From the analysis of five original articles, they showed that, just after single session of HIFU ablation, there was an overall nodule volume reduction ranged between 45% and 68%, depending on nodule size and length of follow-up; no major complications were reported in all of the studies. However, larger-scale, prospective trials with longer follow-up period are indeed required to confirm this.

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# Part II
# Obesity

# Chapter 6
# Obesity: Classification and Diagnosis


**Anna Ferrulli**

## 6.1 Introduction

Despite significant investments into researching obesity, obesity prevalence continues to rise at alarming rates worldwide [1], and the phenomenon is extremely complex. In order to counteract this situation, the obesity epidemic should be strategically tackled at the global level [2].

Several scientific societies agree in defining obesity as a chronic, relapsing disease, underlying pathological disfunctions, and having complications leading to morbidity and mortality. Therefore, the outdated classification of obesity according to the body mass index (BMI) measurement does not reflect the whole complexity of the disease [2]. In the last years, a great effort by the scientific societies has been performed to improve the diagnostic criteria for obesity, taking into account other dimensions such as the etiology, degree of adiposity, and health risks.

This chapter aims to propose an update on the diagnostic criteria of obesity and different classification typologies, reflecting disease pathophysiology and specific complications.

Furthermore, different phenotypes of individuals with obesity, reflecting the adiposity degree, the fat distribution, the genetic profile, etc. have been widely described in this chapter.

Although a globally accepted definition of obesity is still lacking, the different definitions and classifications highlight the heterogeneity of the disease and emphasize the need of a new approach for the cure of obesity [3]. A personalized approach

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based on a multidisciplinary assessment of the patient with obesity, and not only on BMI, should be strongly recommended.

## 6.2 Definition and Diagnosis of Obesity

### *6.2.1 Body Mass Index*

Obesity was defined as a disease by the American Association of Clinical Endocrinologists (AACE) in 2012, by the American Medical Association (AMA) in 2013, and subsequently, by multiple medical professional and national associations [4]. According to the definition of "disease," obesity meets the following essential criteria: (1) impairment of the normal functioning of some aspect of the body; (2) characteristic signs and symptoms; (3) complications that confer morbidity and mortality [5]. A more complete and inclusive definition of obesity has been provided.

A long-term energy imbalance between too many calories consumed and too few calories expended has been commonly identified as the fundamental cause of obesity. However, numerous other factors could affect the chronic positive energy balance in obesity: age, sex, genetics, neuroendocrine factors, gut microbiota, composition, concomitant medications, socio-cultural level, lack of knowledge, homeostatic hunger, uncontrolled eating, and emotional eating [6, 7].

The traditional definition of obesity is based on the BMI compute, a ratio between weight to the squared height ($Kg/m^2$) of a subject. This formula easily approximates body fat percentage and stratifies people into categories; it was developed about 200 years ago by Quetelet and represents an imprecise mathematical estimate [2, 8].

According to the BMI, general population is classified into five categories:

| | |
|---|---|
| BMI < 18.5 $kg/m^2$ | Underweight |
| BMI 18.5–24.9 $kg/m^2$ | Normal weight |
| BMI 25–29.9 $kg/m^2$ | Overweight |
| BMI 30–34.9 $kg/m^2$ | Class I obesity |
| BMI 35–39.9 $kg/m^2$ | Class II obesity |
| BMI > 39.9 $kg/m^2$ | Class III obesity (morbid obesity) |

The use of BMI for the diagnosis of obesity is even now widespread, due to its convenience, safety, and minimal cost, although BMI ignores several significant factors affecting adiposity, leading to a large error and misclassification [2]. Furthermore, the error in the diagnosis of obesity generates important effects on healthcare costs [2].

Except in persons who have increased lean weight as a result of intense exercise or resistance training (e.g., bodybuilders), BMI usually correlates with percentage of body fat, but this relationship is independently influenced by sex, age, and race

**Table 6.1** WHO classification of overweight and obesity (1998)

| | BMI (kg/m$^2$) | Obesity class | Disease risk | |
|---|---|---|---|---|
| | | | Men ≤ 102 cm; women ≤ 88 cm | Men > 102 cm; women > 88 cm |
| Underweight | <18.5 | | – | – |
| Normal | 18.5–24.9 | | – | – |
| Overweight | 25.0–29.9 | | Increased | High |
| Obesity | 30–34.9 | I | High | Very high |
| | 35–39.9 | II | Very high | Very high |
| Extreme obesity | ≥40 | III | Extremely high | Extremely high |

[9]. For example, in the South Asia population, the BMI-adjusted percent body fat is greater than other populations. In the United States, obesity is defined as a BMI of 27.3 kg/m$^2$ or more for women, and a BMI of 27.8 kg/m$^2$ or more for men. These definitions were based on the gender-specific 85th percentile values of BMI for persons 20–29 years of age. In children, obesity is defined as ≥95th percentile of BMI (overweight as ≥85th percentile) as a function of age and gender using CDC growth charts [10].

In 1998, however, the National Institutes of Health (NIH) Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults adopted the World Health Organization (WHO) classification for overweight and obesity [11, 12]. In this classification, waist circumference has been added as an additional parameter to define the risk of morbidity, in addition to BMI. According to the WHO classification, an increased risk for comorbid conditions (hypertension, type 2 diabetes mellitus, and cardiovascular disease) has been assigned to individuals with higher BMI compared to individuals with normal weight (BMI of 18.5–25 kg/m$^2$) (Table 6.1). This classification is characterized by a predominant applicability for the Caucasian population. For example, Asian populations are known to be at increased risk for diabetes and hypertension at lower BMI ranges than those for non-Asian groups due to predominance of central fat distribution. Consequently, the WHO has suggested lower cutoff points for consideration of therapeutic intervention in Asians: a BMI of 18.5–23 kg/m$^2$ represents acceptable risk, 23–27.5 kg/m$^2$ confers increased risk, and 27.5 kg/m$^2$ or higher represents high risk [11, 13]. According to the WHO classification, an increased waist circumference can also be a marker for increased risk even in persons with normal body weight.

### *6.2.2 Adiposity*

Nowadays, the whole scientific community has recognized that the BMI cannot be the only tool for diagnosing and classifying obesity. In fact, obesity is a remarkably heterogeneous condition with varying cardiovascular and metabolic manifestations across individuals, which may be different depending on gender and age [14, 15]. In 2017, a more complete and inclusive definition of obesity has been provided by the

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) in a position statement; in fact, it was defined as an adiposity-based chronic disease (ABCD) [16].

Adipose tissue is an extraordinarily dynamic, metabolically active organ involved in multiple biological processes. In humans, two principal types of adipose tissue can be recognized: the brown adipose tissue (BAT), localized in supraclavicular and paravertebral regions, and the white adipose tissue (WAT). The latter includes subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) surrounding abdominal organs [3]. A significant association between the excess of fat deposition in VAT and in deep SAT and an increased mortality and morbidity risk has been demonstrated [17, 18].

A pathological expansion of fat mass and/or unhealthy distribution of body fat could induce dysfunctions of adipose tissue, leading in turn to cardiometabolic complications such as dyslipidemia, insulin resistance, hypertension, atherosclerosis, and adverse cardiac remodeling [15, 19, 20]. Although it is well known that visceral/ectopic fat accumulation represents the major contributor to cardiometabolic risk above and beyond the BMI, fat distribution assessment into clinical practice remains crucial for an initial screening. For this reason, the European Association for the Study of Obesity (EASO) has recently argued that the simple measure BMI should continue to be used within International Classification of Diseases (ICD)-11, associated with a deeper assessment and classification of obesity typology [2].

## 6.3 Classification of Obesity

Based on the size and distribution of adipose tissue, four different phenotypes of obesity could be identified.

### *6.3.1 The Metabolically Unhealthy Obesity (MUO)*

Individuals with BMI $\geq$ 30 kg/m$^2$, body fat percentage > 30%, and high visceral fat mass, associated with metabolic syndrome, type 2 diabetes, and atherosclerotic cardiovascular diseases, are defined as suffering from MUO [21]. Insulin resistance and abdominal obesity play a crucial role in the pathophysiology underlying the development of unhealthy obesity. The term "insulin resistance" usually indicates resistance to the effects of insulin on glucose uptake, metabolism, or storage. In obesity and type 2 diabetes, a decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle, and an impaired suppression of hepatic glucose output have been observed [22]. These functional defects may be due to an impaired insulin signaling in all three target tissues and, in adipocytes, to a downregulation of the major insulin-responsive glucose transporter, GLUT4. Moreover, in both muscle and adipocytes, insulin binding to its receptor, receptor

phosphorylation and tyrosine kinase activity, and phosphorylation of insulin receptor substrates (IRSs) are reduced. Advances over the last decade have expanded our understanding in the role of adipocytes in the development of insulin resistance. A wide variety of molecules including hormones such as leptin, cytokines (e.g., TNF-α) and substrates (e.g., fat-free acids) have been released from the adipose tissue and have been involved in the regulation of energy balance and glucose homeostasis, suggesting a crucial role of the adipose organ in affecting insulin sensitivity and secretion, through cellular and molecular mechanisms [21].

Studying hormonal differences after an oral glucose tolerance and assessing an impaired glucose homeostasis test may be useful to identify individuals with propensity for a MUO phenotype [23]. Higher plasma glucose-dependent insulinotropic polypeptide, lower postglucose load glucagone-like-peptide-1 (GLP-1), and higher levels at baseline and after glucose load have been reported in individuals with MUO, suggesting a deficiency in glucagon suppression, as one of the possible underlying mechanisms [24]. Compared to subjects with metabolically healthy obesity (MHO), MUO individuals show a decreased adipose tissue expression of genes involved in glucose uptake and lipogenesis. Furthermore, the subjects had an omental adipocyte size greater than MHO, while subcutaneous adipocyte size was related to metabolic health, and possibly progression from hepatic steatosis to fibrosis [21]. Liver, muscle, and adipose tissue insulin action has been foud to be directly related to intrahepatic triglyceride (IHTG) content in individuals with obesity [25], specifically the progressive increase in IHTG content is associated with progressive impairment of insulin action in liver, skeletal muscle, and adipose tissue, therefore the assessment of IHGT could be useful to establish to entity of metabolic dysfunction in obesity [25].

In MUO subjects, increased blood pressure, plasma triglyceride levels, very low density lipoprotein (VLDL) apoB100 concentrations, VLDL apoB100 secretion rates, and decreased plasma adiponectin concentrations, insulin sensitivity in the liver, skeletal muscle, and adipose tissues account for an increased risk for cardiovascular diseases [21].

### *6.3.2 The Metabolically Healthy Obesity (MHO)*

Despite the high BMI, individuals with MHO exhibit a healthy metabolic profile, characterized by high insulin sensitivity, favorable lipid profile and low pro-inflammatory cytokine levels in plasma and adipose tissue [26]. Establishing whether an individual with obesity can be defined "metabolically healthy" is not easy; in fact, more than 30 different definitions have been used in different studies. In most cases, MHO was defined as having ≤2 of the following five metabolic syndrome criteria: high systolic and diastolic blood pressures, high plasma triglycerides concentration, low HDL-C concentration, high fasting blood glucose, and a large waist circumference (>102 cm for men; >88 cm for women); or ≤1 abnormal component excluding waist circumference [27]. Additional criteria, including high plasma total cholesterol, LDL-cholesterol, and C-reactive protein concentrations,

**Table 6.2** Proposed criteria for the diagnosis of metabolically healthy obesity (MHO)

| | |
|---|---|
| Basic criteria | |
| Absence of diagnosis or therapy for cardiometabolic diseases | Absence of prediabetes, T2D, hypertension, dyslipidemia, NAFLD, CKD, or CVD; or treatment with blood pressure, lipid, or diabetes medications |
| Healthy cardiometabolic profile | |
| Fasting triglycerides | <95 mg/dL |
| HDL-C | ≥40 mg/dL in men and ≥50 mg/dL in women |
| Fasting glucose | <100 mg/dL |
| 2-h OGTT glucose | <140 mg/dL |
| Blood pressure | <130/85 mmHg |
| Advanced criteria | |
| Intrahepatic lipid content (for those not having NAFLD diagnosis) | <5% of liver volume by imaging or<br><5% of hepatocytes with intracellular triglycerides by histology |
| Insulin sensitivity | GIR >8 mg/kg FFM/min during an HECP (insulin infusion rate: 40 mU/m$^2$/min) |

*CKD* chronic kidney disease, *CVD* cardiovascular disease, *FFM* fat-free mass, *GIR* glucose infusion rate, *NAFLD* nonalcoholic fatty liver disease, *HECP* hyperinsulinemic-euglycemic clamp procedure, *OGTT* oral glucose tolerance test, *T2D* type 2 diabetes

2-h blood glucose concentrations during an oral glucose tolerance test, and indices of insulin sensitivity/resistance [based on: the homeostasis model assessment of insulin resistance (HOMA-IR) score, the Matsuda index (an index of whole-body insulin sensitivity), the glucose infusion rate during a hyperinsulinemic-euglycemic clamp procedure, and the insulin suppression test] have also been used to determine MHO [28].

In order to avoid that people who are reported as having MHO are often not truly healthy, recently, Smith et al. [28] proposed more rigorous criteria, based on (a) the absence of cardiometabolic diseases, (b) a healthy cardiometabolic blood profile, (c) the absence of advanced criteria, such as normal insulin sensitivity and normal intrahepatic lipid content (Table 6.2).

The prevalence of MHO is extremely variable due to the different criteria used to define metabolic health, and ranges from 6% to 60% of adults with obesity [29, 30]. In general, MHO is more common in women than in men, in younger than in older adults, in people with BMI < 35 kg/m$^2$ than in people with BMI of 35 kg/m$^2$ or higher, and in the European population than in those from Africa, South America, and South Asia (Indian ancestry) [28]. Although MHO has been described as a benign condition, many studies have shown that MHO condition increases by itself the risk for CVD, chronic kidney disease, and fatty liver disease. In this regard, Schroder and colleagues, who followed a cohort of obese patients for 10 years, showed a progression from MHO to metabolically unhealthy obesity (MUO), highlighting that the MHO phenotype does not seem to be a harmless condition [31].

### 6.3.3 The Metabolically Obese Normal Weight (MONW) Phenotype

This obesity phenotype has been described for the first time in the 1980s by Ruderman et al. [32]. This category includes individuals who are not obese by standard weight tables but who, nonetheless, have metabolic disabilities that are typically associated with adult-onset obesity.

Individuals with MONW exhibit a higher percentage of VAT, a high fat mass, hyperinsulinemia, lower insulin sensitivity, dyslipidemia, and higher plasma levels of pro-inflammatory cytokines [3]. As for the MHO, the prevalence of this condition varies from 7% to 20%, depending on the number of metabolic abnormalities and considered cut points. In most cases, patients with MONW are older, former smokers, hypertensive, and sedentary than healthy individuals [33]. To identity MONW, higher waist circumference (women: 75.5 vs. 73.1 cm; men: 88.0 vs. 85.1 cm), higher glycated hemoglobin (6.1% vs. 5.3%), higher triglycerides (1.47 vs. 1.11 mmol/L), and higher levels of high-sensitive C-reactive protein (0.81 vs. 0.51 mg/L), and lower levels of HDL-cholesterol (1.28 vs. 1.49 mmol/L) should be considered [21].

Two other useful markers to identify MONW phenotype could be: the triglycerides index [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)]/2 which is higher compared to normal weight population [34], and an excessive deposition of VAT compared to overweight or obese subjects, called "thin-on-the-outside fat-on-the-inside" (TOFI) [35].

In these individuals, cardiometabolic complications may go undetected for years because normal body weight masks the need for early detection and treatment.

In order to improve this diagnosis, the measure of waist circumference should be recommended in men with a BMI > 23.8 kg/m$^2$ and in women with a BMI > 22.5 kg/m$^2$.

### 6.3.4 Normal Weight Obese (NWO) Syndrome

Excessive body fat (>30%) despite normal body weight (BMI 18.5–24.9 kg/m$^2$) has been described as normal weight obesity (NWO) syndrome. Sex- and age-adjusted cutoff values for NWO have been proposed by some investigators. These were defined as the combination of a normal BMI and an increased body fat percentage: 20–39 years, >19% and >32%; 40–59 years, >21% and >33%; and 60–79 years, >24% and >35% for men and women, respectively.

Obviously, this condition predisposes to the development of noncommunicable chronic diseases, especially cardiometabolic diseases. NWO individuals exhibit higher blood pressure, increased fasting glucose levels, and worse lipid profile compared to normal weight subjects [36].

The mechanisms underlying the NWO status could be identified in higher oxidative stress level and early inflammation status [37]. Several single-nucleotide

polymorphisms (SNPs) related to inflammatory genes have been identified in NWO; they concern the IL-6 gene (strong correlation between HOMA-IR and body fat percentage) [38], IL-15 receptor-alpha and methylenetetrahydrofolate reductase (MTHFR) enzyme (relationship between adipose tissue and skeletal muscle) [33], TNF-α gene (sarcopenic obesity susceptibility) [39], TP53 codon 72 in exon 4 (reduction of appendicular skeletal muscle mass index with increased sarcopenia risk) [40].

Together these conditions lead to an increased risk of cardiovascular diseases mortality which is 2.2-fold higher compared with that of individuals with low total body fat mass [41]. Worldwide prevalence has been estimated near to 10%, although there is a wide variation between the studies carried out thus far. This variation is due to ethnic differences, different methodologies used to assess body composition, and different cutoff points established for the diagnosis of NWO. NWO conditions occur more frequently in women than in men, especially aged over 55 years.

### *6.3.5 Sarcopenic Obesity (SO)*

Sarcopenic obesity is a clinical and functional condition characterized by the coexistence of excess fat mass (FM) and sarcopenia [42]. Sarcopenia is defined as a reduced skeletal muscle mass or myopenia, with consequent muscle dysfunction with low muscle strength (dynapenia) and performance. Sarcopenic obesity is more common in older individuals, but this condition can affect also younger patients with disability, during acute or chronic diseases [chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, cancer, after bariatric surgery (particularly in the absence of nutritional supervision)], HIV infection, or submitted to long-lasting incongruous dietary regimens and weight cycling [42].

The prevalence of SO ranges from 2.75% to over 20%, depending on the applied diagnostic criteria and the methods of body composition assessment. Sarcopenic obesity is characterized by increased mortality and functional limitations, representing an important public health concern [43, 44].

Several pathways seem to be involved in the pathogenesis of the obesity/muscle impairment syndrome. For example, *age-related changes in body composition* lead to a muscle mass and strength progressive decline; both visceral fat and intramuscular fat tend to increase, while subcutaneous fat in other regions of the body declines. Fat infiltration into muscle is associated with lower muscle strength and leg performance capacity [45]. *Physical inactivity* represents another important risk factor for body weight gain; conversely, obesity leads to physical inactivity and decreased muscle strength. In turn, muscle atrophy induces reduction in metabolic rate both at rest and during physical activity and may further aggravate the sedentary state, all of which can cause weight gain [46].

Pro-inflammatory cytokines, such as IL-6 or TNF-α, produced by adipose tissue (especially visceral fat) or infiltrating macrophages, induce *inflammation*, accelerating muscle catabolism. A positive correlation has been shown between pro-inflammatory cytokines and fat mass, and a negative correlation with muscle mass [47]. Increased pro-inflammatory cytokine levels could affect protein metabolism both directly,

**Table 6.3** Clinical features of obesity phenotypes

| | MUO | MHO | MONW | NWO | SO |
|---|---|---|---|---|---|
| BMI (kg/m$^2$) | >30 | >30 | 18.5–25 | 18.5–25 | >30 |
| VAT/FM | High VAT | Low VAT | High VAT | FM > 30% | High VAT |
| FFM | Normal/low | High | Normal | Normal | Low |
| Metabolic complications | Present | Absent | Present | Absent | Present |
| Cardiovascular complications | Present | Absent | Present/silent | Present | Present |

through its effect on muscle amino acid balance, and indirectly, through insulin sensitivity [21]. In fact, an involvement of inflammatory molecules in the etiopathogenesis of *insulin resistance* has been demonstrated through a cross-talk between cytokine receptors and insulin receptor signaling [48]. Since insulin is a powerful anabolic hormone, insulin resistance may result in muscle catabolism in individuals with obesity.

*Depressed secretion of growth hormone* (GH) and insulin-like growth factor I (IGF-I), consequent to high circulating free fatty acids levels in obesity, *reduced testosterone* circulating levels, and *malnutrition/weight loss* could be considered other possible mechanisms contributing to muscle impairment in individuals with obesity.

The diagnosis of SO represents a key problem and requires body composition evaluation, metabolic, functional, and genetic approaches.

The main clinical features of obesity phenotypes are reassumed in Table 6.3.

## 6.4 Secondary Causes of Obesity

Secondary causes of obesity are rare and can be classified into endocrinological, genetic, and iatrogenic etiologies. About 2–3% of "essential" obesity in pediatric age is of endocrine or genetic origin (secondary obesity) [49]. Actually, this percentage could be higher, since secondary causes of obesity are generally underdetected and undertreated. Therefore, the evaluation of individuals with obesity should include screening for potentially treatable endocrine, neurologic, and genetic conditions, other than assessing the degree of obesity and screening for the associated comorbidities.

The main secondary causes of obesity are reassumed in Table 6.4.

### *6.4.1 Endocrine Causes*

#### 6.4.1.1 Cushing's Syndrome

Pituitary or adrenal tumors, ectopic adrenocorticotropic hormone (ACTH) secretion, or exogenous glucocorticoids could induce a hypercortisolism condition [50]. Cortisol is involved in the regulation of metabolisms of carbohydrate (by promoting gluconeogenesis and glycogenesis in the liver and by decreasing the sensitivity of peripheral tissue to insulin, with consequent increase of glucose plasma level),

**Table 6.4** Secondary causes of obesity

| |
|---|
| Endocrine causes |
| – Hypothyroidism<br>– Cushing syndrome<br>– Polycystic ovary syndrome<br>– Growth hormone deficiency<br>– Hypothalamic obesity<br>– Hypogonadism<br>– Pseudohypoparathyroidism |
| Genetic causes |
| *Monogenic obesity* |
| – Leptin and leptin receptor deficiency<br>– POMC deficiency<br>– Melanocortin receptor 4 deficiency<br>– Prohormone convertase deficiency<br>– BDNF and TrkB insufficiency<br>– SIM 1 insufficiency |
| *Syndromic obesity* |
| – Prader–Willi syndrome<br>– Bardet–Biedl syndrome<br>– Beckwith–Wiedemann syndrome<br>– Alstrom–Hallgren syndrome<br>– Carpenter syndrome<br>– Cohen syndrome |
| Iatrogenic causes |
| *Drugs* |
| – Antidiabetic drugs: Insulin, sulfonylureas, thiazolidinediones, inhibitors of dipeptidyl peptidase 4 (DPP-4)<br>– Central acting drugs: Clozapine, olanzapine, amitriptyline, paroxetine, carbamazepine, gabapentin, valproates |
| *Smoking cessation* |
| Eating disorders |

protein (by increasing peripheral protein catabolism), and lipid (by enhancing the activation of lipoprotein lipase in adipocytes, and in turn, by increasing fat accumulation). Glucocorticoids are also involved in the differentiation of adipose stromal cells into mature adipocytes. It has been found that the glucocorticoid action is regulated by the activity of the 11β-hydroxysteroid dehydrogenase, in particular type 1, which is widely expressed in adipose tissue and enhances the local effect of cortisol by promoting the conversion of inactive cortisone into active cortisol [51].

Central obesity occurs in 80–90% of individuals with Cushing's syndrome and is characterized by a predominant localization of the adipose tissue in the face (moon face), neck, dorsocervical area (buffalo hump), supraclavicular area (fat pads), retro-orbital space (exophthalmos), trunk, and abdomen, with wasting of the extremities.

Diagnosis of Cushing's syndrome is primarily based on the signs and symptoms of the disorder. Nevertheless, a significant number of these patients present only with simple obesity or with type 2 diabetes mellitus. A study has found a significant rate (9.33%) of Cushing's syndrome in a population of patients with simple obesity, suggesting that patients with obesity should be routinely screened for Cushing's syndrome [52].

#### 6.4.1.2 Hypothyroidism

The link between obesity and autoimmune thyroid dysfunction (AITD), the main cause of hypothyroidism in adults, is now well established. In fact, the prevalence of AITD in obesity has been reported to be 12.4% in children and between 10% and 60% in adults [53]. This relationship is not surprising because thyroid hormones regulate energy metabolism and thermogenesis and play a critical role in glucose and lipid metabolism, food intake, and the fatty acids oxidation [54].

The main contributor of weight gain in hypothyroidism is the reduced resting energy expenditure (REE), which comprises around 60% of total energy expenditure in adult man. Measurable differences in REE have been described also with smaller variation in thyroid function.

Eisenberg and Distefano [55] studied in a population of thyroidectomized patients the association between the administered and adsorbed doses of levothyroxine T4 (L-T4) and serum TSH levels, showing that a change in serum TSH from 4.0 to 0.4 mU/L corresponds to a quite substantial (approximately 40%) increase in the absorbed dose of L-T4.

A 7–8% difference in REE corresponds to a daily difference in metabolism of around 10 g of lipid. Thus, assuming unaltered energy intake and activity energy expenditure, differences in thyroid function tests might theoretically be associated with several body weight variations [56].

The accumulation of fluid rich in glycosaminoglycans may represent another mechanism contributing to body weight gain in hypothyroidism [50].

Regardless of AITD, higher TSH levels (at the upper limit of the normal range or slightly increased) have been observed in obese children, adolescents, and adults, with a positive correlation with BMI [53]. Despite the higher plasma TSH levels, TSH receptors are less expressed on adipocytes of obese vs. lean individuals, inducing downregulation of thyroid hormone receptors and thyroid hormone action, thereby further increasing plasma TSH and FT3 concentrations and constituting a condition of peripheral thyroid hormone resistance [57]. This sequence of events would be reversed by weight loss, which restores the size and function of mature adipocytes [57].

The last European Society of Endocrinology Clinical Guidelines on the Endocrine Work-up in Obesity recommended to test all patients with obesity for thyroid function and to treat overt hypothyroidism (elevated TSH and decreased FT4) in obesity irrespective of auto-antibodies positivity [58].

#### 6.4.1.3 Polycystic Ovaries Syndrome (PCOS)

Obesity represents an important risk factor for the clinical and biochemical manifestations of PCOS in women who are genetically predisposed [6]. Studies have shown that about 50% of women with PCOS are obese [50].

A different hormonal environment has been observed in women affected from PCOS and obesity, compared to normal-weight PCOS-affected women [59]. Primarily, women with obesity, particularly those with the abdominal obesity phenotype, are usually more insulin resistant and more hyperinsulinemic than their normal-weight counterparts [60].

In turn, hyperinsulinemia increases androgen levels via stimulation androgen biosynthesis in the ovarian theca cell and via suppression of sex hormone binding globulin (SHBG) by the liver [50].

In fact, the presence of obesity, particularly the abdominal phenotype, in PCOS women appears to increase the availability of active androgens and estrogens and worsen hirsutism, menstrual cyclicity, and fertility rate. A key role in the pathogenesis of ovarian hyperandrogenism in PCOS is played by hyperactivity of the P450c17 enzyme, which is located in the ovarian theca-interstitial cells and in the adrenal gland [61].

Weight loss and insulin-sensitizing agents, such as metformin, have been associated with improvement of hyperandrogenism and metabolic parameters of PCOS.

#### 6.4.1.4 Growth Hormone Deficiency

GH and IGF-1 exert important metabolic actions and regulate body composition, REE, bone mineral density, and lipid metabolism. Specifically, GH inhibits lipoprotein lipase, increases hormone-sensitive lipase, stimulates adipocytes lipolysis, enhances protein synthesis, and increases muscle mass.

Growth hormone (GH) deficiency in adults is characterized by decreased muscle mass, increased trunk fat deposition, and reduction of total body water. A GH deficiency should be supposed in individuals with a history of hypothalamic or pituitary disease, with subnormal serum insulin-like growth factor-1 (IGF-1) concentration or subnormal serum GH response to a potent stimulus such as insulin-induced hypoglycemia [50].

The relationship between GH deficiency and obesity is complex and bidirectional. Although primary GH deficiency leads to centripetal adiposity, visceral obesity could be associated with a secondary reduction in serum GH levels [62]. Increased concentrations of leptin, insulin, free fatty acids (FFAs), and IGF-1 seem to be involved in modulation of GH release [63].

#### 6.4.1.5 Hypogonadism

Obesity and male hypogonadism are often associated, there is a two-way relationship between the two conditions. Data from prospective studies show that patients with hypogonadism are at increased risk of becoming obese. On the other hand,

among obese patients, the incidence of androgen deficiency is high [64]. Hypogonadism impairs fertility, sexual function, bone mineralization, fat metabolism, and cognitive function, deteriorates muscle mass, and alters body composition [65]. However, hypogonadism is often underdiagnosed as secondary cause of obesity, despite its great impact on quality of life. Hyperestrogenism, metabolic endotoxiemia, and hyperleptinemia represent the three major risk factors in the pathogenesis of hypogonadism [66].

The increased adipose tissue in obesity induces an overexpression of the enzyme aromatase, with consequent increased conversion of testosterone into estradiol. In turn, the hyperestrogenism decreases lutein hormone (LH) pituitary secretion through a negative feedback action that impairs the synthesis and production of testosterone from Leydig cells [67].

Concerning the metabolic endotoxemia, an hypercaloric and hyperlipidic diet might facilitate the transition of bacterial endotoxins from gut lumen into the blood stream. The reduced testosterone levels in obesity and its immunosuppressive action result in a reduced ability of the individual to fight infections [66].

Furthermore, the hyperleptinemia observed in individuals with obesity inhibits the precursor of testosterone, the human chorionic gonadotropin (hCG)-stimulated androstenedione. Leptin receptors have been found to be expressed in murine and human Leydig cells [68].

In women, menopause condition is often associated with body weight gain. The loss of estrogen and progesterone and the rapid decline of GH induce increased lean body mass and increased visceral fat and visceral fat/subcutaneous fat ratio, with prevalent abdominal obesity.

#### 6.4.1.6 Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) type 1a is an inherited condition (autosomal dominant) characterized by target organ unresponsiveness to several hormones, including TSH, PTH, LH, and FSH, due to inability to activate adenyl cyclase.

PHP type 1a is caused by the germline loss of functional mutations in the gene encoding of the subunit of $G_S$ (*GNAS1*), a protein coupling the membrane hormone binding domain with adenylate kinase.

These genetic mutations are responsible for reduced lipolytic response to epinephrine (due to decreased intracellular cAMP levels), accelerated differentiation of fibroblasts to adipocytes and GH deficiency, and consequently of the body weight gain.

Somatic features of PHP type 1a (Albright's hereditary osteodystrophy) include short stature, obesity rounded face, subcutaneous ossifications, and shortening and widening of long bones in the hands and feet (brachydactyly mostly affecting the fourth and fifth rays), and less frequently, mental retardation, in association with hyperphosphatemia and hypocalcemia.

#### 6.4.1.7 Hypothalamic Disorders

Obesity associated with damage of the hypothalamic region is characterized by hyperphagia.

Craniopharyngioma (especially following surgery), inflammatory processes such as sarcoidosis and tuberculosis, vascular damage, head trauma, and cranial radiotherapy could be implicated in the pathognesis of hypothalamic obesity [69]. In the more severe conditions, hypothalamic obesity could be associated with multiple endocrine dysfunctions as amenorrhea or impotence, diabetes insipidus, and thyroid or adrenal insufficiency [69]. Other symptoms such as convulsion, hypothermia or hyperthermia, somnolence, headache, vomiting, and visual disturbances may occur in individuals with hypothalamic obesity [21, 69].

### *6.4.2 Genetic Causes*

Obesity is a complex, heritable trait influenced by the interplay of genetics, epigenetics, metagenomics, and the environment. Single-gene and syndromic causes of obesity can be distinguished. Obesity based on mutation of one gene has been defined as monogenic obesity; it mainly involves the hypothalamic leptin–melanocortin pathway, which is known to play a critical role in the regulation of energy homeostasis.

#### 6.4.2.1 Leptin and Leptin Receptor Deficiency

Leptin receptor (LepR) deficiency is an autosomal-recessive endocrine disorder causing early onset severe obesity, hyperphagia, and pituitary hormone deficiencies, such as hypothalamic hypothyroidism and hypogonadotropic hypogonadism. However, recognition is challenging and prevalence is unknown. A recent epidemiological study estimated the prevalence of LepR deficiency in European population, corresponding to 1.34 per one million people [70]. Other features reported in patients with LepR deficiency are hyperinsulinemia and frequent infections, probably related to a reduction in circulating CD4+ T cells, abnormal T-cell proliferation and abnormal release of cytokines.

The leptin deficiency is due to homozygous frameshift or missense mutations of the OB gene (7q31.3), which are inherited as an autosomal recessive trait. The diagnosis of congenital leptin deficiency has been confirmed by analyzing serum leptin levels or the presence of mutations in the OB gene. The treatment consists of the administration of physiological doses of leptin, resulting in substantial improvement of body weight, reduced appetite, and normal pubertal development [50].

#### 6.4.2.2 POMC Deficiency

Pro-opiomelanocortin (POMC) is the precursor of ACTH, lipotropin, α-melanocyte-stimulating hormone (α-MSH), β-MSH, and endorphin. POMC peptides produced by hypothalamus act as endogenous ligands for the melanocortin 4 receptor (MC4R), a brain-expressed Gαs-coupled GPCRs involved in weight regulation [50].

POMC is associated with ACTH deficiency, hyperphagia with severe early onset obesity and red hair pigmentation.

#### 6.4.2.3 MCR4 Deficiency

Among the causes of monogenic obesity, MCR4 deficiency represents the most frequent (1–2.5% of individuals with obesity). The melanocortin 4 receptor (MC4R) is involved in energy balance control and mediates most of the anorectic effects of leptin [50]. Mutations in the *MC4R* gene are associated with accelerated linear growth that is disproportionate for the degree of obesity and leads to increased adult final height. GH pulsatility is maintained in MC4R deficiency, suggesting a role for MC4R in controlling hypothalamic somatostatinergic tone. Individuals carrying MC4R mutations exhibit significantly higher fasting insulin levels. Both of these factors may contribute to the accelerated growth phenotype characteristic of MC4R deficiency [71]. Nowadays, no specific therapy for MCR4 deficiency exists.

Several congenital and genetic disorders may be associated with severe obesity. Syndromic forms of obesity often joined dysmorphic features, developmental delay, and mental retardation.

#### 6.4.2.4 Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a multisystem disorder with an estimated prevalence in several studied populations of 1/10,000–1/30,000 [72]. The absence of paternally expressed imprinted genes at 15q11.2-q13 through paternal deletion of this region (65–75% of individuals), maternal uniparental disomy 15 (20–30%), or an imprinting defect (1–3%) represent the causes of Prader–Willi syndrome [72], leading to the lack of the small nuclear ribonucleoprotein polypeptide N (*SNRPN)* gene.

Clinically, PWS is characterized by severe hypotonia with feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity, delay in motor milestones and language development. All individuals have some degree of cognitive disability [72]. The physical aspect is characterized by short stature, facial dysmorphism, strabismus, scoliosis, slender hands with a hypoplastic ulnar bulge, and hypopigmentation of hair, eyes, and skin. Furthermore, individuals with PWS (both males and females) develop hypogonadism, with consequent genital hypoplasia, incomplete pubertal

development, and often, infertility, GH insufficiency, type II diabetes mellitus (especially, individuals with obesity).

Obesity management is crucial in the care of patients with PWS to prevent several metabolic complications [50].

Other less frequent syndromic forms of obesity and their clinical features are summarized in the Table 6.5.

**Table 6.5** Syndromic forms of obesity

| Syndromes | Gene mutation | Short stature/ decrease in height velocity | Delayed psychomotor development | Other clinical features |
|---|---|---|---|---|
| Prader–Willi | 15q11.2-q13 | Yes | Yes | Facial dysmorphism, hypotonia, small hands and feet, hypogonadism |
| Bardet–Biedl | *BBS1, BBS4, BBS9, BBS10* | Yes | Yes | Polydactyly, retinitis pigmentosa, hypogonadism, kidney disorders |
| Alstrom | ALMS1 | Yes | No | Hearing loss, dilated cardiomyopathy, hypergonadotropic hypogonadism, hypothyroidism, acanthosis nigricans resulting from hyperinsulinemia |
| Cohen | VPS13B/ COH1 | Yes | Yes | Microcephaly, hypotonia, retinal dystrophy, myopia, thick hair and eyebrows, long eyelashes, down-slanting and wave-shaped eyes, smooth or shortened nasal philtrum, and prominent upper central incisors |
| Carpenter | RAB23/ MEGF8 | Yes | Yes | Macrosomia, umbilical hernia, craniosynostosis, brachydactyly, cutaneous syndactyly, preaxial polydactyly in the toes and postaxial polydactyly in the hands, congenital cardiac malformations, hypogonadism, cryptorchidism |
| Albright's hereditary osteodystrophy (AHO) | GNAS | Yes | Yes | Round face, brachydactyly, subcutaneous ossifications, pseudohypoparathyroidism, hypocalcemia |
| WAGR | 11p13 region PAX6/WT1 | Yes | Yes | Wilms tumor, aniridia (absence of the colored part of the eye, the iris), genitourinary anomalies, mental retardation |

### 6.4.3 Iatrogenic Causes

#### 6.4.3.1 Medication

Several medications can induce obesity by promoting hunger and by decreasing resting state metabolism [69]. Drug categories that are most frequently associated with weight gain are: antidepressants (citalopram, mirtazapine, amitriptyline, paroxetine), antipsychotics (olanzapine, lithium, clozapine, quetiapine, risperidone, ziprasidone), anti-epileptics (carbamazepine, gabapentin, valproic acid), antidiabetics (insulin, sulfonylurea derivates), anti-hypertensives (α-adrenergic blockers, β-adrenergic blockers), corticosteroids, proton pump inhibitors, protease inhibitors, anti-histamines [69].

### 6.4.4 Eating Disorders

Eating disorders are serious psychiatric disorders characterized by abnormal eating or weight-control behaviors. Among eating disorders, bulimia nervosa and binge eating disorder are often accompanied by, or can lead to obesity (30–45%) [73, 74].

Bulimia nervosa is characterized by recurrent episodes of binge eating (i.e., eating large amounts with loss of control) and compensatory behaviors to prevent weight gain: self-induce vomiting, or less frequently, inappropriate use of medicines, fasting, extreme exercise [75].

Binge eating disorder is characterized by distressing, recurrent episodes of binge eating, with fewer compensatory behaviors than in bulimia nervosa [75]. Feelings of lack of control and distress may play a role in the pathogenesis of binge eating disorder. Specifically, stress leads to increased appetite (in comfort food), induces abdominal obesity, and may counteract the effects of a healthy diet [69].

Bulimia nervosa and binge eating disorder are often associated with neuropsychiatric disorders such as atypical depression, attention deficit hyperactivity disorder (ADHD); about 15% of patients have multiple comorbid impulsive behaviors, including substance abuse, impulse buying, compulsive shopping, and multiple sexual relationships [75].

Interactions between impairments in cognitive control and increased emotional reactivity, food-cue reactivity, and craving may underlie emotion dysregulation and promote binge eating disorders.

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# Chapter 7
# Complications of Obesity


**Caterina Conte**

## 7.1 Introduction

Obesity is associated with a constellation of systemic complications. Obesity-related metabolic abnormalities are mostly due to adipose tissue dysfunction and ectopic fat deposition in skeletal muscle, liver and other organs and tissues. Individuals with obesity have greater fat and lean body mass, along with greater energy expenditure at rest, greater cardiac output, increased heart rate and blood pressure and a greater mass of pancreatic beta cells than individuals without overweight or obesity. All these metabolic and haemodynamic maladaptations to excess body mass and adiposity, along with an underlying state of chronic low-grade inflammation triggered by adipose tissue dysfunction, contribute to excess workload for organs and systems, eventually leading to organ damage and dysfunction. This chapter will focus on complications associated with obesity and the pathogenic mechanisms underlying them.

## 7.2 Metabolic Syndrome

The term "metabolic syndrome" identifies a cluster of metabolic risk factors that increase the risk of type 2 diabetes and atherosclerotic cardiovascular disease [1, 2]. The metabolic syndrome is characterized by abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides and apolipoprotein B-containing lipoproteins and reduced high-density lipoprotein cholesterol [HDL-C]), increased arterial blood

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pressure and impaired glucose metabolism (insulin resistance, impaired fasting glucose, type 2 diabetes). Individual components of the metabolic syndrome are entangled with obesity, with elevated blood pressure exhibiting the strongest association. The prevalence of metabolic syndrome ranges from 43% to 78% in men with obesity and from 24% to 65% in women with obesity [3].

### *7.2.1 Altered Glucose and Lipid Metabolism*

Obesity and abdominal obesity are potent determinants of insulin resistance and type 2 diabetes [4–6], insulin resistance being present even in obese subjects with normal glucose tolerance [7]. As high as 85% of individuals with type 2 diabetes have overweight or obesity [8]. Diabetes risk increase versus normal weight controls is greater in younger than older subjects, ranging from 1.38-fold to 3.07-fold in individuals with high BMI older than 85 years or aged 35–44 years, respectively [9]. The pathophysiology of insulin resistance in obesity is complex and involves adipose tissue dysfunction, lipotoxicity, gut dysbiosis and low-grade chronic inflammation [10–12]. In brief, adipose tissue expansion may associate with inadequate vascularization leading to adipose tissue hypoxia, fibrosis and eventually adipocyte death [13]. These events trigger macrophage infiltration, with low-grade inflammation and release of proinflammatory cytokines (e.g. tumour necrosis factor alpha [TNF-α], interleukin 6 [IL-6] and IL-1β) that promote and sustain adipocyte dysfunction and insulin resistance. These phenomena result in increased lipolysis with release of free fatty acids (FFAs) from adipose depots, especially visceral adipose tissue [14]. Excess lipid availability in obesity leads to ectopic accumulation of triglycerides and bioactive lipid metabolites such as diacylglycerol (DAG), ceramides and acylcarnitines in liver and skeletal muscle [15–17], where they interfere with insulin signalling through different pathways. Insulin resistance in skeletal muscle results in decreased glucose utilization and storage, increasing glucose availability to other metabolic pathways such as de novo lipogenesis in the liver. Furthermore, visceral adipose tissue lipolysis delivers FFAs to the liver through the portal vein, providing substrates for the production of large triglyceride-rich very low-density lipoproteins (VLDL) [18, 19]. Increased secretion of chylomicrons from the gut and impaired hepatic and peripheral clearance of triglycerides and triglyceride-rich lipoproteins also contribute to obesity-associated dyslipidaemia [20].

### *7.2.2 Metabolic Dysfunction-Associated Fatty Liver Disease*

The definition of **metabolic dysfunction-associated fatty liver disease (MAFLD)** has been recently proposed to describe hepatic steatosis associated with overweight/obesity, type 2 diabetes, or metabolic abnormalities (i.e., abdominal

obesity, elevated blood pressure, low HDL cholesterol, high triglycerides, prediabetes, homeostasis model assessment [HOMA]-insulin resistance ≥2.5 units or elevated high-sensitivity C-reactive protein) in normal weight individuals [21, 22]. According to some [21, 22] but not all [23] experts, the term MAFLD should replace the definition of non-alcoholic fatty liver disease (NAFLD), which encompasses non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and advanced fibrosis and cirrhosis. NAFLD is strictly associated with all components of the metabolic syndrome. Approximately one-quarter of the European population is affected by NAFLD [24], its prevalence increasing with increasing BMI, from nearly 70% in those who are overweight (BMI 25–29.9 kg/m$^2$) up to 90% in individuals with obesity (BMI ≥30 kg/m$^2$) [25], particularly those with severe obesity undergoing bariatric surgery [26]. As the new definition is very recent, few epidemiological data are available on MAFLD. It has been reported that the new definition has a similar prevalence compared with NAFLD, but it may have a lower incidence [27]. MAFLD is associated with increased risk of hepatocellular carcinoma, cirrhosis, cardiovascular disease, renal disease and cancer [28].

As compared with the previous definition "NAFLD", the term MAFLD emphasizes the role of metabolic risk factors in the pathophysiology of liver steatosis, overweight/obesity being one of the main features needed for diagnosing MAFLD. In the liver of individuals with metabolic abnormalities, FFA overflow from lipolysis and dietary lipids, de novo *lipogenesis* stimulated by hyperinsulinemia and/or impairments in FFA disposal (FFA oxidation and re-esterification into triglycerides that are secreted as very low density lipoproteins [VLDL]) eventually lead to accumulation of triglycerides and liver steatosis, which can evolve into steatohepatitis and in some cases lead to cirrhosis [29]. Mitochondrial dysfunction and production of toxic lipid metabolites resulting from overwhelmed FFA metabolism in the liver trigger oxidative stress, endoplasmic reticulum stress and proinflammatory pathways, i.e. the main mechanisms underlying the development of inflammation and fibrosis [29]. In addition, functional and compositional alterations in gut microbiota may affect several metabolic pathways, enhancing de novo lipogenesis and sustaining alterations in glucose and lipid metabolism that perpetuate liver damage [30]. Gut dysbiosis may also increase intestinal permeability, thus allowing translocation of microorganisms and microbial products into the portal circulation (metabolic endotoxemia) and eventually triggering pro-inflammatory processes in the liver [31].

Lipid accumulation in the liver initiates hepatic insulin resistance, which enhances gluconeogenesis and decreases glycogen synthesis and glucose uptake, with a net increase in hepatic glucose production that, along with impaired glucose uptake by insulin-resistant skeletal muscle, contributes to raising blood glucose. Initially, pancreatic beta cells increase insulin production in an attempt to overcome insulin resistance, leading to chronic hyperinsulinemia. In the long term, the ability of pancreatic beta cells to secrete insulin declines, leading to impaired insulin secretion, hyperglycaemia and overt type 2 diabetes [32].

### 7.2.3 Elevated Blood Pressure

Obesity is a strong risk factor for primary hypertension [33, 34], with 60–85% of individuals with obesity having elevated blood pressure [3]. Several mechanisms are involved, including activation of the sympathetic nervous system (SNS), kidney compression by excess visceral, perirenal and renal sinus fat, stimulation of the renin–angiotensin–aldosterone system (RAAS) and aldosterone-independent mineralocorticoid receptor activation [35]. Sympathetic overdrive in obesity reflects disease severity [36], is strongly associated with visceral adiposity and may be due to chronic hypoxemia secondary to an imbalance between oxygen demand and supply (increased demand and altered respiratory mechanics) [35]. Interactions between adipokines, inflammatory cytokines and central autonomic regulatory pathways most likely play a role [37]. Importantly, SNS overactivity is reversible with weight loss [38]. Activation of the RAAS in obesity involves secretion of angiotensinogen, mineralocorticoids and mineralocorticoid releasing factors (e.g., leptin) by dysfunctional adipose tissue [39, 40]. Overdrive of the SNS may also increase renin secretion by the juxtaglomerular apparatus of renal nephrons [39]. Renin converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by the angiotensin-converting enzyme 1, leading to vasoconstriction, adrenal aldosterone secretion and retention of sodium and water by the kidneys. Dysfunctional adipose tissue in obesity releases angiotensinogen, mineralocorticoids and adipokines such as leptin that enhance the secretion of mineralocorticoids, further activating the RAAS [34, 39, 40]. Compression of the kidney and renal arteries by excess fat tissue can also contribute to the onset of arterial hypertension due to increased activity of the RAAS that, together with aldosterone-independent mineralocorticoid receptor activation, increases renal sodium resorption. As in a vicious cycle, endothelial dysfunction and vascular stiffening secondary to hypertension, increased systemic vascular resistance due to neurohormonal stimulation, low-grade chronic inflammation and oxidative stress may further worsen blood pressure control and lead to hypertensive heart disease [41, 42].

### 7.2.4 Metabolically Healthy and Unhealthy Obesity

It has been proposed that some people with obesity and fewer or no metabolic alterations may not be at increased cardiovascular risk. These individuals are referred to as metabolically healthy obese individuals [43]. The prevalence of metabolically healthy obesity ranges between 12% and 35% depending on the type of population and the definition of metabolic health used, with wide geographical variations [3, 44]. Individuals with metabolically healthy obesity are relatively protected against the development of cardiometabolic diseases compared to those with obesity and metabolic alterations. Recent studies suggest that alterations in adipose tissue function and body fat distribution are key factors underlying the metabolic altered

phenotype, which is characterized by lower subcutaneous fat mass, adipocyte hypertrophy, a pro-inflammatory adipose tissue phenotype and a reduced ability to accumulate triglycerides in adipose tissue that may cause ectopic fat deposition and visceral fat inflammation, thus contributing to the development of insulin resistance and chronic cardiometabolic diseases [43]. However, metabolically healthy obesity is most likely a transition phase towards a metabolically unhealthy state, as suggested by studies demonstrating a 34% and 58% increased risk of developing cardiovascular events in metabolically healthy overweight and obese individuals, respectively, as compared with metabolically healthy normal weight controls [45] and that those with metabolically healthy obesity are four times more likely to develop type 2 diabetes than normal weight controls [46].

## 7.3 Vascular System

### *7.3.1 Cardiovascular and Cerebrovascular Disease*

**Ischemic heart disease**, **heart failure** and **stroke** all have hypertension and obesity-associated metabolic alterations as their main pathophysiological mechanisms. Hyperproduction of proinflammatory adipokines (e.g. leptin, TNF-α, IL-6, IL-18 and resistin) and reduced secretion of anti-inflammatory adipokines such as adiponectin by dysfunctional adipose tissue, particularly visceral adipose tissue, play a fundamental role in the development of atherosclerosis and cardiovascular disease in obesity [41, 47]. Locally, epicardial adipose tissue, i.e. the visceral adipose tissue of the heart situated between the myocardium and the visceral layer of the pericardium, is a potential source of inflammatory mediators and an independent cardiovascular risk factor that associates with fatal and non-fatal cardiovascular events [48]. It has been reported that the risk of death from ischaemic heart disease or stroke increases by 39% per 5 kg/m$^2$ increase in BMI [49]. More recent evidence confirmed that adult individuals with overweight/obesity have an earlier onset of incident cardiovascular disease, a greater proportion of life lived with cardiovascular morbidity, and shorter overall survival compared with adults with normal BMI. In particular, the lifetime risk for incident cardiovascular disease (including fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, congestive heart failure and cardiovascular death) in men and women is 21% and 32% greater for overweight, 67% and 85% greater for obesity and 3.1-fold and 2.5-fold higher for morbid obesity, respectively, as compared with normal weight [50]. Although obesity as assessed by BMI shows a strong association with cardiovascular morbidity and mortality, BMI does not inform on body composition and regional fat distribution, and individuals with similar BMI may have different cardiometabolic risk [51]. Abdominal adiposity as assessed by waist circumference is a strong and independent predictor of all-cause and cause-specific mortality, and measurement of waist circumference should complement BMI in the assessment of patients with

obesity [52]. Atherosclerotic cardiovascular and cerebrovascular disease is not the only obesity-associated complication affecting the circulatory system.

### *7.3.2 Prothrombotic State*

Individuals with obesity are at increased risk of **venous thromboembolism**, including deep vein thrombosis and pulmonary embolism (PE). The risk of VTE increases by 37–47% for each 1-standard deviation higher BMI [53] and is 53% higher in those with substantially increased waist circumference (i.e. ≥102 cm for men and ≥88 cm for women) as compared with individuals without abdominal obesity [54]. The increase in intra-abdominal pressure secondary to excess adiposity hinders the venous return from the lower limbs, causing venous stasis (also favoured by a sedentary lifestyle) and predisposing to deep vein thrombosis of the lower limbs and potentially life-threatening pulmonary embolism [55]. Low-grade chronic inflammation [56] and impaired fibrinolysis [57] associated with obesity may also contribute to a thrombogenic state. Furthermore, Mendelian randomization analyses support a causal association between genetically predicted obesity and venous thromboembolism [58, 59].

## 7.4 Respiratory System

Obesity strongly impacts the respiratory system. The increase in intra-abdominal pressure due to excess adiposity, together with the narrowing of the upper airways caused by the pressure of the surrounding soft tissues, the increase in adipose tissue in the mediastinum and—in patients with sarcopenic obesity—a reduction in the mass of respiratory muscles, impair chest expansion, causing hypoventilation and hypoxemia [60, 61]. **Obstructive sleep apnoea** (OSA) is a sleep-related breathing disorder characterized by periodic narrowing and collapse of the pharyngeal airway during sleep. Having OSA increases the risk of cardiometabolic disease [62–64], cognitive impairment and dementia [65, 66]. Obesity is the main risk factor for OSA, which is present in as high as 40% of individuals with obesity [67]. Excess body mass is often accompanied by an increase in adipose tissue within the tongue and pharynx, making the upper airways more prone to collapse during sleep. Reduction of lung volume due to increased abdominal fat and recumbent posture during sleep as well as impaired neuroanatomic breath control due to hormonal imbalances may also contribute to narrowing of the airway [68].

Individuals with obesity have an increased respiratory rate to compensate for hypoventilation and hypoxemia due to altered respiratory mechanics. In the **obesity-hypoventilation syndrome** (OHS), obesity-induced alterations in the respiratory mechanics and a reduction in the central respiratory drive that hampers the compensatory increase in respiratory rate eventually lead to daytime hypercapnia. The

syndrome is defined by the combination of obesity, sleep-disordered breathing and awake daytime hypercapnia (awake resting $PaCO_2 \geq 45$ mm Hg at sea level), after excluding other causes for hypoventilation [69]. OHS is estimated to affect 8–20% of individuals with obesity who seek evaluation for sleep-disordered breathing and is associated with increased risk of mortality, chronic heart failure, pulmonary hypertension and hospitalization due to hypercapnic respiratory failure [70]. Most patients (90%) with OHS have concomitant OSA [71]. The two disorders have been called into question as responsible for **pulmonary hypertension**, which is found in 50–88% of patients with OHS and in 20–47% of patients with OSA [72]. Chronic thromboembolic pulmonary disease, left ventricular hypertrophy, chronic heart failure (either with preserved or reduced ejection fraction) may also contribute to pulmonary hypertension in subjects with obesity.

Obesity and overweight are also associated with **asthma**. The risk increases with increasing BMI category, from 1.2-fold in overweight up to 3.3-fold in those with morbid obesity as compared with normal weight individuals [73]. Asthma in obesity appears to be more severe than in normal weight individuals, in both children and adults. The pathogenic mechanisms linking obesity and asthma are not fully understood, but specific nutrient imbalances (e.g. vitamin D deficiency, excess dietary saturated fatty acids or fructose), gut dysbiosis, hereditary factors, alterations in cytokine (IL-6) and adipokine (leptin and adiponectin) levels contributing to inflammation and obesity-induced metabolic abnormalities likely play a role [74].

## 7.5 Gastrointestinal System

Gastrointestinal complications of obesity may involve all portions of the gastrointestinal tract. **Gastroesophageal reflux disease** (GERD) encompassing non-erosive reflux disease, erosive esophagitis, and Barrett's oesophagus is a common finding in obesity, being present in approximately 50–60% of obese individuals [75, 76]. The risk of GERD is 73% greater in patients with obesity, and abdominal obesity increases by nearly twofold the risk of erosive esophagitis and Barrett's oesophagus as compared with normal weight controls [77, 78]. Increased intra-abdominal pressure causing an increase in intragastric pressure is the main mechanism linking obesity and GERD, although obesity-associated metabolic abnormalities and gastric distension secondary to overeating may also play a role [79]. Further obesity-associated complications involving the upper gastrointestinal tract include oesophageal dysmotility, oesophageal adenocarcinoma that may arise from Barrett's oesophagus, erosive gastritis and gastric cancer [80]. **Colonic diverticulosis** is another common finding in obesity. Its prevalence has been reported to be nearly 50% in adults with obesity undergoing colonoscopy, and the risk of diverticular disease is 40% greater in those with obesity as compared with normal weight individuals [81, 82]. Increased intra-abdominal pressure due to excess visceral fat, gut dysbiosis leading to increased methane production and greater intraluminal pressure and unhealthy eating habits (e.g. low fibre

consumption) likely explain the association between colonic diverticulosis and obesity [82]. Other obesity-associated complications involving the lower gastrointestinal tract include colonic polyps and colorectal cancer [80] and inflammatory bowel disease [83].

**Gallstone disease** (cholelithiasis) is another prevalent complication that affects individuals with obesity. In fact, risk factors for gallstone disease include obesity and several obesity-associated factors, such as rapid weight loss, weight cycling, high-calorie diet, medications, type 2 diabetes, metabolic syndrome, dyslipidaemia, smoking and sedentary lifestyle [84, 85]. Gallbladder disease has been reported in approximately a quarter of patients with severe obesity, and the risk of developing gallstones increases by 63% every 5-unit increase in BMI [85, 86]. Increased cholesterol synthesis and secretion in to the bile leading to cholesterol saturation and gallstone formation may explain, at least in part, the association between obesity and gallstone disease [87, 88]. It has also been proposed that gallstone disease (and cholecystectomy) increases the intrahepatic triglyceride content and contributes to liver insulin resistance [89]. As in a vicious cycle, liver insulin resistance might promote gallstone disease by increasing bile lithogenicity [89]. Finally, obesity is also associated with liver steatosis (NAFLD/MAFLD), hepatic cirrhosis, hepatocellular carcinoma and diseases of the pancreas (acute pancreatitis and pancreatic cancer) [80].

## 7.6 Kidney and Urinary System Disorders

### *7.6.1 Chronic Kidney Disease*

Having obesity increases the risk of developing albuminuria without kidney failure (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 $m^2$) by 51% and chronic kidney disease (CKD) stage 3 or worse (estimated glomerular filtration rate below 60 mL/min/1.73 $m^2$) by nearly 30% [90]. A progressive increase in the incidence of histologically diagnosed obesity-related glomerulopathy, from 0.2% in 1986–1990 to 2.0% in 1996–2000, has been reported [91]. CKD in obesity may arise secondary to uncontrolled hypertension and atherosclerosis, or chronic hyperglycaemia, but the risk of CKD has also been reported to be independently associated with obesity and no metabolic abnormalities [92, 93]. Haemodynamic adaptations to obesity play a major role in the development of CKD. Initially, excess body weight is associated with renal vasodilation and glomerular hyperfiltration. Compression of the renal tubules, hyperglycaemia, high protein intake, hyperinsulinemia and elevated blood pressure, impaired renal autoregulation and mineralocorticoid receptor activation have been postulated as contributing factors [35]. Over time, worsening hypertension and other obesity-related risk factors for CKD (e.g. type 2 diabetes, altered lipid metabolism and hyperuricaemia) lead to progression of kidney damage and eventually end-stage renal disease [94].

### 7.6.2 *Other Disorders*

Obesity is also associated with other urological complications, such as urinary incontinence and nephrolithiasis. Incontinence risk increases by 20–70% per 5-unit increase in BMI [95]. Both BMI-defined obesity and central obesity have been associated with urinary incontinence in both sexes, and with stress urinary incontinence in women [96]. Sex differences may be related to biomechanical and neuroendocrine factors. In women with obesity, the increase in intra-abdominal pressure and pelvic fat can stress the pelvic floor and alter urodynamics, predisposing to **stress incontinence** [97]. Men have greater pelvic floor strength and may be less susceptible to these mechanisms. A neurogenic component due to obesity-associated peripheral neuropathy may also be involved [97]. Obesity and abdominal obesity have also been associated with overactive bladder, especially in women [96, 98]. The risk of **kidney stone disease** is also increased in patients with obesity, being 1.3- to 2.1-fold that of normal weight individuals [99]. Obesity-related factors may also affect the composition of kidney stones, with hypertension, type 2 diabetes and visceral fat being associated with higher risk of uric acid stones [100, 101]. More in general, all individual components of the metabolic syndrome may contribute to the development of kidney stone disease [102].

## 7.7 Musculoskeletal System

### 7.7.1 *Bone and Joint Diseases*

Excess weight imposes a mechanical overload on the joints, making obesity a risk factor for the development of **osteoarthritis**. Proinflammatory adipokines and cytokines secreted by both visceral and local (e.g. intra-articular) fat depots may also be involved in the development of osteoarthritis and other obesity-associated musculoskeletal disorders [103]. Obesity increases the risk of knee osteoarthritis by 2.7- to 4.5-fold as compared with normal weight [104, 105]. An increase in compressive load on the spine, together with the loss of muscle mass often seen in patients with obesity, may cause biomechanical changes and posture alterations leading to **degeneration of the intervertebral discs** and **low back pain** [103]. The obesity pandemic is deemed responsible for the increasing incidence and prevalence of **gouty arthritis** due to the deposition of uric acid crystals. Hyperuricemia is often associated with insulin resistance and the state of chronic low-grade inflammation that characterizes excess adiposity [106]. Consistently, the risk of developing gout in those with obesity is more than twice the risk of normal weight individuals [107]. It has been proposed that obesity-associated chronic low-grade inflammation may impact bone mass [108]. However, there is evidence that increasing BMI and insulin resistance are associated with increased bone mineral density and do not affect fracture risk [109].

### 7.7.2 *Sarcopenic Obesity*

The definition "sarcopenic obesity" indicates obesity with altered body composition due to low skeletal muscle function and mass. Several metabolic changes occur in the skeletal muscle of individuals with obesity that may negatively impact muscle mass and function. Inflammation and oxidative stress exert catabolic effects and may induce anabolic resistance in skeletal muscle, ectopic fat accumulation results in lipotoxicity, alterations in muscle stem cell may determine a shift towards adipocyte differentiation, and mitochondrial dysfunction leads to less efficient energy production and exacerbated oxidative stress [110]. Furthermore, individuals with obesity reduce their level of physical activity as the disease progresses, due to functional limitations imposed by increasing body mass and musculoskeletal complications. Physical inactivity further worsens skeletal muscle health [111]. Prevalence estimates of sarcopenic obesity vary widely depending on the definition used, ranging from nearly 3% to over 20% [112]. Despite being associated with significantly increased morbidity and mortality [113], sarcopenic obesity is often overlooked. The European Association for the Study of Obesity (EASO) has suggested using a simple, rapid and inexpensive method such as the SARC-F questionnaire [114] to identify sarcopenia, possibly in conjunction with the hand-grip test [115] for assessing muscle strength [116]. However, the most adequate diagnostic criteria for sarcopenic obesity are still debated [112].

## 7.8 Reproductive System

Obesity is associated with **impaired fertility** in both men and women. In women of childbearing potential, excess leptin interferes with the development of the dominant follicle and maturation of oocytes in the ovary and alters endometrial receptivity [117]. In normal conditions, leptin is involved in the regulation of gonadotropin-releasing hormone (GnRH) pulsatile secretion from the pituitary [118]. In obesity, central leptin resistance reduces GnRH secretion, affecting the release of gonadotropins. Obesity, especially abdominal obesity, is also associated with an increase in free circulating androgens, which may contribute to anovulation [117]. In patients with polycystic ovary syndrome (PCOS) who undergo assisted reproduction therapy, obesity is associated with lower pregnancy and live birth rates [119]. Pregnant women with obesity are at increased risk of **adverse pregnancy outcomes** such as gestational diabetes, hypertensive disorders of pregnancy [120] and miscarriage [121]. Furthermore, in utero exposure to obesity may alter gene expression and induce metabolic abnormalities in the offspring [122].

In men with obesity, **hypogonadism** is common, due to an increase in circulating oestrogens secondary to enhanced conversion of testosterone to oestradiol by adipose tissue aromatases [123]. Leptin resistance may also play a role by altering the hypothalamus–pituitary–testes axis [123]. Hypogonadism may lead to impaired

spermatogenesis and subfertility, as well as with **erectile dysfunction**, which may also be a consequence of the psychological impact of obesity [124].

## 7.9 Neurological and Psychological Disorders

Individuals with obesity are at increased risk of neuro psychiatric diseases. An association between obesity, **cognitive impairment** (e.g. deficits in learning, memory and executive functioning) and **dementias** such as Alzheimer's disease and vascular dementia has been reported, neuroinflammation and obesity-related comorbidities (e.g. hypertension) being the most likely underlying pathogenic mechanisms [125]. Obesity-associated chronic low-grade inflammation may precipitate local inflammation within the hypothalamus, affecting synaptic plasticity, contributing to neurodegeneration, and initiating brain atrophy. These events lead to disturbances of extra-hypothalamically-mediated cognitive function [126]. Obesity, particularly abdominal obesity, is associated with a 26–38% increased risk of **depression** [127]. The relationship is bidirectional, with obesity increasing the risk of developing depression, and vice versa. Biological (genetics, hyperactivation of the hypothalamic–pituitary–adrenal axis due to elevated cortisol levels and immunoinflammation, neuroendocrine regulators of energy metabolism including leptin and insulin and gut dysbiosis), psychological and behavioural factors have been postulated to play a role in this bidirectional association [128]. **Weight stigma**, i.e. the social rejection and devaluation that accrues to those who do not comply with prevailing social norms of adequate body weight and shape [129], may also deeply impact mental health. The greater the weight stigma, the worse the physiological health status of overweight and obese adults, with greater odds of eating disturbances, depressive symptoms, anxiety and body image dissatisfaction [130].

Finally, emerging evidence indicates that individuals with obesity are at increased risk of **peripheral neuropathy**, even in the absence of altered glucose metabolism [131, 132]. The prevalence of polyneuropathy has been reported to be lowest (3.8%) in lean controls, intermediate (11.1%) in subjects with obesity and normoglycaemia and highest (34.6%) in subjects with obesity and diabetes [131].

## 7.10 Nutritional Deficiencies

Epidemiological evidence indicates that **vitamin D deficiency** is extremely common in people with obesity [133]. Several mechanisms have been hypothesized to explain the association between hypovitaminosis D and obesity, including a lower dietary intake of vitamin D, reduced exposure to sunlight due to less outdoor physical activity, reduced intestinal absorption, reduced hydroxylation in adipose tissue and 25 (OH) D sequestration in adipose tissue [134]. It has been hypothesized that vitamin D deficiency could contribute to obesity or hinder weight loss, affect

calcium balance, impair immune response or have a causal role in insulin resistance [135], but studies that assessed the metabolic effects of vitamin D supplementation in obesity have yielded conflicting results [136, 137]. Several other nutritional deficiencies likely due to poor dietary habits have been reported in people with obesity, including vitamin B1 (thiamine), iron, folate and zinc deficiency [138–141].

## 7.11 Cancer

The International Agency for Research on Cancer (IARC) has identified 13 cancers associated with overweight and obesity, namely adenocarcinoma of the oesophagus, gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast cancer, endometrium, ovary, renal cell carcinoma, meningioma, thyroid cancer and multiple myeloma [142]. In contrast to other cancers, cancers associated with obesity have become more frequent during the past two decades, accounting for up to 40% of all cancers [49, 143]. The number of cases is highest in high-income countries and is expected to rise in low- and middle-income countries [142]. Mechanisms linking obesity and cancer development include increased levels of insulin and insulin growth factor 1, altered adipokine production and subclinical chronic low-grade inflammation, dysfunctional adipose tissue microenvironment, gut dysbiosis causing increased gut permeability, inflammation and carcinogenic metabolite production, certain dietary habits common among people with obesity (e.g. increased red and processed meat or low fibre consumption) and altered steroid metabolism with increased oestrogen levels targeting breast and endometrium [144, 145]. Of note, a reduction in excess body fatness through intentional weight loss may counteract the mechanisms involved in cancer development and help prevent obesity-associated cancers [146].

## 7.12 Immunity and Infections

An association between obesity and **infections** has emerged in recent years [147]. Subjects with obesity are more prone to infections, and obesity appears to affect the outcome of certain infectious diseases, particularly viral respiratory infections such as influenza and, as recently and widely demonstrated, coronavirus disease 2019 (COVID-19) [148, 149]. Having obesity increases by 46% the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and by 113%, 74% and 48% the risk of hospitalization, intensive care unit admission and mortality for COVID-19, respectively [150]. Several obesity-related factors may increase the susceptibility of individuals with obesity to infectious diseases, including altered respiratory mechanics, dysregulated immune system and comorbidities such as diabetes or atherosclerosis [147, 150, 151]. Recent evidence from studies on COVID-19 indicates that abdominal adiposity plays a key role [152, 153], likely due to

proinflammatory mediators secreted by dysfunctional visceral adipose tissue and reduced lung expansion imposed by the increase intra-abdominal pressure caused by excess abdominal fat. Individuals with obesity are also at an increased of developing **infectious complications** such as sepsis, pneumonia and bacteraemia following surgical procedures, *Helicobacter pylori* infection and exhibit a lower antibody response to certain vaccinations including influenza, hepatitis B and tetanus [151].

Finally, obesity has also been associated with certain **autoimmune diseases** such as autoimmune thyroiditis, rheumatoid arthritis, multiple sclerosis, psoriasis and psoriatic arthritis [154]. Evidence also exists of a link between obesity and autoimmune diabetes.

## 7.13 Conclusions

Obesity is a chronic and complex disease that significantly increases all-cause and cardiovascular mortality [49]. Individuals living with obesity are burdened by a constellation of complications that deeply impact health status and quality of life [155]. Use of BMI is very practical, but BMI does not reflect body composition and the complexity of obesity. Measurement of waist circumference [52] and tools such as the Edmonton obesity staging system (EOSS) [156] or the Cardiometabolic Disease Staging (CMDS) system [157] should be included in the assessment of obesity-related health risk, as they may better reflect morbidity and mortality associated with increased adiposity.

Weight loss interventions may reduce both obesity-associated morbidity and mortality [158, 159]. Implementing multidisciplinary strategies to prevent obesity and achieve weight loss in those with overweight/obesity is therefore of the utmost importance.

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# Chapter 8
# Techniques to Study Metabolism


**Roberto Codella**

## 8.1 Introduction

Metabolism comprises all anabolic and catabolic reactions occurring in the body to maintain tissue homeostasis [1]. In this process substrates are continuously transformed into energy and vice versa. The terms metabolic rate and energy expenditure are normally used synonymously. In the international system, the basic unit of energy is joule; however, energy is conventionally expressed as calorie (more frequently as kcal), which corresponds to the quantity of heat required to increase the temperature of 1 kg of water by 1 °C. The assessment of individual's metabolic rate is critical for researchers, nutritional and sport personnel as well as for clinicians. An orthodox clinical approach to serious conditions such as anorexia nervosa, morbid obesity or critical patients has to rely on the measurement of metabolic rate and substrate oxidation of the affected subjects [2, 3]. Similarly, elite athletes can largely benefit from data coming from substate utilization and energy consumption to perfect their physical performance. In this light, various techniques, with specific target of application, have been developed during the time to cover the growing needs of evaluating metabolism in various conditions and for different purposes.

In this section, the principal methods currently adopted to measure body energy expenditure and substrate utilization to assess quantity and quality of metabolic processes are elucidated.

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## 8.2 Direct Calorimetry

Direct calorimetry enables the evaluation of the total energy consumption. The process takes place via the assessment of total body heat production in confined space, usually represented by a thermically isolated chamber [4, 5] (Fig. 8.1). Direct calorimetry is a highly reliable and accurate technique, usually adopted as "gold standard" for energy expenditure evaluation. On the other hand, direct calorimetry represents an expensive and time-consuming technique to assess energy expenditure. This makes this method poorly suitable for routine evaluation of energy expenditure in clinic or fitness facilities [4, 5]. Its functioning is based on the principle according to which all body reactions ensue into heat production. Therefore, the technique provides the measurement of a subject's heat production. The study subject enters a thermically isolated chamber, whose walls embed hydraulic pipes through which water flows at a steady rate. Temperature and volume of the water flowing through the pipes are known and constantly measured throughout the study. A constant supply of $O_2$ and $CO_2$ removal are provided. Moisture is also removed through a proper apparatus. The subject can either rest or engage in physical activity. Body heat production is measured as a difference between the temperature of incoming and outgoing water. A further quota of heat released by the subject through skin or by airway evaporation can be accurately measured through appropriate gear [4]. By adding up the two energy components, a total energy expenditure can be calculated with a relatively high accuracy. The technique is often adopted as

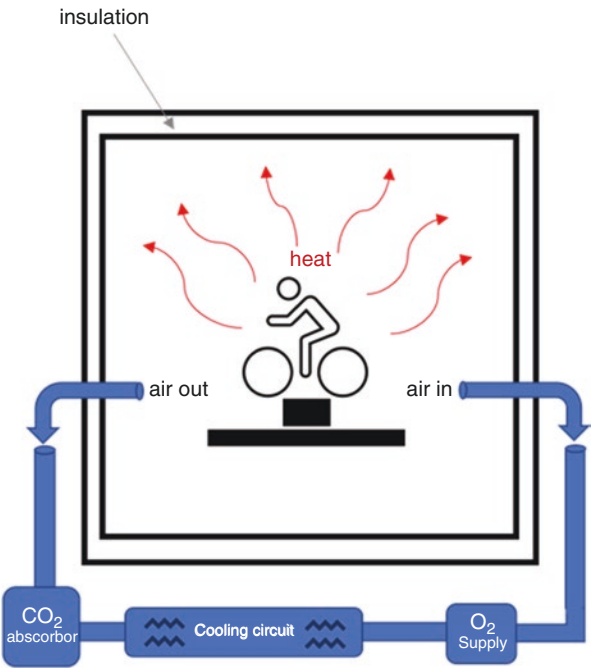


**Fig. 8.1** A schematic representation of calorimetric chamber

standard method for the evaluation of accuracy of alternative methodologies for the assessment of energy expenditure [6]. The subject has to remain confined in the chamber for 24 h. As a consequence, direct calorimetry is not intended to be employed for short measurement sessions. The technique does not provide any clue about the oxidation of the energy substrates (carbohydrates, lipids, protein), which limits the employment of direct calorimetry to research activities or to the study of thermoregulation. Furthermore, not all the heat measured by the device is necessarily produced by the body: ergometers or other gear can generate additional heat, if used. Finally, as mentioned the technique is relatively expensive and does not detect rapid changes in energy expenditure, thus resulting poorly suitable for evaluation of the largest part of sports or activities.

## 8.3 Indirect Calorimetry

Indirect calorimetry relies on the principle that almost all the inhaled $O_2$ through the airways is utilized for substrate oxidation and then converted into energy and $CO_2$ (with a residual of $H_2O$ and urea) [7–9]. In this light, the measurement of $O_2$, $CO_2$ fluxes ($VO_2$ and $VCO_2$) and urinary nitrogen excretion can give information about the amount (and type) of substrate oxidation and the energy expended. The operating principle on which indirect calorimetry is based follows several assumptions: (a) the contribution of anaerobic metabolism is rather small and then negligible during the so-called *steady state* (see further); (b) in a mixed diet with balanced macronutrient composition, for each litre of $O_2$ inhaled, 4.82 kcal is produced [9, 10]. Weir's equation allows to derive energy expenditure knowing the inhaled $O_2$ ($VO_2$) and exhaled $CO_2$ ($VCO_2$) values, measured via the spirometry:

$$\text{Energy expenditure} = 3.941\ VO_2 + 1.106\ VCO_2 - 2.17\ N_2\,(\text{urinary})$$

As mentioned, since the protein oxidation, in a normal fed subject with average diet, can be considered negligible (1% error out of 12–13% of kcal deriving from protein oxidation) [8], the equation can be simplified as follows:

$$\text{Energy expenditure} = 3.941\ VO_2 + 1.106\ VCO_2$$

Assuming a relatively small difference in accuracy measure between the two methods [7], indirect calorimetry presents some advantages compared to direct calorimetry. Indirect calorimetry devices are smaller and less expensive, and the procedure requires far less time (around 40 min) compared to direct calorimetry, to assess energy expenditure. Moreover, this method provides data on substrate utilization, which can be an instrumental information for clinicians and sportive professionals. Such advantages make the indirect calorimetry the most convenient and widely used technique to assess energy expenditure in clinic and fitness facilities [7]. Nevertheless, also indirect calorimetry requires a specific apparatus and a strict

adherence to correct procedures when performed in order to avoid biases. In addition, it is only to be adopted in resting individuals or in specific sport activities in which the *steady state* can be easily reached and maintained for a sufficient period of time (1 min or longer) [11]. *Steady state is* a condition in which $O_2$ and $CO_2$ flows are in equilibrium and only dependent on substrate oxidation [11]. Indirect calorimetry therefore ensures the acquisition of two types of critical data: (a) energy expenditure and (b) type of substrates oxidized, through respiratory quotient (RQ) determination. RQ is calculated as the ratio between $VCO_2$ and $VO_2$ ($VCO_2/VO_2$). RQ principle relies upon the occurrence that every substrate, in its oxidation pathway, uses up and produces a definite quota of $O_2$ and $CO_2$. For example, RQ for carbohydrate is around 1.0, meaning that the $O_2$ employed and $CO_2$ produced in the oxidation process are equal, as showed by the equation:

$$C_6H_{12}O_6 + 6O_2 \Leftrightarrow 6CO_2 + 6H_2O + \text{energy}\left(38\ \text{ATP and heat}\right)$$

The oxidation of a single glucose molecule produces six molecules of $CO_2$ (plus energy) and requires six molecules of $O_2$, resulting in a ratio 6/6 ($CO_2/O_2$) = 1. The RQ for lipids is approximately 0.7 [10]. As for glucose, the oxidation of palmitic acid (used as a paradigm of fatty acid molecule) requires 23 molecules of $O_2$ and produces 16 molecules of $CO_2$; the ratio in this case is 16/23 = 0.696. Same reasoning can be applied to protein. Subjects consuming a diet containing a balanced mix of carbohydrates, protein and fats present a RQ around 0.82 [10].

Therefore, the indirect calorimetry analysis allows to derive the percentage of substrate utilization according to how measured RQ values are close to specific RQ of the substrates (0.7–1) (Table 8.1). This enables, for example, estimating the type (ketogenic, high fat, high carbohydrate) of diet being consumed by the subjects as well as monitor the clinical and nutritional state of critical patients (eating disorder-affected, hospitalized, patients with cachexia) [7, 12]. This technique presents several minor limitations: (a) the need to reach and to maintain for an adequate period of time the *steady state*; (b) difficult to correctly estimating $VCO_2$ (respiratory $VCO_2$ is not stable and could not precisely reflect the $CO_2$ actually being released by tissues); (c) the occurrence of possible biases deriving from the assumption that $O_2$ remains constant during the test; (d) inability to assess energy expenditure for anaerobic activities.

From a practical standpoint, the analysis can be carried out according to two different modalities: (a) *closed-circuit* spirometry; (b) *open-circuit* spirometry. Both are worthful and comparable as level of accuracy in the evaluation of energy expenditure and RQ. Nevertheless, some minor differences make the *open circuit* system preferentially used for measures of subjects practicing physical activity [13].

**Table 8.1** Respiratory quotient (RQ) of the main oxidized compounds

| | | |
|---|---|---|
| RQ | Carbohydrates | 1.0 |
| | Lipids | 0.703 |
| | Proteins | 0.833 |

(a) *Closed-Circuit Spirometry*

In the *closed-circuit* spirometry, the individual is forced to breathe the air contained in sealed cylinder (spirometer) filled with $O_2$. The quantity of $O_2$ used up by the subject is measured (usually, $O_2$ consumption is the only variable evaluated). The spirometer is a closed system, in which the subject undergoing the test rebreathes exclusively the gas present in the apparatus [8]. No external air is intended to penetrate into the spirometer during test execution, as not to modify $O_2$ volume, thereby the subject has to remain mouthpiece (and nose-clipped). The volume difference between beginning and end of the test represents the quota of $O_2$ consumed for oxidative purposes. As above-mentioned, since each litre of $O_2$ produces 4.82 kcal, the total amount of energy expended in a certain range of time can be calculated through a software. A specific accessory device (usually a canister filled with potassium hydroxide) is involved in the absorption of exhaled $CO_2$ and air moisture. This is particularly important in order to avoid any replacement of $O_2$ with a non-absorbed $CO_2$, which could lead to potential measurement biases in $O_2$ volumes. Such occasion usually occurs when the exhaled volumes of $CO_2$ are extremely high (such as during exercise), thus overcoming absorption capacity. This prevents the extensive adoption of closed-circuit spirometry during exercise measurements, especially in vigorous activities [14]. Air temperature can also influence the gas volumes in the device: the higher temperature of exhaled air can affect air volume, leading to potential underestimation of energy expenditure [8]. Furthermore, since only measuring $O_2$ volumes, the closed-circuit spirometry does not allow to calculate RQ and therefore determining substrate oxidation, condition that limits its applicability to selected conditions. *Closed-circuit* spirometry is typically employed in hospitals or clinics to evaluate energy expenditure of patients [7]. The technique is largely unsuited for measuring energy expenditure during sport activity owing to its structural limitation and possible biases occurring at very high respiratory volumes exchanged.

(b) *Open-Circuit Spirometry*

The open-circuit chamber method was one of the earliest types of calorimetry devices developed [15]. In the open-circuit system, the subject directly inhales ambient air and expires into a separate outlet. Alternatively, ambient air can be supplied by a mechanical ventilator through a specific device (e.g., a canopy, mask), in which the subject exhales. $O_2$ and $CO_2$ concentrations are sensed by a dedicated sampling system. Indeed, during exhalation, the gases pass through an apparatus that measures the volume of air and the exhaled $O_2$ and $CO_2$. The sampled air is corrected for standard conditions and the volume of $O_2$ and $CO_2$ and then analysed [15]. $VO_2$ and $VCO_2$ are derived from these measurements as the difference between inhaled and exhaled $O_2$ and $CO_2$ volumes. The *open-circuit* system is typically employed to measure the resting energy expenditure in healthy subjects or subjects affected by clinical conditions (obesity, underfed and critical ill patients) [9, 12, 15], in order to correctly establish daily energy requirements for a nutritional intervention. The examination is carried out in a confined space and takes about 30–40 min. The patient

breaths through a mask or a canopy, in a room kept in condition of thermoneutrality (21–25 °C). The subject is required to be in a fasted state (from at least 12 h); respiratory exchanges have to reach the *steady state* to reach significative results [11]. As reported above, the *steady state is* a condition in which $O_2$ and $CO_2$ flows are in equilibrium. *Open-circuit spirometry* an unsuited technique to measure energy expenditure during anaerobic physical activity (partly or totally) or any type of exercise in which the *steady state* cannot be reached for a sufficient length of time [16]. Other variants such as the *bag method*, the *computerized* and the *portable systems* enable to evaluate respiratory exchange in different conditions and during sport activities.

The *bag method* is a subtype of the *open-circuit system* employed to evaluate $O_2$ flow during ergometry work or several types of non–lactic acid producing sport activities in which the steady state can be reached. The bag technique is rather fast compared to other methods (takes less than 10 min to be carried out). The actual duration depends on exercise intensity and the intrinsic limitation of the technique (for longer periods, $O_2$ can diffuse through the bag).

Portable devices can be worn during physical exercise, thus permitting measurement of energy expenditure during sport performance [13]. Nevertheless, flaws such as weight or movement impediment can affect correct measurement, especially during vigorous exercise and in kids.

## 8.4 Doubly Labelled Water

The method was developed in the 1950s by the physiologist Nathan Lifson. Due to high accuracy, doubly labelled water still represents the reference method for measuring energy expenditure in a free-living context and in nutrition research [17]. This technique entails the adoption of a "labelled" water in which both constituents of water molecule are replaced by their respective isotope deuterium [$^2H$] and 18-oxygen [$^{18}O$] which can be analysed by a detector, once disposed through urine and breath [17, 18]. The technique requires specific devices for measurements (mass spectrometry) and specific isotopes, thus resulting expensive. Doubly labelled water is an accurate and reliable strategy to estimate total energy expenditure in a certain period of time, due to relatively slow isotope turnover [18]. A dose of labelled water ($^2H_2{}^{18}O$) is swallowed by the subject and distributes throughout the body. After 5–7 days or normal daily activity, the subjects are analysed for isotopes quantification. The hydrogen and some of the $O_2$ of doubly labelled water are eliminated through the urine, whereas part of the $O_2$ is exhaled in the form of $CO_2$. Since the same amount of $O_2$ is eliminated as water and $CO_2$, the measurement of hydrogen and $O_2$ isotopes in body's water can be used to determine the $CO_2$ production [19]. Knowing the overall quantity of body water, total energy expenditure can therefore be estimated from daily $CO_2$ production and isotope turnover in the urine. The accuracy of this method is appreciable (>98%) [19]. Compared to the other techniques, the doubly labelled water does not require bulky structures and a no strict attention

to lifestyle procedures [17]. As mentioned above, the major issue affecting this technique is represented by the high cost of isotopes and spectrometry. Noteworthy, doubly labelled water is not suitable for estimating short-time energy expenditure, for example during physical exercise. These occurrences suggest the technique as preferentially adopted for estimating energy expenditure in research investigations or for the validation of surrogate methods for assessing energy expenditure.

## 8.5 Accelerometer/Metabolic Holter

The accelerometer represents a potential alternative method for measuring energy expenditure in free-living conditions as well as during physical exercise. The accelerometer is a device that is worn by means of an elastic band on the upper triceps side of the master arm and monitors several physiological parameters. Subject's baseline data (e.g. age, sex, weight, height) are provided by the user and therefore computed by the software to adjust data measured by the device [20]. The device employs a combination of different sensors to implement multiple measures. The adoption of multiple sensors is critical for overcoming disambiguation and improve measurement accuracy: (a) a sensor detecting heat flow measures the amount of heat dissipated by the body; (b) a thermistor for measuring skin temperature; (c) a sensor for evaluating the galvanic skin response (changes in sweat activity that are reflective of a subject's emotional state); (d) a further sensor monitors near-body temperature. The accelerometer detects the position of the body in the space, thus providing information on body position. In this regard, accelerometers can measure acceleration in one direction as well as on more than one (anteroposterior, mediolateral and vertical, in the triaxial accelerometers). The accuracy and reliability of accelerometers in the evaluation of energy expenditure in free-living conditions as well as during sport activity has been tested in different studies [20, 21]. Despite some evidence suggesting positive results, the accuracy of accelerometers in measuring energy expenditure is still a matter of debate, thus its applicability in clinical practice is controversial. For example, accelerometers seem to largely overestimate energy expenditure in obese individuals probably due to the poor mechanical efficiency of these subject's movements [20, 21]. Furthermore, accelerometers do not provide any information on the substrate utilization. These limitations prevent, de facto, routinely adoption of accelerometers as reliable devices in research and clinical practice.

## 8.6 In Vivo Magnetic Resonance Spectroscopy (MRS)

The in vivo magnetic resonance spectroscopy (MRS) is an analytical, radiation-free technique that allows to assess cellular metabolites concentrations, monitor metabolic fate of biochemical substrates and measure chemical exchange

processes in conditions of *steady state* [22–24]. MRS operating principle is the same as conventional magnetic resonance. MRS employs magnetic fields and radio wave to activate MR-sensitive nuclei ($^{1}$H, $^{31}$P and $^{13}$C) of biological compounds and cellular constituents. A specific apparatus then acquires the signal and elaborates a detailed image depicting the distribution of the element adopted for the analysis of the chosen pathway. The selective employment of different nuclei allows to achieve information on distinct metabolic processes. MRS can be adopted in research as well as in clinical diagnostic as a replacement for needle biopsy. Indeed, it enables both physicians and researchers to obtain biochemical insights about tissues metabolic processes and their response to specific stimuli in a non-invasive fashion.

### *8.6.1 $^{1}$H-MRS*

$^{1}$H represents the most sensitive nucleus for MRS investigation. $^{1}$H-MRS technique is capable of distinguishing muscle tissue from fat, bone and connective tissue. $^{1}$H-MRS permits the quantification of intramyocellular lipids, lactate production and the evaluation of total muscle creatine content [25, 26]. Furthermore, this technique gives insights about metabolite diffusion in a single muscle cell [22] and tissue deoxygenation [27]. Nevertheless, $^{1}$H-MR results can be hard to evaluate due to the ubiquity of hydrogen atoms in biological molecules. $^{1}$H-MRS can be affected by the presence of a large percentage of water that can generate confounding signals. However, recent water suppression techniques have enabled the detection of metabolites present at low concentrations [28] (Fig. 8.2).

### *8.6.2 $^{13}$C-MRS*

$^{13}$C-MRS employs $^{13}$C carbon isotope to identify biochemical structures. $^{13}$C carbon nuclei are intravenously orally administered. The incorporation of $^{13}$C nuclei into specific substrates permits monitoring of the metabolic fate of such compounds in a definite time range. In this technique, the signal is generated from carbon 1 of the glycogen molecule. The incorporation of labelled [$^{1\text{-}13}$C]-glucose into glycogen allows the measurement of muscle glycogen synthesis rates [29]. The infusion of $^{13}$C-enriched glucose or acetate $^{13}$C-MRS has also been employed to assess tricarboxylic acid (TCA) cycle flux of substrates. The technique relies on the principle that ongoing TCA cycle can be evaluated by a specific pattern of $^{13}$C-enrichment in molecule of glutamate (glutamate reflects TCA turnover kinetics, since in tight equilibrium with ketoglutarate). [$^{2\text{-}13}$C]-acetate has been used to

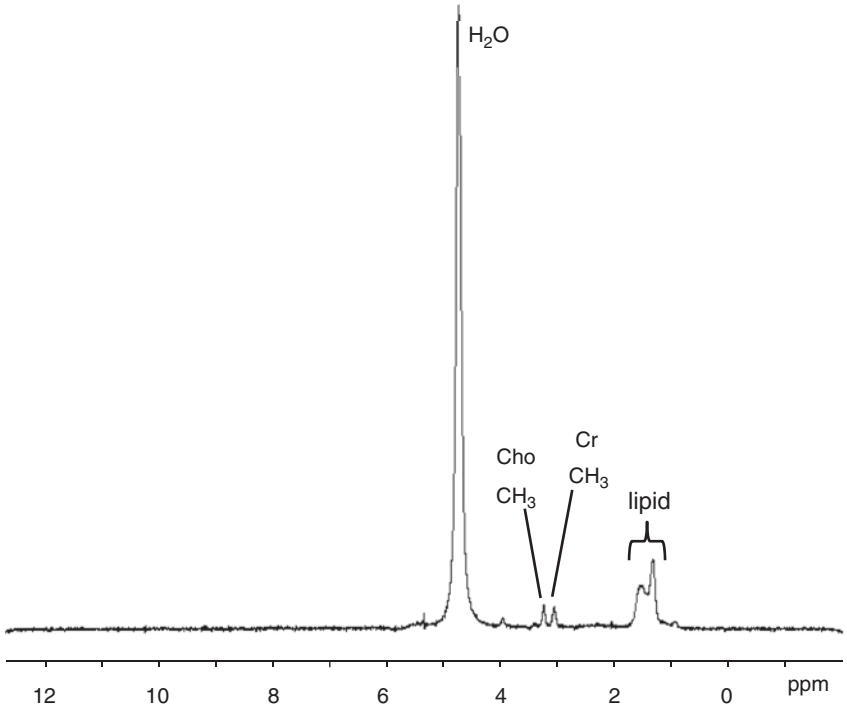


**Fig. 8.2** $^{1}$H-MR spectrum

determine TCA cycle activity to assess mitochondrial coupling [22]. Although its potential application is in the investigation of metabolic processes involving substrate oxidation, $^{13}$C-MRS remains a technique affected by poor sensitivity (Fig. 8.3).

### *8.6.3 $^{31}$P-MRS*

This technique has substantially helped the comprehension and the regulation of human energy metabolism. It has also contributed characterizing dysmetabolic conditions typical of obesity and diabetes such as mitochondrial dysfunction from a biochemical standpoint [30]. $^{31}$P-MRS is one of the most sensitive among MRS procedures. $^{31}$P nucleus is naturally present in all biological molecules containing

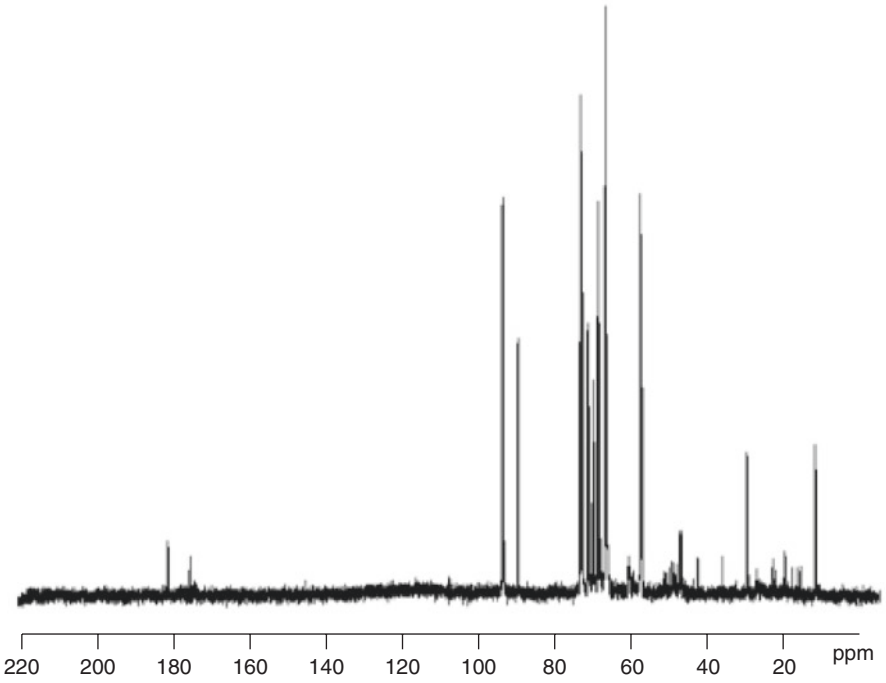


**Fig. 8.3** $^{13}$C-MR spectrum

the phosphoric functional group. This occurrence avoids the exogenous administration of the isotope. The phosphorus spectra can then be employed to quantify the presence and fluxes of phosphate intermediates such as ATP, inorganic phosphate and phosphocreatine, enabling the analysis of kinetics of energy metabolism [31]. For example, $^{31}$P-MRS is a technique adopted for the study of bioenergetics in the skeletal muscle during exercise and recovery, replacing muscle biopsies.

$^{31}$MRS ensures the estimation glycogenolytic rates and aerobic ATP synthesis [32] and muscle oxidative capacity in different conditions such as ischaemic exercise, aerobic exercise under steady-state conditions or during work jumps and mixed exercise [33].

$^{31}$P-MRS also permits to indirectly estimate intracellular PH, since $H^+$ concentration in a specific tissue can be retrieved by quantifying inorganic phosphate biochemical shift.

When investigating ischemic exercise, glycogenolysis-derived ATP production can be directly calculated from changes in pH, corrected for the number of protons consumed by phosphocreatine hydrolysis [33]. In mixed exercise, both glycogenolysis-derived and oxidative ATP synthesis can be estimated through an estimation of total proton production and total ATP turnover (Fig. 8.4).

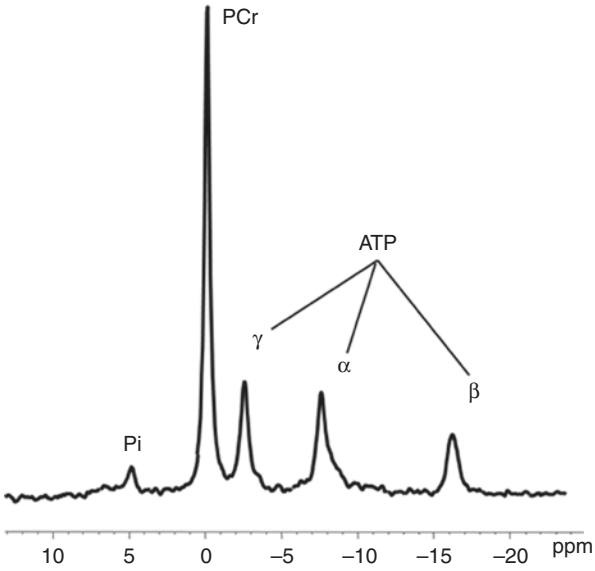


**Fig. 8.4** $^{31}$P spectrum obtained from a hindlimb mouse muscle

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# Chapter 9
# Obesity: Medical and Surgical Treatment


**Daniele Tassinari, Alessandro Giovanelli, and Carmela Asteria**

## 9.1 Introduction

The United Nations (UN) has recently sounded the alarm on the "globalization of obesity." An alarm that is as worrying as the contrasting alarm of world hunger. The rate of overweight and obese people continues to rise worldwide, and while hunger is linked to demarcated zones, obesity can be considered of epidemic proportions. Out of the 20 countries where obesity increased more rapidly, eight are African. A problem, according to FAO, arising from food being more and more industrialized, highly processed with very little nutrition but a large amount of fats, sugar, salt, and chemical additives. According to recent UN data, there are 821 million people suffering from hunger (11% of the world population) compared to two billion overweight people of which 672 million are obese. About 3.4 million people die every year as a result of problems related to obesity [1].

The World Health Organization (WHO) has estimated that from 1975 to today, the number of obese people in the world has tripled, and the trend continues to escalate, forecasting that one fifth of the global population will be affected by 2025 [2]. In 2016, approximately 13% of the world's population was obese and 39% overweight. Another alarming fact is the continuous rise of this disease among the young: in 2016, 41 million children below the age of 5 years and above 340 million youths between the ages of 5 and 19 years were overweight or obese.

Obesity is therefore to be considered, in all respects, a threat to public health and, at the same time, an actual economic threat. The health costs which derive from the need to treat the serious health problems associated with obesity such as diabetes, hypertension, dyslipidemias, obstructive sleep apnea, musculoskeletal disorders (osteoarthritis), cardiovascular diseases, venous stasis disease and thromboembolic

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disorders, chronic kidney disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, some cancers including colon, liver, gallbladder, breast, endometrial, ovarian, prostate, and kidney are high [3].

At this point, the silent killer in our society, diabetes, deserves a special mention. It has been estimated that this disease, which is in continuous growth, will increase over 50% in the next 10 years [4, 5]. If we consider that more than 7% of deaths concerning people with a body mass index (BMI) >25 kg/m$^2$ are attributed to type 2 diabetes mellitus (T2DM) and/or cardiovascular diseases [6] and that at this moment we have an obese population of 672 million, we can say that 47 million deaths may be caused by these pathologies.

Obesity is a preventable disease, and the proper education in relation to nutrition and an efficient campaign to raise public awareness concerning the problem are undoubtedly the best weapons against this social plague. However, how can we contrast the problem in patients diagnosed with the disease? The aim of this chapter is to offer a view on the medical and surgical therapeutic options available for obese patients.

## 9.2 Medical Treatment

### *9.2.1 Pharmacological Treatment Options for Obesity Care*

Using pharmacotherapy for weight management is consistent with treating obesity as a chronic and life-threatening disease that requires a multifactorial and long-term approach, encompassing behavioral intervention, dietary change, and appropriate medical treatment. Bariatric surgery is a very effective intervention for achieving weight loss and ameliorating obesity-related comorbidities, but with greater risks and higher costs if compared to nonsurgical interventions, and thus it is not always feasible for all obese subjects. Thus, pharmacotherapy, with an efficacy level that falls between that of lifestyle and surgical interventions, can bridge the gap that exists.

Lifestyle interventions based on diet, exercise, and behavior modification represent the milestone of treatment for overweight and obese individuals. However, these approaches are characterized by lack of success in the long term for the majority of patients. In particular, it has been demonstrated that behavioral interventions can result in at best a 5–8% mean body weight loss during the first 6 months of treatment but one-third to two-thirds of lost weight is regained within 1-year and almost all weight is regained within 5 years [7]. This is partly due to the reduction in energy expenditure that inevitably attends weight loss. In one report, maintenance of body weight at 10% below the baseline weight in obese subjects was associated with an 8 kcal/kg reduction in total energy expenditure [8].

Biological defense mechanisms are a major obstacle to weight loss. Several overlapping neurohormonal signals and environmental factors in our “obesogenic”

environment aimed at maintaining body fat mass as a survival measure [9, 10]. For any obesity prevention or treatment strategy, including pharmacotherapy, to be successful, it will have to be able to suppress these adaptive responses and permanently change the defended level of body weight/adiposity. Current guidelines recommend that individuals who fail to respond to lifestyle interventions after 6 months of treatment, and have a BMI of ≥30 kg/m$^2$ or a BMI of ≥27 kg/m$^2$ with an obesity-related comorbidity may be considered for weight loss medication treatment [11]. In particular, weight loss medications are indicated in patients with excess body weight who (a) achieve modest benefit with lifestyle intervention after 6 months and need additional weight loss; (b) lose some weight with lifestyle intervention but have difficulty maintaining weight loss; (c) have made numerous unsuccessful attempts at losing weight with diet and exercise; and (d) are unable to comply with recommended lifestyle changes due to chronic severe medical conditions. Nowadays, six drugs for weight management have been approved by the US Federal Drug Administration (US FDA): five medicines for long-term use (orlistat, phentermine/topiramate, lorcaserin, bupropion/naltrexone and liraglutide) and only one for short-term use (phentermine). Needless to say, these drugs have to fulfill the strict safety and efficacy standards established by the FDA for the development of anti-obesity pharmacotherapeutics. In particular, they require trials of ≥1 year's duration and enrollment of >4500 subjects (3000 subjects randomized to active doses of the product and no fewer than 1500 subjects randomized to placebo) [12]. Moreover, in order to grant approval for a weight loss pill, the FDA looks for at least a 5% reduction in weight over a year. It should be noted that a reduction in body weight by 5–10% significantly lowers inflammatory and pro-thrombotic makers, as well as chronic disease incidence [13, 14]. Therefore, the goal of treatment is not only to reduce weight, but more importantly to improve the comorbid conditions associated with obesity. The association between obesity, particularly intra-abdominal/visceral fat and the risk of developing cardiovascular disease (CVD), type 2 diabetes, osteoarthritis, certain forms of cancer, sleep apnea, asthma, and nonalcoholic fatty liver disease (NAFLD) has been well established [15, 16]. Cytokines, such as interleukin 6, tumor necrosis factor alpha, resistin, and plasminogen activation inhibitor-1 secreted from fat cells have been implicated in the pathogenesis of these diseases, in part, by promoting local and systemic states of inflammation and thrombosis [17–19]. Healthcare professionals should be familiar with the basic principles regarding the pharmacotherapy of obesity and medication should not be viewed as a panacea for obesity treatment, but as in other chronic diseases, as a next-step treatment option for those continuing a healthy lifestyle regiment. Pharmacotherapy can also be considered an adjunct to bariatric surgery when additional weight loss is required or to prevent weight regain after weight loss surgery.

The objective of this chapter is to provide a profile of the effectiveness, the security and the side effects of the current anti-obesity drugs. The reviewed anti-obesity medications reported in this chapter include medicines approved for short-term use, drugs for chronic weight management, off-label medications for weight control and a hint to future anti-obesity pharmacotherapeutics.

#### 9.2.1.1 FDA-Approved Medications for Weight Management in the Short-Term

Drugs approved to treat obesity have been on the market since the 1950s.

Until the approval of dexfenfluramine in 1996 for chronic weight management, weight loss medications such as phentermine, diethylpropion, phendimetrazine, benzphetamine, and mazindol were approved in the US in 1959 for short-term use only, about 12 weeks. With the exception of fenfluramine, all drugs approved before 1996 were structurally related to amphetamine, although they differed in their effects on enhancing the turnover of norepinephrine and dopamine, thus differing in their abuse potential. Fenfluramine, first approved in 1973, was withdrawn worldwide 24 years later, along with its newly approved isomer, dexfenfluramine, in 1997 following echocardiographic demonstration of increased risk of mitral and aortic regurgitation among patients treated with these drugs. Phentermine remains available today and represents the most prescribed ant obesity drug for short-term weight management in the US (Table 9.1).

#### 9.2.1.2 FDA-Approved Medications for Weight Management in the Long Term

Nowadays, five weight loss drugs—orlistat, phentermine/topiramate, lorcaserin, bupropion/naltrexone, and liraglutide—were approved by the FDA and commonly commercialized in order to improve, in association with diet and physical activity, weight loss and its long-term maintenance (Table 9.2).

In 1997, another drug, sibutramine (trade name Meridia), a centrally acting serotonin-norepinephrine reuptake inhibitor, was approved for long-term treatment of obesity. However, the manufacturer voluntarily withdrew the drug worldwide at the request of the FDA in 2010 after the results of an outcome study in patients with high-risk cardiovascular conditions, known as the SCOUT trial [20]. This study revealed that patients with preexisting cardiovascular conditions had major adverse cardiovascular events (MACE) with sibutramine treatment relative to a placebo (hazard ratio, 1.16; 95% confidence interval 1.03–1.31; $P$ # 0.02).

**Table 9.1** Medications for weight management in the short term

| Drug | Year of approval | Still used | Comments |
|---|---|---|---|
| Phentermine | 1959 | X | Most prescribed in the USA—withdrawn in the EU (2000) |
| Diethylpropion | 1959 | X | |
| Phendimetrazine | 1959 | X | |
| Benzphetamine | 1960 | X | |
| Mazindol | 1973 | | Discontinued in 1999 |
| Fenfluramine | 1973 | | Discontinued in 1997 |

**Table 9.2** Medications for weight management in the long term

| Drug | Mechanism of action | Years of approval | Main Phase III studies (duration) | Dose | Weight loss change (kg or %) | HbA1c change (%) | Lipid change (%) | Diabetes | Main adverse effects | Contraindications |
|---|---|---|---|---|---|---|---|---|---|---|
| Orlistat | Selective inhibitor of the pancreatic lipase | 1999<br>Comments: Approved for pediatric obesity (2003) | XENDOS (4 years) | 120 mg TID[c] | 1 Y:<br>2.89 kg | No effects | Reduce total an LDL<br>No effects on HDL and triglycerides | Risk reduction of 37.3% | Spotting on underwear, flatulence, urgent bowel movements, fatty or oily stools, abdominal pain or discomfort, and incontinence | Chronic malabsorption, cholestasis or known hypersensitivity, warfarin, and LT-4 therapy |
| Phentermine + topiramate | Phentermine is a norepinephrine agonist in the SNC while topiramate is an anticonvulsant drug | 2012<br>Comments: Marketed to reduce teratogenicity risk | EQUIP (56 weeks)<br>EQUATE (28 weeks)<br>CONQUER (52 weeks)<br>SEQUEL (2 years) | 3.75 mg/23 mg QD[a]<br>15 mg/92 mg QD[a]<br>15 mg/92 mg QD[a]<br>7.5 mg/46 mg QD[a]<br>15 mg/92 mg QD[a]<br>15 mg/92 mg QD[a] | 3.5%<br>9.3%<br>9.21%<br>6.6%<br>8.6%<br>10.5% | Improvement of glucose/insulin levels | Improvement in triglycerides HDL and LDL cholesterol | Reduction in progression to type 2 diabetes in the treated patients | Paresthesia, dizziness, dry mouth, constipation, dysgeusia, and cognitive dysfunction | Cardiac history such as coronary disease, uncontrolled hypertension, and cerebrovascular disease<br>History of glaucoma, hyperthyroidism, treatment with monoamine oxidase inhibitors, and stones |

(continued)

**Table 9.2** (continued)

| Drug | Mechanism of action | Years of approval | Main Phase III studies (duration) | Dose | Weight loss change (kg or %) | HbA1c change (%) | Lipid change (%) | Diabetes | Main adverse effects | Contraindications |
|---|---|---|---|---|---|---|---|---|---|---|
| Lorcaserin | Selective serotonin receptor agonist | 2012 | BLOSSOM (1 year)<br>BLOOM (2 years)<br>BLOOM-DM (1 year) | 10 mg BID[b]<br>10 mg BID[b]<br>10 mg BID[b] | 3.1%<br>3.6<br>≥5.0% | Improvement in HbA1c<br>0.9% reduction | Improvements in HbA1c<br>HbA1c decreased significantly | Improvements in total cholesterol and triglycerides circulating levels | Headache, dizziness, feeling tired, dry mouth, cough, nausea, constipation, back pain, or low blood sugar (in people with diabetes), and serotonin syndrome | Pregnancy |
| Bupropion/ naltrexone | Blocking auto-inhibitory feedback on POMC neurons | 2014 | COR-1 (56 weeks)<br>COR-II (56 weeks)<br>COR-BMOD (56 weeks)<br>COR-diabetes (56 weeks) | Starting dose: 8 mg/90 mg<br>Increasing dose by 1 tablet each week until a total dose of 2 tablets BID[b]<br>8 mg/90 mg (first week)<br>16 mg/180 mg (second week)<br>24 mg/270 mg (third week)<br>32 mg/360 mg (from fourth week) | 6.1%<br>5.2%<br>9.3% | 0.6% reduction | Improvements in HDL cholesterol and triglyceride levels in all of the COR trials | | Nausea, vomiting, constipation, dry mouth, headache, dizziness, insomnia, and anxiety | History of seizures, bulimia or anorexia nervosa, severe depression, suicidal ideation, or suicide attempts. Chronic treatment with opioids and in those abruptly stopping alcohol, benzodiazepines, barbiturates, or antiepileptic drugs |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Liraglutide 3.0 mg | Glucagon like peptide-1 (GLP1) agonist | 2014 Comments: Approved at a lower dose (1.8 mg) to treat T2D in 2010 | SCALE Obesity and Prediabetes (1 year)<br>SCALE Diabetes (1 year)<br>SCALE maintain study (1 year) | 3.0 mg QD[a]<br>3.0 mg QD[a]<br>3.0 mg QD[a] | 0.5% to >10%<br>6.0%<br>6.2% | Greater reduction<br>Similar findings | Greater improvements of lipid levels especially triglycerides<br>Similar findings | Incidence of prediabetes significantly lower<br>Similar findings | Moderate nausea, vomiting, and abdominal pain. Other side effects include diarrhea and injection site reactions | Type 2 multiple endocrine neoplasia syndrome<br>History of pancreatitis, chronic kidney disease, medullary thyroid cancer.<br>Caution for antidiabetic medications |

[a]Once daily (QD)
[b]Twice daily (BID)
[c]Three times daily (TID)

In 1999, another compound was approved by the FDA for the long-term use in weight management: orlistat (trade name Xenical/Alli). This drug is still present on the market and will be described below.

There was considerable enthusiasm for cannabinoid receptor-1 antagonists when rimonabant, the first drug in that class, was approved in the European Union in 2006. However, due to increased frequency of mood disorders and suicidal behaviors [21], it received a negative recommendation from an FDA advisory committee, resulting in the manufacturer withdrawing the new drug application (NDA). In 2008, the European Medicines Agency (EMA) ordered removal of rimonabant from European markets.

More recently, two new obesity medications were approved by the FDA in 2012 (phentermine/topiramate combination, trade name Qsymia, and lorcaserin, marketed as Belviq) and two in 2014 (bupropion/naltrexone, marketed as Contrave and liraglutide 3.0, marketed as Saxenda).

## Orlistat

It is a selective inhibitor of the pancreatic lipase. This enzyme is responsible for the cleavage of triglycerides into monoglycerides and fatty acids. If the lipase is blocked, the triglycerides are not digested, and therefore, lesser calories are introduced in the organism. Since the digestion and consequent absorption of fatty acids are shared with lipophile vitamins (A, D, E, K), an integration may be needed. On average, 120 mg of orlistat taken three times per day will decrease fat absorption by 30% [22]. Orlistat as a lower dose of 60 mg three times daily, called Alli, is approved for over-the-counter use in the United States [23].

### *Efficacy*

Orlistat is effective at producing modest weight loss. In the meta-analysis of orlistat [24], the estimate of the mean weight loss for orlistat-treated patients was 2.89 kg (CI 2.27–3.51 kg) at 12 months.

### *Effect on Body Weight*

Rossner et al. [25] found that subjects receiving orlistat lost significantly more weight in the first year of treatment, and fewer regained weight during the second year of treatment than those taking placebo. The drug was also significantly more effective than placebo in 2-year randomized double-blind studies involving >700 patients [26]. During the second year of treatment, when patients were switched from a hypocaloric diet to a eucaloric diet, orlistat recipients regained significantly less weight than placebo recipients. Several evidences indicate that orlistat beyond 12 weeks should be suggested only if the patients have lost at least 5% of their initial body weight and should be continued for as long as there are clinical benefits.

*Effect on Metabolism*

It has been shown that orlistat reduces the incidence of type 2 diabetes (T2D) in obese subjects, improving insulin sensitivity and lowering serum glucose levels. In the 4-year, double-blind, prospective study by Targerson et al. (XENDOS), 3305 patients were randomized to lifestyle changes plus either orlistat 120 mg or placebo, three times daily [27]. Participants had a BMI of 30 kg/m$^2$ and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of T2D and change in body weight. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $P < 0.001$) and similar between orlistat recipients with impaired (5.7 kg) or normal glucose tolerance (NGT). The cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% ($P = 0.0032$). Also Hollander and coworkers [28] studied patients with obesity and type 2 diabetes who were not receiving insulin treatment. Orlistat administration resulted in improved glycemic control, determined via serum blood glucose levels and HbA1c measurements.

Moreover, orlistat is effective in the early and significant improvement of cardiovascular risk factors, such as waist circumference, systolic and diastolic blood pressure, lipids (reduce total and LDL; no effect on HDL and triglycerides), and HbA1c% levels, compared to diet alone. Lindgarde examined the impact of orlistat on cardiovascular profiles in obese subjects demonstrating that the administration of this drug is associated with greater weight loss outcome, as well as reduction in HbA1c, LDL, and total cholesterol [29].

*Safety and Adverse Effects*

This medication has few contraindications: chronic malabsorption, cholestasis (due to a few documented cases of rare but fatal liver injury), or known hypersensitivity. In addition, it should be avoided in patients with a history of calcium oxalate stones as orlistat can increase levels of urinary oxalate. Finally, there are some drug interactions to consider. Orlistat may enhance the anticoagulant effect of warfarin due to reduced absorption of the fat-soluble vitamin K. Moreover, orlistat may interfere with the absorption of L-T4. Thus, patients on L-T4 should be advised to separate these medications by 4 h.

The most common side effects of orlistat are oily spotting on underwear, flatulence, increased number and urgent bowel movements, fatty or oily stools, abdominal pain or discomfort, and inability to control stool (incontinence). The gastrointestinal side effects are the main reason for orlistat discontinuation, but these symptoms are usually mild to moderate and may go away during treatment as the body adjusts to the medicine. It is possible to ameliorate the adverse gastrointestinal events administering natural fibers (psyllium mucilloid) together with orlistat [30].

Phentermine/Topiramate

It is a newly approved (July 2012) weight loss drug that combines both phentermine and topiramate. This controlled-release, single-tablet combination is marketed as Qsymia, and it is available in four strength combinations which include phentermine mg/topiramate mg extended release: 3.75/23 mg (starting dose), 7.5/46 mg (lowest treatment dose), 11.25/69 mg or 15/92 mg (maximum treatment dose). The medication should be initiated at the lowest dose and taken in the morning to avoid insomnia. The dose can be slowly titrated after 2 weeks if the patient tolerates it well. If patients fail to achieve significant weight loss at 12 weeks (at least 3% of their total body weight), the dose can be further increased. However, if a patient fails to respond thereafter, the medication should be discontinued. Phentermine is a norepinephrine agonist in the central neural system while topiramate is an anticonvulsant drug used in the treatment of epilepsy and migraine prophylaxis. Phentermine increases norepinephrine (more than dopamine) release and reduces its uptake in hypothalamic nuclei, leading to weight loss by suppressing appetite [31]. Moreover, phentermine acts as an adrenergic agonist that activates the sympathetic nervous system and increases resting energy expenditure [32]. Topiramate induces weight loss by promoting taste aversion and decreasing caloric intake [33]. This synergic combination of the two drugs allows to use lower doses with the same efficacy and a lesser risk of toxicity.

*Efficacy*

There are at least four major clinical trials of note that have evaluated the efficacy and safety of phentermine/topiramate combination therapy and that were instrumental in the ultimate FDA approval of Qsymia: EQUIP, EQUATE, CONQUER and SEQUEL.

*Effect on Body Weight*

The 1-year EQUIP trial, a Phase III 56-week randomized-controlled trial, enrolled 1267 patients with obesity (mean BMI of 42.0 kg/m$^2$) and showed 3.5% in the starting dose group (3.75 mg/23 mg) and 9.3% placebo-subtracted weight loss in the top treatment dose (15 mg/92 mg) group [34].

The EQUATE study is another randomized double-blind placebo-controlled Phase III trial over a 28-week period which confirmed the superiority of the phentermine/topiramate combination to the individual components alone [35, 36]. The mean weight loss achieved for the maximum dose combination was ~9.21% compared to 6.06% in the max dose phentermine alone and 6.44% in the max dose topiramate alone groups.

The 52-week CONQUER trial randomized 2487 patients with obesity and a mean BMI of 36 kg/m$^2$ with comorbidities including hypertension, dyslipidemia, prediabetes, diabetes, or abdominal obesity to either placebo, mid-dose treatment dose (7.5 mg /46 mg), or maximum treatment dose (15/92 mg) with results showing

6.6% and 8.6% placebo-subtracted weight loss in the mid and maximum dose arms, respectively [37].

Data of the SEQUEL study have shown that patients who take the highest dose of Qsymia (phentermine 15 mg/topiramate 92 mg) can achieve up to a 10.5% weight loss after 2 years of treatment. In addition, a 10% weight loss was achieved by >50% of subjects in the treatment groups, whereas <12% of placebo reached this goal [38].

*Effect on Metabolism*

The treatment with phentermine/topiramate combination is associated with improvement in cardio metabolic parameters including both systolic and diastolic blood pressure, waist circumference, triglycerides, high-density lipoprotein (HDL) and LDL cholesterol (see EQUIP and CONQUER trials [36, 37] and glucose/insulin levels, as reported in the SEQUEL study. This latter study also demonstrated a reduction in progression to type 2 diabetes in the treated patients [39].

*Safety and Adverse Effects*

Safety concerns include an increase in heart rate and elevation in blood pressure. Phentermine-topiramate is not recommended for patients with significant cardiac history such as coronary disease, uncontrolled hypertension and cerebrovascular disease. In addition, routine monitoring of both blood pressure and heart rate should be initiated during treatment.

The most common side effects include paresthesia, dizziness, dry mouth, constipation, dysgeusia, and cognitive dysfunction (e.g., impairment of concentration/attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties). Phentermine/topiramate exposure carries an increased risk of cleft lip/palate in infants exposed to the combination drug during the first trimester of pregnancy [40]. Women of child-bearing age should have a pregnancy test prior to starting the medicine and be using contraception while taking it. If a patient does become pregnant during therapy, the medication should be immediately discontinued.

Other contraindications include patients with a history of glaucoma and hyperthyroidism and patients receiving treatment or within 14 days following treatment with monoamine oxidase inhibitors (MAOIs). Topiramate can increase the risk of acidosis and renal stones so should be used cautiously in patients who have had stones previously [41, 42].

Finally, few lab abnormalities are associated with the use of Qsymia including a reduction in serum bicarbonate, elevated creatinine, and reduction in potassium. Routine lab monitoring of serum creatinine, bicarbonate, and potassium is recommended at baseline and periodically throughout treatment.

## Lorcaserin

Lorcaserin (marketed as Belviq) is a selective serotonin receptor agonist (~15–100-fold selectively of the central serotonin 5-HT2C receptor over the 5-HT2A and 5-HT2B receptors) [43], which is located in the hypothalamus where appetite and metabolism are controlled. This medicine was approved in the USA in 2012 and became available almost a year later due to a delay in receiving DEA (Drug Enforcement Administration) classification for abuse potential. Lorcaserin increases satiety by binding to the 5-HT2C receptors on anorexigenic pro-opiomalocortin (POMC) neurons in the hypothalamus [44] and stimulating alpha-melanocyte-stimulating hormone (α-MSH) production, which leads to melanocortin 4 receptor (MC4R) activation.

Lorcaserin is available as a 10 mg tablet twice daily and a once daily 20 mg XR tablet.

### *Efficacy*

On reviewing the lorcaserin new drug application (NDA) in 2010, the FDA noted [45] that the mean weight loss associated with lorcaserin was about 3% greater than that with a placebo and therefore did not satisfy the first (5% difference in weight between active drug and a placebo) of two efficacy criteria set forth in the FDA guidelines. However, lorcaserin 10 mg twice daily dose satisfied, by a slim margin (47% vs. 23%), the second efficacy criterion (35% of patients losing ≥5% weight and at least double the proportion of the placebo-treated group).

Three clinical studies provided evidence for approval of lorcaserin. There are Phase III trials:

- BLOOM (Behavioral modification and Lorcaserin for Overweight and Obesity Management), which evaluated 3182 patients over a 2-year treatment period [46].
- BLOSSOM (Behavioral modification and Lorcaserin Second Study for Obesity Management), which evaluated 4008 patients over a 1-year treatment period [47].
- BLOOM-DM (Behavioral modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus), which evaluated 604 obese and overweight patients with type 2 diabetes over a 1-year treatment period [48].

### *Effect on Body Weight*

In the BLOOM trial, patients were treated with lorcaserin 10 mg or placebo twice daily for 52 weeks, in conjunction with diet and exercise [46]. At week 52, all subjects were re-randomized to either placebo or lorcaserin for an additional year. At 1 year, the average placebo-subtracted weight loss was 3.6%, and 47% of the subjects taking lorcaserin lost >5% as compared to 20.5% in the control group. Subjects who showed a weight loss of >5% in year 1 were maintained on lorcaserin treatment in year 2 and were able to maintain their weight loss better than those who had been switched to placebo.

In the BLOSSOM study, patients were treated with placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily. After 1 year, the group assigned to lorcaserin 10 mg twice daily showed an average placebo-subtracted weight loss of 3.1% [47].

*Effect on Metabolism*

The BLOOM study also showed significant improvements in blood pressure, heart rate, HbA1c, total cholesterol, and triglycerides circulating levels in the lorcaserin vs. placebo group [46].

The BLOOM-DM study demonstrated that mean HbA1c decreased significantly more in the lorcaserin groups as compared to placebo, as did fasting plasma glucose. In particular, a reduction of HbA1c of 0.9% was observed in those on lorcaserin as compared to 0.4% reduction in the placebo group. On the basis of this data, lorcaserin could represent a useful weight management tool for overweight and obese type 2 diabetic patients [48].

*Safety and Adverse Effects*

Common side effects with lorcaserin may include headache, dizziness, feeling tired, dry mouth, cough, nausea, constipation, back pain, or low blood sugar (in people with diabetes).

A potentially life-threatening side effect from lorcaserin is serotonin syndrome. Patients on selective serotonin reuptake inhibitors (SSRIs) may be at increased risk for this side effect with lorcaserin. Because the safety of lorcaserin coadministered with drugs that affect serotonergic system such as MAOIs, SSRIs, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) has not been established or systematically evaluated, FDA recommends caution when using lorcaserin in patients taking these drugs [49, 50]. As far as the increased risk of serotonin-associated cardiac valvular disease is concerned, due to its selective agonism for the 5-HT2C receptor, lorcaserin should not be associated with cardiac valvular effects and the lorcaserin development program has focused on excluding this possibility. To date, no statistically significant difference in echocardiographic findings for aortic insufficiency or mitral regurgitation has been noted in lorcaserin vs. placebo in studies up to 2 years in duration [51, 52].

Due to its potential side effects on fetal development, pregnancy test prior to starting lorcaserin is recommended, as well as contraception while taking it.

Bupropion/Naltrexone

In September 2014, FDA approved the combination tablet bupropion/naltrexone, marketed as Contrave, for weight loss management [53, 54]. Brupopion, a marketed antidepressant that is also approved for smoking cessation, is a dopamine and norepinephrine reuptake inhibitor. It is thought to induce weight loss via activation of

hypothalamic POMC neurons, which then subsequently stimulate the MC4R via release of α-MSH, resulting in reduced food intake and increased energy expenditure [53]. Naltrexone, a current treatment for opiate addiction and alcoholism, works synergistically with bupropion, possibly by blocking auto-inhibitory feedback on POMC neurons, thus leading to sustained enhanced neuronal firing [54].

The recommended dosage of bupropion/naltrexone combination is as follows: 1 tablet with 8 milligrams of naltrexone HCI and 90 mg of bupropion HCI once daily for the first week, twice daily for the second week, three times daily for the third week, and four times daily for the fourth week, and beyond (total 32 mg naltrexone/360 mg bupropion).

*Efficacy*

Four trials in the Contrave Obesity Research (COR) Phase 3 program (COR-I, COR-II, COR-BMOD, and COR-Diabetes) provided evidence for approval of bupropion/naltrexone in long-term weight loss management. They were conducted to evaluate the efficacy and safety of Contrave compared to placebo. All four trials were 56-week multicenter, randomized, double-blind, placebo-controlled trials. The co-primary endpoints were the proportion of patients achieving at least 5% weight loss and percent change in body weight compared to placebo. Secondary endpoints included multiple measures of cardio metabolic risk, quality of life, control of eating, and glycemic control. Contrave was generally well tolerated.

*Effect on Body Weight*

The COR-I, COR-II, and COR-BMOD trials enrolled patients who had a body mass index (BMI) of 30–45 kg/m$^2$ and uncomplicated obesity or BMI 27 kg/m$^2$ or greater with dyslipidemia or hypertension [55, 56]. The COR-Diabetes trial enrolled patients with BMI greater than 27 kg/m$^2$ with type 2 diabetes with or without hypertension and/or dyslipidemia [57].

In the COR-I trial, mean change in body weight was −1.3% (SE 0.3) in the placebo group, −6.1% (0.3) in the naltrexone 32 mg plus bupropion group ($p < 0.0001$ vs. placebo) and −5.0% (0.3) in the naltrexone 16 mg plus bupropion group ($p < 0.0001$ vs. placebo) [49]. Similar results were reported in COR-II [56] and COR-Diabetes [58] trials, but both placebo and bupropion/naltrexone groups achieved greater weight loss (−5.2% and − 9.3%, respectively) after 1 year when they were given an intensive behavior modification program [57].

*Effect on Metabolism*

The COR-Diabetes trial showed a significantly greater 0.6% reduction in HbA1c levels from baseline, compared to a 0.1% reduction in placebo [58].

In all of the COR trials, secondary cardiovascular endpoints (improvements in waist circumference (WC), visceral fat, HDL cholesterol, and triglyceride levels) were met in the treated group [55–58].

*Safety and Adverse Effects*

Bupropion/naltrexone is associated with a high incidence of gastrointestinal (nausea, vomiting, constipation, dry mouth) adverse effects in addition to headache, dizziness, insomnia, and anxiety. If approved, it will likely be contraindicated in those patients with a history of seizures, a history of bulimia or anorexia nervosa, severe depression, suicidal ideation, or suicide attempts. Moreover, it should be avoided in patients receiving chronic treatment with opioids and in those abruptly stopping alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.

## Liraglutide 3.0

Liraglutide is an injectable glucagonlike peptide-1 (GLP-1) agonist initially approved in 2010 for the treatment of T2D at the dose of 1.8 mg daily. Liraglutide 3.0 mg (trade name Saxenda) was successively approved by the US FDA in December 2014 for long-term weight loss management. GLP-1 binds to its specific receptor and enhances glucose-dependent insulin secretion by the pancreatic beta cells, increases intracellular c-AMP leading to insulin release in the presence of elevate glucose circulating levels, inhibits gastric emptying, increases satiety, and decreases calories ingestion through central nervous system (CNS). Indeed, animal studies have shown that peripheral administration of liraglutide results in uptake in specific brain regions regulating appetite, including the hypothalamus and brainstem [59, 60].

*Efficacy*

The liraglutide NDA for obesity included three Phase III trials (SCALE Obesity and Prediabetes; SCALE Diabetes and SCALE Maintain study) of 1 year or more that primarily examined the efficacy of liraglutide 3.0 mg/day.

*Effect on Body Weight*

The SCALE Obesity and Prediabetes study was a 56-week, randomized, placebo-controlled, double-blind clinical trial involving 3731 patients who did not have type 2 diabetes and who had a BMI of at least 30 kg/m$^2$ or a BMI of at least 27 kg/m$^2$ with treated or untreated dyslipidemia or hypertension [61]. Patients were assigned in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients) and both groups received counseling on lifestyle modification. The co-primary endpoints were the change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight. The mean weight change with liraglutide was 8.0% vs. 2.6% with a placebo at 1 year. The study excluded patients with diabetes but enrolled those with prediabetes who were followed for an additional 2 years for a total of 3 years to examine whether liraglutide treatment could reduce the risk of developing

T2D (56). For patients with prediabetes at baseline, liraglutide treatment was associated with a mean weight change of 6.1% vs. 1.9% with a placebo. The time to onset of T2D over 3 years was estimated to be 2.7 times longer with liraglutide than with a placebo [62].

Also the SCALE Diabetes study is a 56-week, randomized, placebo-controlled, double-blind clinical trial which demonstrated significantly greater mean weight loss than placebo (6.0% vs. 2%) [63]. Finally, in the SCALE Maintain study, 422 overweight/obese patients without diabetes were randomized to liraglutide 3.0 mg or a placebo to examine weight maintenance after they had achieved an average 6.0% weight loss with a low-calorie diet [64]. During the maintenance phase, participants in the liraglutide 3.0 group lost an additional 6.2% compared to 0.2% with placebo ($P < 0.0001$) [64].

*Effect on Metabolism*

As far as the secondary endpoints (HbA1c, glucose levels, waist circumference, lipids, and blood pressure) is concerned, the SCALE Obesity and Prediabetes trial showed a significant greater improvement of these parameters in treated group than in placebo [61].

There was a greater reduction in HbA1c, fasting glucose, and fasting insulin levels in the liraglutide group than in the placebo group. Liraglutide was also associated with a lowering of plasma glucose levels and higher insulin and C-peptide levels relative to placebo during an oral glucose-tolerance test. These letter effects were greater in patients with prediabetes than in those without ($P < 0.001$). The prevalence of prediabetes was significantly lower in the liraglutide group than in the placebo group at week 56, a finding that was consistent with the improvement in glycemic control with liraglutide. Type 2 diabetes developed in more patients in the placebo group than in the liraglutide group during the course of treatment.

As far as the cardio metabolic variables is concerned, systolic and diastolic blood pressure decreased more in the liraglutide group than in the placebo group by week 56 (4.2 mmHg vs. 1.5 mmHg). All measures of fasting lipid levels, especially triglycerides, as well as levels of high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin showed greater improvement in the liraglutide group than in the placebo group.

Similar findings were observed in the SCALE Diabetes study as regard of HbA1c, triglyceride, and HDL cholesterol levels [63].

*Safety and Adverse Effects*

The most common side effects associated with GLP-1 agonists include mild to moderate nausea, which tends to be transient, vomiting, and abdominal pain. Other side effects include diarrhea and injection site reactions. Patients to avoid the use of GLP-1 agonists are those with a history of pancreatitis, because of the increase in

amylase/lipase activity mediated by GLP-1 and chronic kidney disease. Caution should be used with patients taking other antidiabetic medications, which can predispose them to hypoglycemia, including sulfonylureas, and it is not recommended to use liraglutide in conjunction with insulin. Moreover, it was found in the SCALE Diabetes trial [63] that liraglutide may increase heart rate by 2.0/min. Finally, as liraglutide causes thyroid C-cell tumors in rats and mice, it is contraindicated in patients with a personal or family history of medullary thyroid cancer or in patients with type 2 multiple endocrine neoplasia syndrome.

### *9.2.2 Off-Label Medications for Weight Control*

A variety of drug classes, described below in this chapter, approved for other uses have been utilized off-label to promote weight loss in patients who are obese (Table 9.3). In this case, their prescription is "off-label." Categories of drugs used off-label may include metformin, the antiseizure medication topiramate as well as zonisamide, the antidepressant bupropion, and pramlintide which mimics the actions of amylin. Combination treatments of these drugs also represent off-label use, although they have been utilized by some practitioners. According to the ENDO guidelines for pharmacotherapy of obesity [65], physicians without expertise in weight management or endocrinology are advised against prescribing off-label medications. If providers choose to prescribe a medication for weight loss that is not approved for this indication or is not approved for chronic administration, they should advise patients that this approach has not been evaluated for safety and efficacy.

#### 9.2.2.1 Metformin

Metformin (trade name Glucophage) is an antihyperglycemic agent that acts by decreasing production of glucose by the liver and possibly increasing peripheral insulin sensitivity. Although the label for metformin specifies diabetes as the sole indication, the drug has been prescribed with increasing frequency for overweight and obese patients with impaired fasting glucose, following a report that long-term metformin delayed or prevented diabetes and induced weight loss in such patients [66]. Metformin is known to induce modest weight loss (−1.1 kg) based on meta-analyses of RCTs [67, 68], even in patients without glucose abnormalities. Thus, metformin is commonly prescribed off-label as an adjunct to weight loss [69, 70], although the mechanism of action on body weight is still unknown.

The most common side effects of metformin are nausea, flatulence, diarrhea, and bloating. The most serious side effect is lactic acidosis, but this is rare (<1/100,000) [71].

**Table 9.3** Off-label medications for weight control

| Drug | Mechanism of action | Main use | Dosage | Weight loss change (kg or %) | Main adverse effects |
|---|---|---|---|---|---|
| Metformin | Antihyperglycemic agent | Antihyperglycemic agent used to treat diabetes | Up to 2.500 mg per day | ~5.6% | Nausea, flatulence, diarrhea, bloating and lactic acidosis (rare) |
| Topiramate | FDA-approved for treatment of refractory epilepsy | To treat refractory epilepsy | 25–100 mg QD[a] | 5% or 10% of initial weight | Paresthesia, dry mouth, constipation, altered taste sensation, insomnia, dizziness, closed-angle glaucoma (rare) and suicidal thoughts or ideations |
| Zonisamide | Approved for epilepsy | To treat epilepsy | 400 mg QD[a] | −6.8% At least −10% of initial weight | Nausea, vomiting, headaches, and anxiety |
| Bupropion | Norepinephrine-dopamine reuptake inhibitor | Antidepressant | 400 mg QD[a] | −4.4 kg | Insomnia, nausea, pharyngitis, weight loss, constipation, dizziness, headache, and xerostomia |
| Pramlinitide | Mimics the action of the pancreatic hormone amylin | To treat type 1 and 2 diabetes | 120 μg–360 μg BID[b]-TID[c] | −2.27 kg | Nausea |

[a]Once daily (QD)
[b]Twice daily (BID)
[c]Three times daily (TID)

#### 9.2.2.2 Topiramate

Topiramate (marketed as Topamax) was FDA-approved for the treatment of refractory epilepsy in 1996. Weight loss was immediately noted as a side effect [72]. Soon thereafter, reports began appearing that topiramate was effective in treating binge eating disorder [73] and obesity [74]. A survey of US obesity medicine physicians performed in early 2008 and published in 2009 revealed that 50% were prescribing topiramate as monotherapy for obesity [75]. Thus, topiramate has been used off-label for obesity management. Effective doses range between 25 and 100 mg daily. Side effects are dose-dependent and commonly include paranesthesia, dry mouth, constipation, altered taste sensation, insomnia, and dizziness [76]. Rare but serious side effects include closed-angle glaucoma and increase in suicidal thoughts or ideations.

#### 9.2.2.3 Zonisamide

Zonisamide (trade name Zonegran), approved for epilepsy, induces weight loss and has been used off-label alone [77] or in combination with bupropion [78] or phentermine. A 12-month randomized controlled trial of 225 adults, with 97% follow-up, found that a 400 mg dose daily led to significantly greater weight loss than placebo (6.8% vs. 3.7%), as well as a greater proportion losing at least 5% and at least 10% of initial weight [77]. The most commonly reported side effects were nausea, vomiting headaches, and anxiety.

#### 9.2.2.4 Bupropion

Bupropion (marketed Wellbutrin) is another substituted phenethylamine approved as an antidepressant. It acts as a norepinephrine–dopamine reuptake inhibitor and commonly induces modest weight loss [79]. The drug has been used frequently off-label as a weight loss agent, often in combination with phentermine or other weight loss drugs. A pooled analysis of three studies ranging from 6 to 12 months showed additional weight loss relative to placebo of 2.8 kg in patients receiving 400 mg/d bupropion, with total weight loss of 4.4 kg [24].

#### 9.2.2.5 Pramlintide

Pramlintide (trade name Symlin) mimics the action of the pancreatic hormone amylin, which is a peptide co-produced with insulin by pancreatic beta-cells that inhibits postprandial glucose secretion, slows gastric emptying and increases satiety, while decreasing caloric intake [80]. Pramlintide is an injectable agent FDA-approved for diabetes (type 1 and type 2), showed a modest weight loss effect (placebo-subtracted 2.3 kg at 16 weeks, 2.1 kg at 52 weeks) [81–83]. A meta-analysis [84] of eight

studies in patients with type 2 diabetes and obese nondiabetic populations found additional weight loss relative to placebo of approximately 2.2 kg for both groups. Its effect on weight loss is mediated through central (brain) receptors [85] that improve appetite control [86]. After early reports of successful use for weight loss in nondiabetic patients [87], physicians began using it off-label to treat obesity. Nausea is the most common adverse event in patients taking pramlintide.

### *9.2.3 Future Anti-Obesity Targets for Obesity Pharmacotherapy*

Though there are approved anti-obesity drugs available in the USA, given that they do not cure obesity but only achieves moderate reduction in weight loss and, when they are discontinued a weight regain is expected, newer drugs are now in the pipeline for development. These letter include centrally acting agents (setmelanotide, neuropeptide Y antagonist [Velneperit], zonisamide-bupropion [Empatic], and cannabinoid type-1 receptor blockers), gut hormones and incretin targets (new glucagon-like-peptide-1 analogs [Semaglutide and oral equivalents], amylin mimetics [Davalintide, dual amylin and calcitonin receptor agonists], dual action GLP-1/glucagon receptor agonists [Oxyntomodulin], triple agonists [triagonist 1706], peptide YY, leptin analogs [combination pramlintide-metreleptin]), and other novel targets (methionine aminopeptidase 2 inhibitor [Beloranib], lipase inhibitor [Cetilistat], inhibiting sodium-glucose transport protein 2 (SGLT2), triple monoamine reuptake inhibitor [Tesofensine], fibroblast growth factor 21), including anti-obesity vaccines (ghrelin, somatostatin, adenovirus36) [88]. With these new drugs in development, anti-obesity therapeutics have potential to vastly expand allowing better treatment options and personalized approach to obesity care.

### *9.2.4 Conclusion*

The official position of the scientific community on weight loss management is well established. Pharmacotherapy has been shown to be effective in promoting weight reduction and in improving comorbid conditions. The tricky part is finding the right medication for each individual.

The treatment of the obese patients, with the different therapeutic drugs available today, should take place even after obtaining a significant weight loss.

The success of the therapy, both for the doctor and for the patient, consists of achieving and maintaining the established “weight target,” which means a reduction in body weight sufficient to significantly improve the risks associated with obesity, especially cardiovascular ones. In some well-selected subjects, the use of “therapeutic cycles” to be administered over the long term could be suggested. In

particular, after the success of a first course of therapy with satisfactory results, the recurrence over time of negative circumstances involving a recovery/increase in weight may occur. Thus, it is possible to resume the administration of a new cycle of pharmacological therapy, in order to help the patient manage the critical moment. However, the complexity of energy regulation limits the effect of any one drug. Combination therapies increases the number of therapeutic strategies available to the provider. Thus, the pharmacological approach to obesity management may be obviously more practical if a greater number of drugs were available with different molecular targets that can be integrated with each other, as in the case of similar chronic diseases such as heart disease, hypertension, and diabetes. Finally, side effects may occur during treatment, but they can be managed with slow titration and using combinations.

## 9.3 Surgical Treatment

### *9.3.1 Bariatric and Metabolic Surgery (BMS)*

Bariatric and Metabolic surgery (BMS) is considered the most efficient and long-lasting obesity treatment to date. Systematic reviews and meta-analysis of randomized controlled trials [89] have demonstrated that BMS is superior to conservative medical treatment.

Initially defined as "Bariatric" from the Greek *baros* (weight) and *iatrikos* (medicine), it was conceived as a tool to induce considerable weight loss in obese patients. In fact, Bariatric surgery aims to induce the weight loss of between 50% and 80% of the patient's excess weight at the time of surgery. However, it was soon discovered that bariatric surgery went beyond the simple idea of weight loss. The term "bariatric" can be considered reductive given that the main aim of this surgical procedure is not only to lose weight but also to treat and often cure the comorbidities associated with excess weight. These comorbidities reduce the length and quality of the patient's life, damaging not only who is affected by them but also the society that must pay for the healthcare costs generated. In 1978 Buchwald and Varco coined the term "Metabolic Surgery" defining it as "the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain." [90].

### *9.3.2 Patient Selection*

Currently, guidelines indicate BMS candidates as patients who have a BMI $\geq$40 kg/m$^2$ even if comorbidities are absent or patients with a BMI between 35 and 40 kg/m$^2$ in the presence of at least one severe obesity-associated comorbidity (e.g.,

diabetes, hypertension, dyslipidemias, obstructive sleep apnea, musculoskeletal disorders, osteoarthritis, cardiovascular diseases, venous stasis disease, thromboembolic disorders, chronic kidney disease, nonalcoholic fatty liver disease, polycystic ovary syndrome) [91].

Metabolic surgery should also be considered in patients with a BMI between 30 and 35 kg/m$^2$ and poorly controlled T2DM. In 2016, a consensus from Diabetes Organizations worldwide (DSS-II: Diabetes Surgery Summit) recognized metabolic surgery as a standard treatment option for T2DM [92]. A treatment algorithm was proposed *recommending* BMS in all diabetic patients with class III obesity, regardless of their hyperglycemic control and diabetic patients with class II obesity with inadequately controlled hyperglycemia despite lifestyle and optimal medical therapy. The algorithm also *advises* BMS for diabetic patients with class II obesity even if hyperglycemic control is adequate with medical therapy and in diabetic patients with class I obesity with inadequately controlled hyperglycemia despite optimal medical therapy (oral or injectable medications including insulin) [92].

Asian populations have BMI cutoffs that are 2.5 kg/m$^2$ lower with respect to the population in the rest of the world, due to a greater presence of cardiovascular and metabolic diseases even at lower BMI [93]. This characteristic could be owed to the central-visceral distribution of excess fat in Asian populations, despite a relatively low BMI.

Obesity is a multifactorial disease, and to treat it, it is necessary to have a multidisciplinary team caring for the patient. The selection of ideal BMS candidates also goes through an evaluation procedure carried out by a surgeon, an endocrinologist, a psychologist, and an anesthetist in order to exclude factors that would absolutely contraindicate a surgical approach such as severe uncontrolled psychiatric disorder, heart failure, unstable coronary artery disease, severe lung disease, active cancer (or in remission for less than 5 years), portal hypertension, current alcohol or substance abuse. Any contraindication to receiving general anesthesia has to be considered as an absolute contraindication to BMS [94].

Patient motivation to lose weight and improve their quality of life through surgery, associated with a full awareness of the risk–benefit factor involved in every bariatric procedure, is an essential element when selecting an ideal candidate. Before surgery, the patient must try to lose weight in a conservative medically assisted manner and must obtain results, although partial and limited in time. Patients must also show that they are aware of a possible need for nutritional supplementation and of the fundamental importance of long-term postoperative follow-up. They must be able to confront the process of change in nutritional habits, which is essential to reach and maintain results.

### *9.3.3 Surgical Procedures*

Many surgical procedures have been proposed, revisited, and abandoned throughout the years. Currently, the most performed and recognized by the American Society for Metabolic and Bariatric Surgery (ASMBS) are Roux-en-Y Gastric Bypass

(RYGB), Sleeve Gastrectomy (SG), Adjustable Gastric Band (AGB), and Biliopancreatic Diversion with Duodenal Switch (BPD/DS).

The One Anastomosis Gastric Bypass (OAGB), a new emerging procedure that is increasing in popularity, is also worth a mention.

Another increasing figure is the number of patients who, although they have already undergone bariatric surgery, must undergo a second bariatric operation owing to insufficient weight loss, weight regain, or complications related to the first operation. It is becoming more and more common for the bariatric surgeon to have to perform what has been defined as re-do surgery or revisional surgery.

The International Federation for the Surgery of Obesity and Metabolic Diseases (IFSO) reported that 685,874 bariatric and metabolic procedures were performed worldwide in 2016. Among them 634,897 (92.6%) were primary and 50,977 were revisional (7.4%). The most performed primary procedure was SG (*N* = 340,550; 53.6%), followed by RYGB (*N* = 191,326; 30.1%), OAGB (*N* = 30,563; 4.8%), AGB (*N* = 19,332; 3%), and BPD/DS (*N* = 3346; 0.5%) [95].

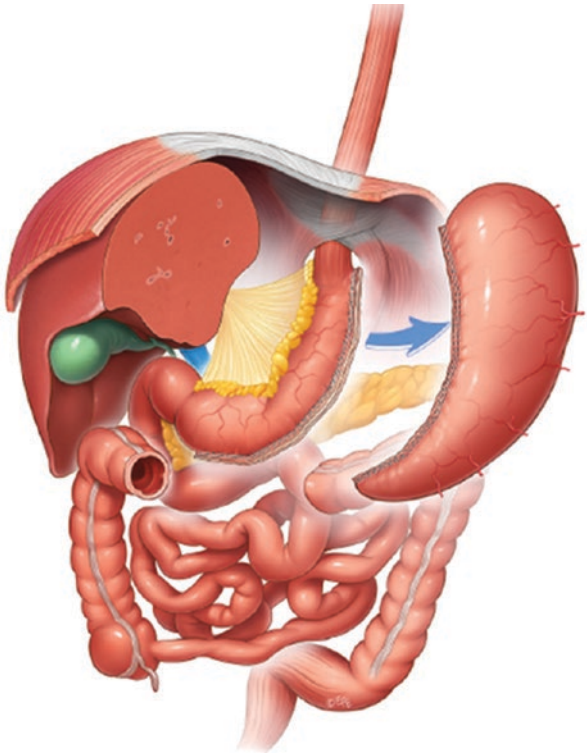

**Fig. 9.1** Sleeve gastrectomy

#### 9.3.3.1 Sleeve Gastrectomy (SG) (Fig. 9.1)

SG was first described in the 1990s by Marceau [96] who aimed to reduce the incidence of marginal ulcers, modifying the traditional biliopancreatic diversion (BPD) according to Scopinaro and performing a vertical gastrectomy along a calibration tube of 60 FR, distant from the gastroesophageal junction without mobilizing the gastric antrum. The aim was to reduce the amount of gastric acid in the ileum. In 1999 Gagner [97] reproduced the same operation for the first time via laparoscopy with duodenal switch. SG was therefore conceived as a first step of a BPD/DS performed in two surgical stages. However, many patients achieved such surprising weight loss results with just the first stage that it was assumed that SG could become a primary bariatric procedure in its own right, leaving the possibility of a second operation open in case of insufficient weight loss or weight gain.

SG has gained fame, as a single procedure, because is considered a safe and efficient operation in the treatment of pathological obesity and its comorbidities. The growing popularity of this operation is owed to the efficiency of the procedure and the relative simplicity of the technique compared to RYGB and BPD/DS. Nevertheless, this operation, like all surgical procedures, has its complications, which can be serious and potentially fatal: bleeding (1.1–8.7%), staple-line leak (0–7%), stenosis (0.2–4%), gastroesophageal reflux (0–30%) [98]. It is therefore important not to underestimate the procedure, to be meticulous during patient preparation and with surgical technique.

SG is performed laparoscopically dissecting the small branches of the gastroepiploic arc and opening the epiploon retro-cavity. Dissection continues along the greater curvature of the stomach until the Angle of His is reached, dissecting also the short gastric vessels. Caudally, dissection is extended approximately 4–5 cm from the pylorus. The stomach is then elevated to expose its posterior wall, and the retro-cavity adhesions are lysed. The Angle of His is completely mobilized, and the left diaphragmatic pillar is exposed. At this point, gastric tubulation is performed through a calibration tube using surgical staplers.

The fourth "International Consensus Summit on Sleeve Gastrectomy" indicated a mean percentage of postoperative EWL of 59.3% after 1 year, 59.0% after 2 years, 54.7% after 3 years, 52.3% after 4 years, 52.4% after 5 years, and 50.6% after 6 years [99]. Recent results from a meta-analysis of randomized controlled trials described EWL of 59.1% after 5 years [100]. SG literature has documented the effects on metabolic pathologies although remission rates vary substantially in the various studies, which describe T2DM remission between 14% and 100%, hypertension between 15% and 93% and sleep apnea between 30% and 100%. Golomb [101] reports complete T2DM remission at 1, 3, and 5 years of 50.7%, 38.2%, and 20.0%, respectively, and hypertension remission of 46.3%, 48.0%, and 45.5%, respectively. Schauer [102] analyzed the T2DM diabetes remission rates after SG, after RYGB, and after medical therapy after 3 years of follow-up and discovered that 24% of patients who underwent SG had complete remission compared to 38% of patients who underwent RYGB and 5% who followed medical treatment. Atkins [103] described T2DM, hypertension, and hyperlipidemia remission of 74.5%,

49.5%, and 26.5%, respectively, after 4 years of follow-up. Other studies [104–106] with mid-term follow-up reported remission rates between 67% and l'86% for T2DM, hypertension and hyperlipidemia.

SG's greater efficiency with respect to other purely restrictive procedures such as AGB leads to the thought that the active mechanisms responsible for SG results not only are restrictive but also involve various other elements such as gastrointestinal motility modification, change to some hormonal systems, alteration of biliary acids, and intestinal microbiota. Unlike AGB, SG provokes rapid gastric emptying [107] and accelerated intestinal motility [108]. It seems that accelerated intestinal motility may contribute to trigger hormonal mechanisms that increase the sense of satiety, as is the case after taking medicines that improve gastric emptying [109].

Hormonal changes after SG mainly involve hormones such as glucagon-like peptide 1 (GLP-1), peptide tyrosine-tyrosine (PYY), leptin, and ghrelin. GLP-1 belongs to the incretin hormone category and is secreted by the L cells in the distal intestine in response to nutrient ingestion. It contributes to improve weight control and glucose metabolism by promoting the secretion of insulin, inhibiting gastric emptying, the secretion of glucagon, and the hepatic production of glucose [110]. SG induces a postprandial increase of GLP-1 which, according to different authors, is comparable to production in RYGB [111–113]. The mechanism through which SG increases GLP-1 secretion is not clear. One hypothesis is that faster gastric emptying post-SG may stimulate the distal intestine to produce GLP-1, another hypothesis is that the gastric tubular pouch post-SG is less sensitive to GLP-1-mediated stimulation that would normally slow down gastric emptying; therefore, the increased secretion of GLP-1 would be an attempt to restore gastric motility mediated by GLP-1 in response to accelerated gastric emptying created by the operation [114]. In addition, given the rapid increase of GLP-1 after food ingestion and presumably before the chyme enters into contact with the L cells, the hypothesis that a "proximal-distal" circuit may likely exist through hormonal [115] or neural [116] pathways mediated by cholecystokinin (CCK) which induces the secretion of GLP-1 without direct mechanical stimulation of the distal intestine should be considered.

PYY is an anorectic peptide released by the L cells in the mucosa of the gastrointestinal tract, especially the ileum and colon, in response to food intake [117]. In addition to reducing appetite, it increases the absorption of nutrients in the ileum, inhibits gastric and pancreatic secretion, reduces gallbladder contraction and slows gastric emptying down. Attenuated PYY secretion has been described in obese patients, in contrast to normal weight subjects, which is associated with a reduced sense of satiety [118]. As in the case of GLP-1, many studies have shown a significant increase of PYY after SG, and the results are comparable to those observed after RYGB [113, 114], which suggests that the mechanism behind these changes is, at least in part, shared.

Ghrelin is a neuropeptide with orexigenic action mainly produced by oxyntic cells in the lining of the gastric fundus [119]. In physiological conditions, ghrelin levels increase during fasting showing a preprandial peak and are suppressed after a meal. Ghrelin also has diabetogenic effects such as the suppression of insulin

secretion [120]. For some time now, we have known that there is an important reduction of ghrelin concentration after SG, which is much more pronounced than in other restrictive procedures [121] and RYGB [112, 113]. This may be owed to the resection of the gastric fundus. Proof that the reduction of ghrelin concentration after SG has a role in weight loss and metabolism improvement is found in the increase of the amount of ghrelin circulating in patients who have lost weight with a diet or through restrictive procedures. In fact, this suggests that weight loss triggers compensation mechanisms to regain weight [122], partly ghrelin mediated, which could be eliminated after SG.

Leptin, which is synthesized in white adipose tissue in proportion to the quantity of body fat [123], reduces food intake and body weight through interaction with the central nervous system. Obese patients have reported a decrease in sensitivity to leptin, and consequently, they show an incapacity to perceive a sense of satiety despite the overabundance of energy reserves stored in adipose tissue [124]. It is not clear whether improvement to leptin resistance has a direct role in weight loss after SG. There seems to be a greater expression of leptin-correlated genes after SG [125], although recent studies suggest that inversion of leptin resistance could be regulated by the increase in availability of some proteins involved in the transduction system [126].

The role attributed to bile acids is gaining importance regarding the regulation of various endocrinal functions such as an improvement on metabolism of carbohydrates and reduction of hepatic steatosis [127]. The increase in bile acid concentration after SG is probably associated with rapid intestinal transit, which increases bile acid availability in the maximum absorption zone, the terminal ileum. It appears that the metabolic effects of bile acids are mediated by the farnesoid X receptor (FXR). Ryan et al. [128] have demonstrated that this transmission mode is fundamental to improve glucose metabolism, to avoid compensatory hyperphagia, and to maintain long-term weight loss.

Another mechanism that influences post-SG results is the variation of intestinal microbiota, which changes and results in bacterial flora that is similar to that of thin subjects [129], though not as evident as in RYGB.

#### 9.3.3.2 Roux-En-Y Gastric Bypass (RYGB) (Fig. 9.2)

The first gastric bypass was described by Mason in 1966, who observed a loss in body weight in patients who underwent partial gastrectomy for gastric ulcer and then hypothesized that the same operation could be performed on obese patients to promote weight loss [130]. Subsequently, the procedure was technically modified on various occasions until it reached its current state. A qualitative leap, from a technical point of view, was made in 1994 when Wittgrove and Clark performed the first laparoscopic RYGB [131]. This made it possible to reduce hospitalization, postoperative pain, respiratory complications, and postoperative wound complications such as infections and hernias.

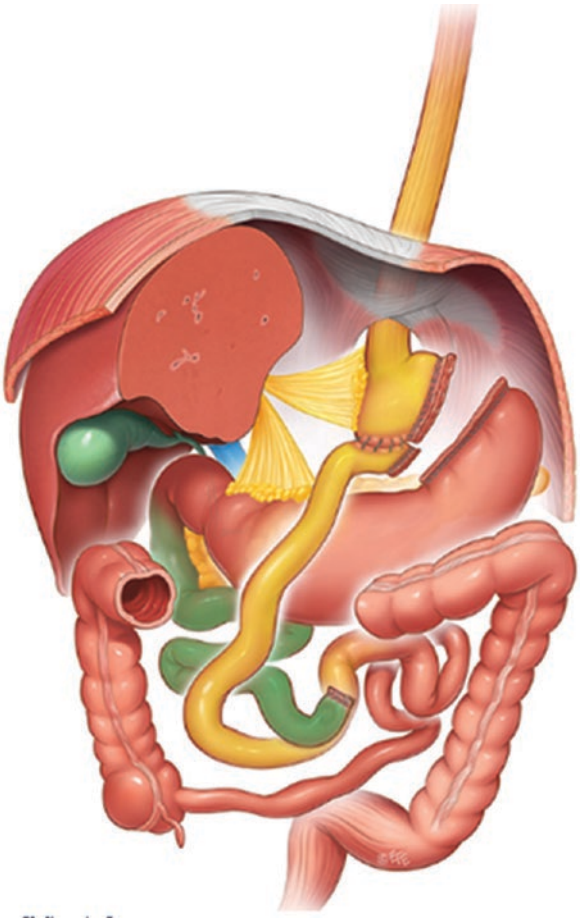

**Fig. 9.2** Roux-en-Y gastric bypass

RYGP has been around for a long time and is still performed all over the world. Although some technical variations have been described, the basic tenets of the procedure remain the same: small, isolated gastric pouch, limited diversion of bilio-enteric secretions, and reproducible, safe anastomotic methods.

The operation consists of creating a small gastric pouch, approximately 15–30 mL, separated from the distal stomach by sequential firings of a laparoscopic linear cutter stapling device around an intraluminal calibration tube. The first firing (about 5 cm wide) is horizontal, beginning no more than 5 cm distal to the esophagogastric junction, subsequent firings (usually no more than 2) are vertically oriented to the angle of His. Then the first portion of the small bowel is divided approximately 50–100 cm beyond the ligament of Treitz (bilio-pancreatic limb), and the distal end of the divided jejunum is brought up and anastomosed to the newly created small gastric pouch. The procedure is completed by anastomosing the proximal intestinal segment to the jejunum approximately 100–150 cm distally

(alimentary limb). In this way, the food ingested, after reaching the small gastric pouch, goes directly through into the mid-jejunum by passing the distal stomach, the duodenum and 50–100 cm of the jejunum. Food digestion comes about only after the alimentary limb has transited (100–150 cm), and the ingested nutrients have found the digestive enzymes coming from the biliary limb. The intestine tract, distal to the executed anastomosis between the alimentary limb and the biliary limb, is defined as the common channel and is the intestinal tract where digestion of food and a great part of nutrient assimilation takes place.

The action mechanisms responsible for weight loss and the improvement of metabolic diseases after RYGB are multiple, complex, and not yet altogether known. A first, relevant component is the small gastric pouch, an important restrictive mechanism inducing patients to reduce food intake, which in turn is one of the most significant reasons for weight loss.

The transection of the stomach can cause denervation of both the vagal and sympathetic fibers in the distal stomach while neural pathways remain intact at a proximal gastric level. At the same time, the alimentary limb remains innervated by celiac vagal branches and is exposed to great quantities of nondigested food, which could alter the neural signals of this intestinal segment. Sensorial terminal structures called intraganglionic laminar endings (IGLE) respond to the tension in the gastric wall, and it is probable that the increase in pressure and the stretching of the pouch by the alimentary limb activate the IGLE early, generating an early sensation of satiety and a reduction of appetite [132, 133].

Another important action mechanism is the rerouting of the food stream that leads to alterations in the signaling between luminal factors and the intestinal mucosa, producing changes in bile acid composition, gut microbiota, and gut hormones. Examples of these changes are a reduction of circulating levels of leptin, ghrelin, and gastrin and an increase of circulating levels of adiponectin, peptide tyrosine tyrosine (PYY3–36), glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), oxyntomodulin, glucose dependent insulinotropic polypeptide (GIP), cholecystokinin, and neurotensin [134]. The neurohumoral action mechanisms are very similar to those described in the paragraph dedicated to SG, even if it has been demonstrated that they are more evident in RYGB.

In RYGB, the increase of GLP-1 was explained by the “hind-gut” hypothesis, in which the increased stimulation of the distal intestine to produce GLP-1 is attributed to the rapid arrival of food at this level, having by-passed the first tract of the intestine.

These complex neurohumoral effects induce a reduced preference for fatty foods, an increased intensity in the perception of sweet taste, which becomes less palatable, a reduced hedonic response to sweet foods, an increase in energy expenditure after a standard meal and a reduced neural activation of the cerebral structures connected to a sense of reward in response to a desire for high-calorie content foods [135–137].

After RYGB, there is a possibility of the patient experiencing a form of discomfort defined as dumping syndrome, which can appear after meals containing high levels of sugar and simple carbohydrates. This unpleasant sensation leads the patient

to avoid these foods. A partial, modest malabsorption of fats can occur when the bypassed intestine is over 200 cm. Although the standard technique does not induce genuine malabsorption of protein or diarrhea, when the portion of bypassed intestine is wide enough, there may be a lack of absorption of some vitamins, mineral salts, calcium, and iron. It may be necessary to take multivitamin complexes together with calcium and iron supplements.

As previously mentioned, RYGB has its alternatives and variations despite being a coded surgical procedure in its essential phases. Among these, we find Banded RYGB, RYGB on Vertical Gastroplasty, Functional RYGB, and Distal RYGB. Banded RYGB (Fobi procedure) foresees the positioning of a "gastric ring" in silicone, of predefined caliber, around the terminal part of the gastric pouch. The aim is to be constant in time and improve the restrictive effect of the operation. However, banded RYGB can have complications related to the gastric ring (e.g., erosion), which in 3% of cases require a new operation.

The possible postoperative complications of RYGB are: mortality (0–0.38%), leak, small bowel obstruction due to internal hernias (1.5–5%), bleeding (0.8–4.4%), anastomotic ulcer or stenosis (up to 5%).

RYGB is still considered the "gold standard" of bariatric surgery producing significant long-term weight loss (60–80% excess weight loss), 84% of T2DM remission, and 75.4% hypertension resolution.

#### 9.3.3.3 Adjustable Gastric Band (AGB) (Fig. 9.3)

The first gastric band procedure was described by Hallberg and Forsell in 1985, at the beginning of the 1990s Catona in Italy and Broadbent in Australia performed the operation laparoscopically implanting a nonadjustable gastric band, and in 1993, Balachew in Belgium described the first laparoscopic adjustable gastric band surgical procedure.

AGB is an operation that does not involve the resection of an organ and is anatomically and functionally reversible. The procedure consists of placing a silicone ring with inflatable balloon around the upper part of the stomach, around 1–2 cm under the cardia, to create a small gastric pouch above the band with a volume of about 25–30 mL. The gastric ring is connected to a small port, which is placed above the muscular fibers of the abdominal wall, through a regulating tube. The port is not visible but is palpable externally allowing the surgeon to inject or remove saline solution 0.9% or iodinated contrast agents and to inflate or deflate the gastric ring to regulate the diameter of the narrow opening that allows the passage of food into the rest of the stomach. The aim is to induce an early sense of satiety. AGB is therefore a surgical procedure that is purely restrictive given that it does not have malabsorption components and does not induce non-weight-related hormonal changes. This means that results are strongly conditioned by the extent to which a patient adheres to a balanced diet made up mainly of solid food. The problem frequently faced by patients is vomiting, especially when food intake occurs rapidly. It is therefore necessary to prolong mastication and avoid drinking during a meal. It is

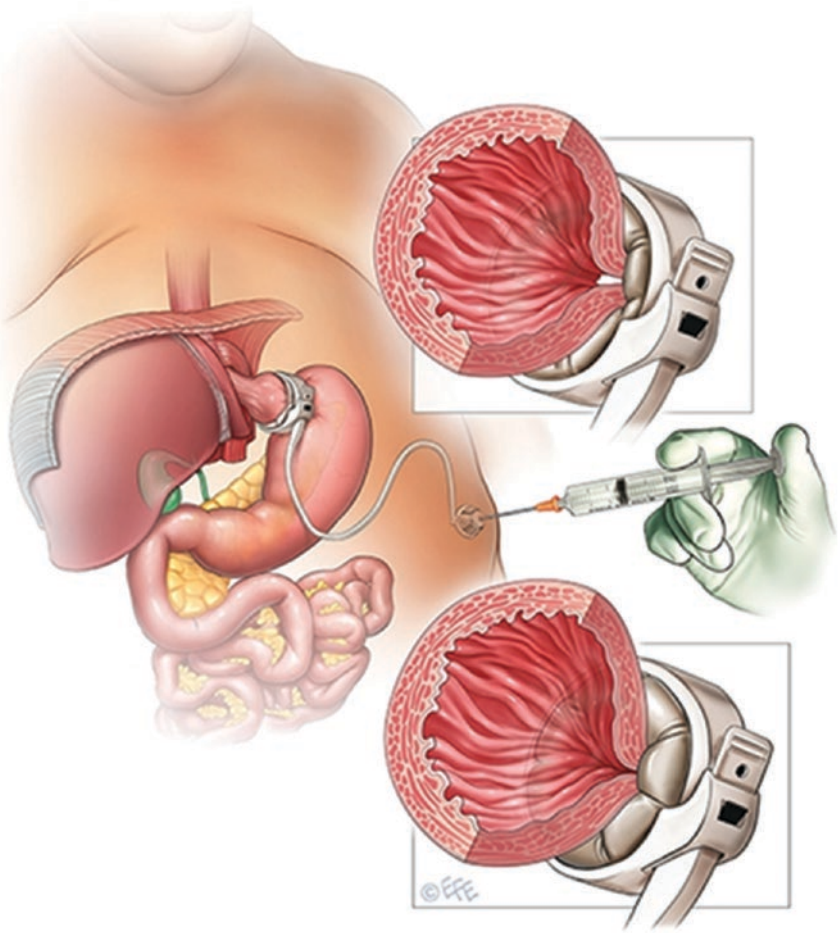

**Fig. 9.3** Adjustable gastric band

easy to undermine the effects of the operation by eating liquid or semi-liquid food with high caloric content which is entirely assimilated and freely goes through the gastric ring without restriction. This is why soft consistency foods should be avoided.

There are two surgical AGB placement techniques: the perigastric technique and the pars flaccida technique. The perigastric technique involves the insertion of the gastric ring through dissection, which should be as close as possible to the gastric wall, starting at approximately 2 cm below the cardia, at the lesser curvature level. The pars flaccida technique, on the other hand, involves the opening of the lesser pars flaccida paying attention to the preservation of the vagal fibers and taking the liver caudate lobe and the right diaphragmatic pillar as a point of reference, performing a blunt dissection toward the angle of His and creating a space through

which to place the gastric band. Currently, the pars flaccida technique is the most performed procedure, given that it is considered less susceptible to complications such as perforations and slippage.

Gastro gastric stitching can be performed on the anterior wall of the stomach in both techniques to stabilize the band anteriorly.

Several meta-analyses and systematic reviews of the literature that included a significant number of gastric band patients reported that weight loss after AGB is variable, ranging from 36% to 56% of the excess body weight at 3–5 years and an average of 48% at long-term follow-up (>10 years) with a wide range of revisions and removals (8–60%) for lack of weight loss, substantial weight regain, or esophagogastric complications [138–142].

AGB is a surgical procedure with a very low immediate postoperative complication rate (perioperative mortality 0.05–0.3%) but can present complications, at times very serious, even years after the operation, which may require re-operation or eventual removal of the band, such as slippage (1–5%), stoma obstruction (1.5%) esophageal and gastric pouch dilatation (4%), erosion (0.8%), gastric necrosis (0.1%), and port infections [143].

These factors, associated with slower and less early weight loss if compared with the other surgical procedures, greater percentage of patients failing to lose at least 50% of excess body weight compared to the other surgeries commonly performed, and the need of strict adherence to the postoperative diet and to postoperative follow-up visits together with the highest rate of re-operation, have made this procedure suffer an important drop in popularity in the last few years, and only 3% of bariatric procedures in 2016 were AGB operations [95].

#### 9.3.3.4 Biliopancreatic Diversion with Duodenal Switch (BPD-DS) (Fig. 9.4)

The Biliopancreatic Diversion with Duodenal Switch (BPD-DS) is a procedure that is characterized by the coexistence of two action mechanisms: the restrictive mechanism and the malabsorptive mechanism. This makes it one of the most efficient bariatric surgery procedures today. The short-term and long-term weight loss that can be achieved with this operation is, in fact, much higher than with any other bariatric procedure.

BPD-DS was described for the first time by Marceao [144] and by Hess and Hess [145], respectively, in 1993 and 1998. The operation emerged as a variant of biliopancreatic diversion (BPD) according to Scopinaro (Fig. 9.5), introducing the duodenal switch and elongating the common absorption channel. It involves a horizontal gastrectomy (with a gastric pouch of approximately 200–300 mL) and Roux-en-Y reconstruction with an alimentary limb of 200 cm, a common channel of 50 cm and gastro-ileal anastomosis.

The changes made by Hess and Marceau aimed to reduce BPD complications such as lack of proteins and vitamins, bone demineralization, marginal ulcers, and dumping syndrome, maintaining the excellent results of BPD in terms of weight loss.

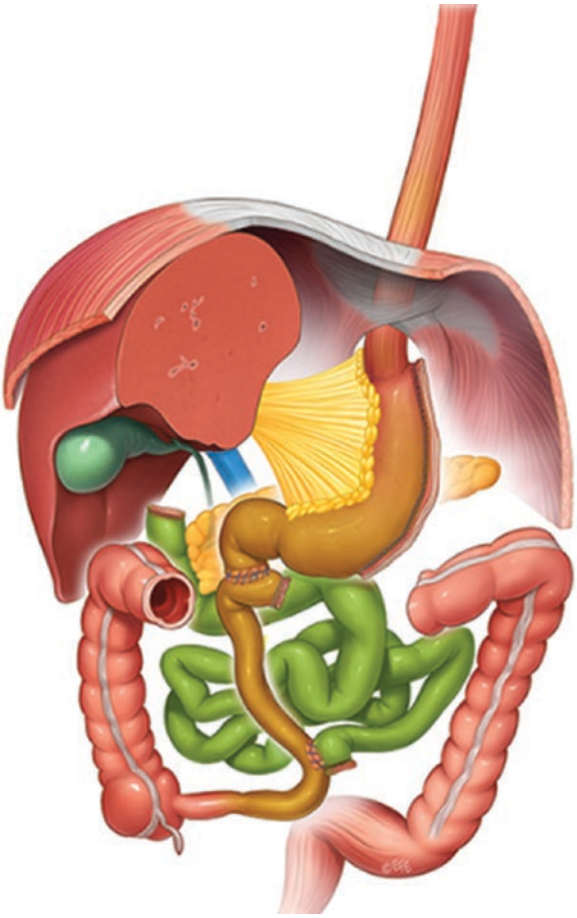

**Fig. 9.4** Biliopancreatic diversion with duodenal switch

In 2000 Gagner published the first series of BPD-DS performed laparoscopically and described the procedure as it is still performed today [146].

BPD-DS is a sleeve gastrectomy with a calibration tube of 60FR (volume of residual stomach 150–200 mL), a duodenal ileostomy and a long Roux-en-Y with an alimentary limb of 250 cm and a common channel of 100 cm. With respect to BPD, BPD/DS preserves the lesser curvature, the antrum, the pylorus, the first duodenal portion, and the integrity of vagal innervation. These anatomical variations may be responsible for better digestion compared to the previous operation and for a reduction in dumping syndrome and marginal ulcer risk. In addition, a longer common channel (100 cm instead of 50 cm) allows for fewer complications related to malnutrition and reduces frequency of diarrhea in the absence of significant differences in terms of weight loss, improving BPD-DS patients' quality of life with respect to those who underwent BPD.

Gagner introduced the concept of "two stage technique" in patients with BMI > 65 kg/m$^2$ after noticing a high rate of mortality and complications (6.5% and

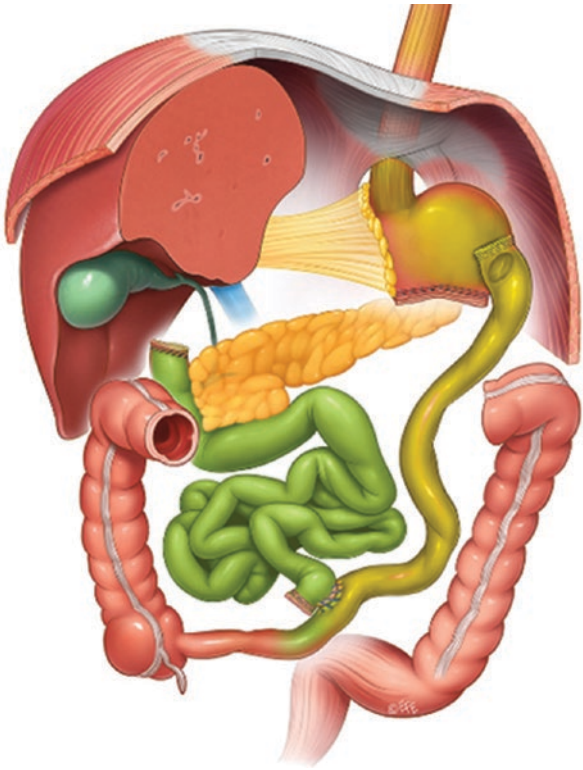

**Fig. 9.5** Biliopancreatic diversion (Scopinaro procedure)

38%, respectively). The first stage is a sleeve gastrectomy, and only after considerable weight loss, the BPD-DS procedure is completed [147]. In this way, it was possible to reduce mortality rates and complications in super-super obese patients.

Among all bariatric procedures, BPD-DS is the procedure that guarantees greater long-term weight loss. Literature reported EWL at 10 years between 74% and 93% [148, 149] and EWL of 70.9% at 20 years. Weight loss was greatest in the super obese category (BMI > 50 kg/m$^2$). As well as being efficient for weight control, BPD-DS has demonstrated that it is better than other procedures for comorbidity control. Bolckmans' recent publication reports a remission rate of 87.5% for T2DM and 80.9% for hypertension; 93.3% of patients normalized total cholesterol levels, 89.7% triglycerides, and 95.0% low-density lipoprotein cholesterol. At the same time, 42.5% of patients were reported to have needed re-operation, including 10.6% for correction of protein malnutrition. Other surgical procedures related to previous BPD-DS are internal hernia repair, incisional hernia repair, adhesiolysis, cholecystectomy, and correction of invalidating reflux.

The possible postoperative complications are: mortality (0–1.9%), gastric fistula (0–4.6% up to 16.7% for revisional procedure), small bowel obstruction due to internal hernias (6–8%), bleeding (1.7–10%), pulmonary embolism (1–3% in open procedures, 0.2–1% in laparoscopic procedures), anastomotic ulcer or stenosis (0.2–1%), and malnutrition (1.4–10.6%).

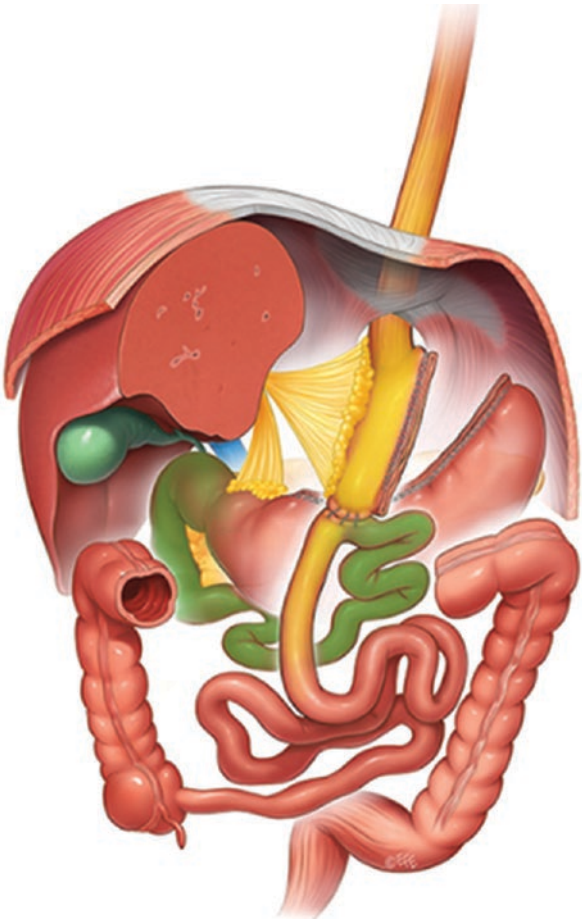

**Fig. 9.6** One anastomosis gastric bypass

Despite its undisputed efficacy, this procedure represents only 0.5% of the bariatric operations performed in the world in 2016 [95].

The reason lies perhaps in the technical complexity of the procedure, in the higher complications and mortality risks compared to AGB, LSG, and RYGB, in its greater potential to cause protein deficiencies and long-term vitamin and mineral deficiencies for which compliance with follow-up visits and strict adherence to dietary and vitamin supplementation guidelines are critical to avoid serious complications.

#### 9.3.3.5 One Anastomosis Gastric Bypass (OAGB) (Fig. 9.6)

The mini gastric bypass is a procedure introduced by Rutledge in 1997, with the objective to simplify and possibly reduce RYGB risks, with reversibility or conversion to a simpler methodology. Successively, many bariatric surgery centers in

Europe and the world adopted this technique for its greater simplicity, reduced operative time, and the excellent results described in terms of weight loss, diabetes, and comorbidities resolution. OAGB is different to RYGB with respect to the conformation of the gastric pouch, which is longer and narrower, and the execution of an omega loop single gastro-jejunal anastomosis at approximately 180–250 cm from the ligament of Treitz [150]. The gastric pouch in OAGB is similar to a SG and is created with a surgical stapler through a horizontal section of the stomach of approximately 4 cm at the angle of the lesser curvature just above the crow's foot, then a vertical resection of the stomach is performed with a 32–36 FR calibration tube upward to the angle of His, similarly to a SG.

In terms of weight loss and resolution of comorbidities, results seem to be excellent. An EWL at 5 years of between 64.9% and 83.9% and at 10 years of around 70% was described [151–154].

Results regarding hypertension resolution (87.5%) and T2DM remission (84.4%) are also included [154].

OAGB is without doubt an efficient procedure when contrasting metabolic syndrome.

Possible complications are: gastric and anastomotic leak (0.6–1.8%), bleeding (0.1–2.5%), anastomotic ulcers (0.6%), protein malnutrition (0.9%), small bowel obstruction (0.1%), and bile reflux (apparently not exceeding 2%).

OAGB has not been recognized in the USA as a standard bariatric procedure yet, but in Europe and Pacific Asia, it has spread rapidly in the last few years making OAGB in 2016 the third most performed procedure in the world after SG and RYGB [95].

### *9.3.4 Metabolic Surgery: The Manipulation of the Gastrointestinal Tract to Condition the Brain*

Energy homeostasis is regulated by a complex communication system between intestine, adipose tissue, and the central nervous system. Thanks to hormonal and neural signs, the central nervous system integrates the information coming from the intestine such as the type and quantity of nutrients ingested and the energy reserves accumulated and consequently, regulates the sense of appetite, satiety, and eating behavior. For example, if energetic values are negative, the system compensates with hyperphagia or increasing a preference for high-calorie foods to restore usual weight, which in obese patients is not "normal" weight but excess weight maintained for a long time that has become "normal" (baseline) in that specific subject, a baseline that the organism will try to return to after each weight loss episode. In this respect, the key to BMS efficacy seems to be the prevention of these compensatory responses, modifying signaling pathways, of either hormonal or neural nature, or even inducing changes at a central nervous system level [155].

Some of these mechanisms seem to be responsible for the changes in preferences regarding palatable foods that the patients report after BMS. These changes are probably mediated by neural networks that control the introduction of food with a homeostatic aim like the brain stem and the hypothalamus and with a hedonic aim like the tegmental ventral area (VTA), the nucleus accumbens, the orbital frontal cortex, the prefrontal cortex, and limbic nuclei. The mesolimbic dopaminergic pathway, which elaborates the hedonistic aspects linked to reward connected to food and other substances, is probably a key point. Various research groups [156–158] have demonstrated differences in response to alimentary stimuli in the brain of obese subjects in comparison with nonobese subjects. BMS can correct these alterations through hormonal and/or neural mechanisms partly mentioned above. A recent study conducted by Faulconbridge et al. [159] confronted, via cerebral magnetic resonance, the neural response to images of high and low calorie food, before and 6 months after surgery, in three groups with severe obesity subjects: one group of patients underwent RYGB (no. 523), one group underwent SG (no. 519) and one was a follow-up group with stable weight (no. 521). At baseline, a liking of high-calorie foods was significantly higher than for low-calorie foods in all three groups. At 6 months of the operation, patients who underwent RYGB and SG showed a significant decrease in preference for high-calorie foods that, on the contrary, was not present in the follow-up group. No group reported significant changes in the liking of low-calorie foods. They also showed that neural elaboration in the VTA, the main area where reward cognition takes place, is altered in response to the stimuli induced by high-calorie foods after BMS. These changes were not documented for the follow-up group. Faulconbridge et al. suggest that ghrelin could be one of the many peripheral substrates that mediate changes in neuronal function after surgery. To support this thesis, there are various factors like the presence of ghrelin-mRNA receptors in the VTA of rats and human beings [160]. The fact is that administration of ghrelin directly in the VTA increases the consumption of rewarding substances like alcohol, cocaine, and amphetamines, while peripheral administration of ghrelin antagonists suppresses that desire [161, 162]. It has therefore been assumed that the postoperative changes in the circulating levels of ghrelin can be involved in the alteration of the hedonic response to food stimuli. It is extremely interesting that Faulconbridge et al. [159] have observed significant changes in neuronal response at the VTA level only and not in the regions of the brain that are responsible for energy homeostasis control (e.g., the hypothalamus).

Earlier studies [163–165] also documented a decrease in preference for foods that are particularly pleasant to the palate after bariatric surgery, in contrast to what is observed when weight loss occurs without surgery. In addition, in contrast to what happens after BMS, circulating leptin levels drop in patients who lose weight with a diet and ghrelin levels increase, consequently hunger also increases together with the weight gain described above.

This partly explains why significant weight loss and long-term result maintenance is easier with BMS compared to simply dieting.

**Acknowledgments** *Images Grant of Rights:* The illustrator and copyright owner, Dr. Levent Efe, CMI grants IFSO and all its members (Dr D. Tassinari) a nonexclusive license to reproduce the artwork in all media.

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# Part III
# Thyroid, Obesity and Metabolism

# Chapter 10
# Thyroid and Obesity

**Vincenzo De Geronimo**

Obesity and thyroid disease have been a field of research and scientific speculation of great interest for years. Both thyroid disease and obesity affect large sections of the population, and a link between these clinical conditions is frequently proposed.

In recent years, the obesity prevalence trends toward reduction in some areas of the world [1]. But the OECD data (OECD) regarding the prevalence and progression of obesity in the world describe a condition reasonably linked to a future growth. In Italy the prevalence of overweight-obesity has reached a rate slightly lower of 50% of population [2] and the "Okkio alla Salute" Survey (year 2019) describes an aggregate prevalence of obesity and overweight that affects just under 30% of the Italian population aged between 8 and 9 years [3] (third class of primary school), although the trend from 2008 to 2019 appears to be downhill.

The frequent presence of thyroid disease and obesity in the same subjects does not seem to be stochastic alone. Although in the idea of many patients, a thyroid disease is the cause of their obesity condition, in 1940 Plummer documented that the weight gain in hypothyroidism was related to increase in body water in myxedematous patients [4].

## 10.1 Obesity and Autoimmune Thyroid Disease

The white adipose tissue, under the leptin action, produces a great amount of cytokines, and many of these are proinflammatory regulators as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Adipose tissue also has a great T lymphocyte and macrophage infiltration, and the dysregulation of signal regulated by TLRs on these cells can triggers autoimmunity [5]. The link between adipose tissue and

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autoimmune thyroid disease, although captivating, has not received much confirmation to date [6–8].

There are, however, a number of reports in favor of a relationship between obesity and thyroid autoimmunity. Song's meta-analysis described an association between obesity and positivity for anti-thyroperoxidase autoantibodies, but not with anti-thyroglobulin autoantibodies and with Graves' disease [9]. An increased prevalence of positivity for anti-thyroid autoantibodies has been documented in subjects undergoing bariatric surgery to treat obesity [10] and in a series of moderate or severe obese patients under the age of 50 years as described by Marzullo et al. [11]. Also, Ying Wu confirmed a positive association between obesity and thyroid autoimmunity in a survey involving 55,891 patients from 51 different provinces in China [12].

## 10.2 Obesity and Thyroid Cancer

The association of obesity with cancer is strong [13]. Papillary thyroid cancer also appears to be suffering from obesity as a risk factor. About 1/sixth of papillary thyroid carcinomas is associated with overweight obesity, and in the same series of patients, an association with anaplastic carcinoma and about 2/third of the larger tumors was shown (>4 cm) [14]. In a Mendelian randomization study, however, the association is not confirmed unless in the presence of type 2 diabetes mellitus [15].

In female population obesity has been associated with an increased risk of thyroid cancer. The reported odds ratio was 1.63 per every 5 BMI points in 6577 Korean women, without familiarity for thyroid cancer, submitted to thyroid ultrasound between 2007 and 2008 [16]. Subjects with BMI >30 kg/m$^2$ have larger papillary thyroid cancer, with a more advanced TNM stage [17].

Genetic factors can promote, under the influence of the condition of obesity, the appearance of thyroid cancer [18], and BRAF-positive thyroid cancer has been observed more frequently in obese subjects [19].

## 10.3 Thyroid Ultrasound Examination in Obese Patients

Ultrasound examination of the thyroid gland in obese patients can be difficult. Obesity patients have an increase in the wideness of the subcutaneous fat. This leads to an increase in the distance between the probe and the gland, imposing the operator to reduce the frequency to be set in the probe and making the view of thyroid gland more difficult at high resolution. The neck of obese subjects is often greater shortness. Consequentially, the thyroid can affect the upper mediastinum, and the study of the central lymph node compartment can be harder. The study of laterocervical lymph node stations, the ability to identify signs of extra glandular invasion

and multifocality, on the other hand, in subjects with BMI >30 kg/m$^2$ of body surface does not seem be trickier [20].

Ultrasonography is fundamental to study and define the risk of malignancy of a nodule and thus delimit which nodules submit to cytological investigation. Applying the criteria postulated by the ATA 2015 and TI-RADS classification system, obese subjects (BMI 47 ± 6.1 vs. 22.8 ± 2.7) although they have a higher prevalence of hypoecogenicity of glandular parenchyma and a higher frequency of nodular pathology, they do not differ in the ultrasound assessment of the risk of cancer from non-obese subjects [21].

## 10.4 Adipocytes and Thyroid Function

In both adult and the pediatric population, the value of TSH can be affected by the condition of obesity [22, 23].

The study of the relationships between body weight and obesity is complicated by the circadian or age-related modifications in the value of TSH and thyroid hormones [24], as well as changes due to season and environmental range of the temperature [25].

There is a great number of studies on association of thyroid function and obesity, but they are not easily comparable. Patients are grouped differently in relation to BMI and thyroid hormones values, and often, there are no information on the number of blood samples made or changes in the TSH and the thyroid hormones between 1 day and another.

In the DanThyr study, while the incidence of obesity is double in subjects with TSH >3.6 mIU/L compared to those with TSH between 1 and 1.9 mIU/L, lower TSH value compared to the higher values determined a difference of about 5.5 kg [26].

This positive association between BMI and TSH was also confirmed in a study with Norwegian population. In a prospective revaluation of the subjects lasting 7 years, those with a higher TSH value showed a greater increase in BMI [27].

An activation of the hypothalamus–pituitary–thyroid axis (HPT axis), typified by increase in the value of $FT_3$, as well as of TSH, has also been observed in the obese population of the United States [28].

Adipocytes express TSH-R (TSH receptor). In samples of human adipocyte tissue, a BMI-related expression of the TSH receptor is observed, and in nutritionally made obese mice, the TSH-R on adipocytes is upregulated [29]. The expression of adipogenetic markers of white adipose tissue (WAT) and "BRown in whITE" (BRITE), leptin and CITED1 (Cbp/p300-interacting transactivator 1), in samples from thyroidectomized subjects was directly proportional to the pre-thyroidectomy condition of thyroid increased functional status [30].

Weight loss is associated with a reduction in TSH value [31, 32] (although not in all works [33]) in euthyroid subjects underwent bariatric surgery, perhaps in relation

to changes in the secretion of leptin. After all leptin produced by adipocytes is an important regulator of the HPT axis.

Iacobellis G et al. have studied the value of TSH, $FT_4$, $FT_3$, adiponectin, and leptin in a population of 87 obese women (BMI 40.1 ± 7 kg/m$^2$) undergoing bariatric surgery. In this examination, the TSH value was correlated with BMI, leptin, leptin/BMI ratio and was inversely related to adiponectin [34]. Also Cappelli et al. have documented the positive association between TSH and BMI. They described, unlike other observations, how the obese subjects could have a lower incidence of thyroid nodular pathology [35].

On a Caucasian population of 880 euthyroid subjects in which TSH was positively associated with hypertriglyceridemia while the value of $FT_3$ showed a positive correlation with HDL cholesterol [Spadafranca et al. [36]]. The value of TSH was found to be lower in the population defined as Metabolically Healthy Non Obesity (MHNO), and the value of $FT_4$, in male population, was on higher average. Metabolically Healthy Obesity (MHO) subject has TSH value higher [data from the sixth Korea National Health and Nutrition Examination Survey (13,873 subjects aged ≥19 years)]. The association between the metabolic risk profile and the $FT_4$ value was discovered inversely proportional in the general population, in the male population, and in younger subjects. No association was found between the risk of metabolic syndrome and the TSH value [37].

In few hyperthyroid patients (six women) undergoing anti-thyroid treatment with methimazole and brought back to euthyroidism, resting energy expenditure (REE) and body weight have been studied. With improved thyroid function, in spite of the reduction in energy intake through reductions of food intake, body weight tended to increase. The resting energy expenditure (REE) was elevated in the untreated subjects and has been progressively reduced with the treatment. The patients had a REE with positive correlation with the value of $FT_3$ and $FT_4$ and negative with the TSH. Both deiodinasic activity of Deiodinase II (DIO II) and thyroid secretory output that has also been determined in this study, confirmed a positive correlation with REE values. Body weight increase, after an initial increase in fat mass, was characterized by an increase in lean mass. Also demonstrated by the increase in in the value of the hand grip strength test (a maximum isometric force exerted by the muscles of the upper limb measuring test) [38]. Weight gain that occurs in the first year after treatment with $^{131}$I for thyrotoxicosis is related to the increase in lean mass [39]. The body composition was examined with dual energy X-ray absorptiometry and computed tomography in nine patients that was observed for 1 year after hyperthyroidism treatment. Body weight appreciably increased compared to baseline detection of 2.7 ± 3.1 kg during the first 3 months and 8.7 ± 1.8 kg at the end of the 12 months. In the first 3 months, the lean mass increased, after 12 months body fat showed an average increase of 4.9 ± 6.6 kg [40] and the visceral and subcutaneous adipose tissue grew during interval between 3 and 12 months mainly.

Data produced from some works that have investigated the liaison between thyroid hormones and resting energy expenditure (REE) appears to be consistent with the absence of correlation between the energy expenditure during rest, ascertained with indirect calorimetry, and TSH in euthyroid subjects. TSH value is a

determinant in the energy expenditure at rest in the population of subjects affected by subclinical hypothyroidism [41] (high TSH value and thyroid hormones value in the normal range). And only in slimmed-down subjects, a positive correlation was observed between the values of $FT_4$ and $FT_3$ on the one side and the energy expenditure at rest on the other [42].

In subjects taking levotiroxine ($LT_4$) as replacement therapy, resting energy expenditure (REE) is 6% less than that in subjects undergoing suppressive therapy and 4% less than that in euthyroid subjects. Despite the normal TSH value. In this work, the free $T_3$ concentration ($FT_3$) correlated significantly with rest energy expenditure (REE). The subject with lower rest energy expenditure had lower $FT_3$ values. No correlation between TSH and REE was found [43].

In 2011 Josh W. et al. carried out a study on hypothyroid patients. The aim of the latter was to investigate whether there was a weight change in hypothyroid individuals after $LT_4$ replacement treatment for post-surgical hypothyroidism and under suppressive therapy. No major differences in body weight were found [44].

Subjects undergo to treatment with $LT_4$ because suffering of hypothyroidism. Despite the increase in resting energy expenditure (REE), determined with indirect calorimetry, hypothyroid patients show a weight loss as a conseguence of lean mass loss. In dual energy X-ray absorptiometry study of body composition, $LT_4$-treated subjects documented a reduction of lean mass compartment and an insignificant decrease of fat mass and bone mass [45]. We can argue that the reduction in body weight observed during the treatment with $LT_4$ is attributable to a loss of excess water retained with glycosaminoglycans deposited in the tissues. The ability to attract water in these substances causes the characteristic myxedema observed in hypothyroidism. In severe hypothyroidism, there is accumulation of glycosaminoglycan in the skin and other districts [46].

$LT_3$-based formulations used instead of $LT_4$, and titrating the dose in order to obtain similar TSH values, would seem to allow greater capacity in the control of body weight and cholesterol value of obese hypothyroid subjects [47]. Despite these results were obtained without determining an increase in heart rate or blood pressure, the data currently available in the literature do not allow recommending its use in this specific population [48]. Even in this case, the reduction in body weight was not attributable to a reduction in fat mass.

Currently there is insufficient evidence to support the treatment of obesity with thyroid hormones. Treatment (replacement therapy), as reported in the guidelines, should be reserved for individuals with obvious signs of subclinical or clinical hypothyroidism [49].

## 10.5 Thermogenesis and Thyroid Hormones

The production of body heat is one of the fundamental process for the maintenance of life and regulation of body weight. It can derive from the so-called inefficiency of the biological reactions fundamental for the survival of the animals (obligatory

thermogenesis), or from other adaptive mechanisms developed from animal species to maintain body temperature in case of the cold exposure (optional thermogenesis, nonshivering thermogenesis [NST]). The temporary muscle contraction (shivering facultative thermogenesis) participates in the optional thermogenesis. The optional thermogenesis is mainly regulated by sympathetic nervous system (SNS) and thyroid hormones and the main site of heat production in mammals is brown adipose tissue (BAT) [50].

The conversion of thyroxine ($T_4$) into triiodothyronine ($T_3$) by deiodinase 2 (DIO II) takes part in the regulation of thermogenesis in BAT (brown adipose tissue) [51].

$T_3$ is able to favor an increase in the maturation of brown/beige adipocytes through the action of the β1 isoform of the thyroid hormone receptor [52]. $T_3$ has been proven effective in increasing mitochondrial turnover (mitochondriogenesis-mitophagy) at the BAT level [53] and in human multipotent adipose-derived stem (hMADS) induces the expression of UCP1 and mitochondriogenesis [54].

Both cold exposure and noradrenaline cause an increase in the activity of deiodinase 2 (DIO II) at the BAT level [55], and in hypothyroid rodents when the stimulation of acute thermogenesis of BAT is induced with norepinephrine, it fails to increase heat production [56].

In mice the induction of adipocyte browning is obtained with pharmacological activation of thyroid hormone receptors with GC-1 (a thyroid hormone receptor-beta-selective agonist) in white subcutaneous adipose tissue (WATsc) [57].

Studying the role of thyroid hormones in the activation of UCP2 and UCP3 is difficult due to their short half-life in the cytosol (about 30 min unlike UCP1 which has a half-life of about 30 h. The weaker available evidence comes from experimental animal studies and is partly determined by the type of feeding used to feed them [58, 59].

Thyroid hormones increase the expression of UCP2 and UCP3 at mitochondrial level in human skeletal muscle cultures as well as the expression of mRNA for UCP2 in adipocytes is increased but without increasing the activity of respiratory chain [60].

Among mice food gathering and consumption takes place mainly overnight. During nocturnal activity, knockout animals for the UCP3 gene, have approximately a 6% reduction in thermogenesis compared to wild-type animals in response to $T_3$ administration. And the administration of $T_3$ in knockout animals for β-adrenergic receptors, in the same work, could maintain body temperature without determining an increase in the expression of UCP1. This experiment demonstrates the role of skeletal musculature in optional thermogenesis [61]. But the thermogenesis induced by thyroid hormones can be UCP1 independent (or indirectly dependent on UCP1) [62]. When $T_4$ or $T_3$ was administered in KO mice for UCP1 under thermoneutrality condition, the increase in measured metabolic activity was similar to that found in wild-type mice [63, 64].

Humans and large mammals have a poorly represented BAT, unlike rodents and animals capable of winter hibernation. For this reason the function of BAT it is no longer considered central in nonshivering thermogenesis (NST) (namely, thermogenesis not linked to muscular contraction).

Hyperthyroid patients presented hyper-uptake of 18F-fluoroglucose at the level of skeletal muscles and not at the level of adipose tissue in a group when studied, as hypothetical activity of BAT, through 18F-fluoroglucose (18F-FDG) positron-emission tomography with computed tomography (PET-CT) first and after treatment with methimazole [nine patients of Zhang Q et al. with Graves' disease] [65].

Maintaining basal metabolic rate (BMR) is the main cause of energy expenditure for the body. The transmembrane gradient in skeletal muscle cells of sodium, potassium, and calcium, resulting in an increase in ATP consumption, is modified by thyroid hormones. $T_3$, in animal models, can stimulate ATP consumption by increasing the intrinsic activity of the sodium-potassium pump. This effect is determined through the transmembrane loss of sodium and potassium ions [66, 67] or by the induction of other metabolic processes such as synthesis of fatty acids [68]. The synthesis of fatty acids can explain about 10% of the increase in energy expenditure that is observed during the switching from hypothyroidism to hyperthyroidism.

Thyroid hormones are able to cause an increase in the number and activity of sodium-potassium pumps [69]. In studies on muscle biopsies from patients with Graves' disease, an increased expression of mRNA for the α2 and β1 subunits of the sodium-potassium pump was observed and correlated to the degree of hyperthyroidism [70]. However, the maintenance of the calcium gradient between cytosol and the endoplasmic reticulum is the most important mechanism in thermogenesis that occurs in skeletal muscles. The sarco/endoplasmic reticulum $Ca^{2+}$ -ATPase (SERCA) pump is considered one of the key mechanisms for muscle thermogenesis. The calcium cycle through the sarcoplasmic membrane is responsible for a share that goes from 30% to 70% of resting energy expenditure (REE) [71]. Thyroid hormones are capable of stimulating the expression of SERCA1 in skeletal muscle [72].

It is now a well-established fact that the regulation of energy metabolism in humans and in rodents involves the action of several mechanisms working together. As stated above bile acid has a role in thermogenesis. In both rodents and humans, the tissue most important to thermogenetic activity expresses the receptor for bile acids, G protein-coupled bile acid receptor1 (GP-BAR1), in addition to Deiodinase 2 (DIO II). The administration of bile acids by binding to GP-BAR1 activates thermogenesis through the involvement of Deiodinase 2 (DIO II) [73].

The role of thyroid hormone receptors, TRα and TRβ, in the induction of thermogenetic mechanisms is different [74]. The TRα, in its isoform 1, is a key target to induce thermogenesis, but the synthesis of UCP1 depends on the TRβ [75].

Thyroid hormones and sympathetic nervous system interact at every level starting from the hypothalamus.

Inhibition of the hypothalamic AMPK by $T_3$ determines an increase in intracellular lipogenesis that stimulates the activity of the sympathetic nervous system (SNS) resulting in an increased expression of BAT activity markers [76].

During fasting, at the pituitary level, a reduction in the expression of DIO II is observed with consequent reduction of $T_3$ production, but at hypothalamic level, in the neurons of the arcuate nucleus that produce orexigenic stimuli, its activity is

increased. The increase in the concentration of $T_3$ at the level of the arcuate nucleus is correlated with the production of NPY and AgRP.

Also the production of TRH is involved in thermogenesis. The neurons of the paraventricular nucleus that produce TRH receive both inhibitory signals by neurons that produce AgRP or NPY and stimulatory input by synaptic projections of the neurons of the ventromedial nucleus that produces αMSH and "cocaine and amphetamine-regulated transcript" (CART). The administration of leptin counteracts the reduction in TRH observed during fasting [77].

## 10.6 Thyroid and Ghrelin

Ghrelin, one of the major players in regulating body weight and food research, has interesting ties to the functioning of the thyroid. Ghrelin is secreted primarily from X/A-like cells of the gastric fundus glands of the stomach but has also been identified in several other tissues [78] as the parafollicular cells of the thyroid [79]. The action of Ghrelin on thyroid hormones seems to be predominantly inhibitory. At central level, in rats, the action of Ghrelin is the modulation of the activation of the hypothalamus–pituitary–thyroid axis through an action on the receptor for cannabinoids type 1 (CB1) [80]. Ghrelin receptors are expressed also in thyroid cells. It seems to be linked to the downregulation of three proteins involved in the synthesis of thyroid hormones: thyroglobulin, sodium-iodine symporter, and thyroperoxidase [81, 82] In hyperthyroid subjects, Ghrelin secretion is reduced compared to subjects with euthyroidism [83, 84]. This could represent a compensatory mechanism in the regulation of thyroid hormone secretion.

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# Chapter 11
# Thyroid Dysfunction and Metabolism: Diagnosis and Follow-Up


**Livio Luzi, Stefano Massarini, Ileana Terruzzi, Anna Ferrulli, and Claudio Cusini**

## 11.1 Background

Thyroid function is the major determinant of whole-body energy balance.

Energy balance is the difference between the metabolizable energy intake (EI) by the body and energy expenditure (EE). ATP is synthetized according to fixed and constant relationships with respect to the consumption of $O_2$ and the production of $CO_2$ and heat. EE is an expression of ATP utilization by the organism. Given the short half-life of this molecule, the amount of ATP used corresponds to what is synthesized.

In sedentary individuals, resting energy expenditure (REE) is the major component (60–80%) of total energy expenditure [1], and it is defined as the amount of energy used by an individual at rest to perform vital functions. Other components of total energy expenditure (TEE) are exercise activity-related thermogenesis (EAT) and non-exercise activity-related thermogenesis (NEAT), which are the most important modifiable variables in the TEE in most people [2]. An additional component of EE is the thermic effect of food (TEF), as the energy expenditure associated with food digestion, absorption, and storage process. Furthermore, another component is the energy dissipation required to maintain core temperature homeostasis, known as adaptive thermogenesis (AT).

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## 11.2 Measurement of Resting Energy Expenditure (REE)

The gold standard procedure for the measurement of REE in clinical practice is the indirect calorimetry (IC) [3].

The measurement of energy expenditure by indirect calorimetry is based on the principle that the organism obtains energy through oxidation of the energy substrates contained in food, a process in which $O_2$ is consumed and $CO_2$ is produced in proportion to the amount of energy generated.

Indirect calorimetry uses $O_2$ consumption and $CO_2$ production as indicative measures of ATP synthesis, hence energy expenditure [1]. Additionally, by measuring the differential in $CO_2$ production versus $O_2$ consumption, IC can generate the respiratory quotient (RQ), which estimates the substrate utilization, in which 1.0 represents all carbohydrate, whereas 0.7 represents all fat oxidation [4].

Indirect calorimetry can be used for several different purposes: weight management (e.g., in the treatment of overweight and obesity), nutrition support (e.g., to monitor the nutritional status of underweight or overweight patients in intensive care units), and metabolism research in humans and/or animals or in diabetic patients (e.g., the organism's ability to adapt to nutrient oxidation, to energy availability and its implications on lipid accumulation and insulin resistance). Furthermore, indirect calorimetry has represented the gold standard for the assessment of thyroid function [5].

The examination is performed under thermal neutrality conditions (22–26 °C). Subjects must be awake and alert in a supine position for about 20 min, in a state of fasting for at least 12 h, in complete psychological and physical relaxation, and must not have performed physical activity in the previous 48 h.

While predictive equations estimate the REE, IC measures (not only estimates) the REE. This difference is used in expressing measured REE as a percentage of the predicted REE estimated by the Harris–Benedict formula, thus identifying an adequate and a non-adequate to predicted REE.

Direct calorimetry, instead, considers the release of heat as an indicative measure of ATP synthesis/consumption, hence of energy expenditure. During examination, the subject needs to be in a metabolic chamber that allows to measure heat production for at least 24 h. This methodology has provided important data, especially relative to the regulation mechanisms of thermogenesis [1, 6]. However, the elevated cost, the duration of the exam, and the impossibility to measure real-life conditions make this procedure of marginal use in clinical practice.

A different methodology for the estimation of EE is based on the administration of water doubly labeled with stable isotopes ($^2H_2$ and $^{18}O$) and the measurement of the differential disappearance of hydrogen vs. oxygen molecules as measured by mass spectroscopy [7]. This method calculates the subject's TEE over a relatively long period of time, through the measure of $CO_2$ production [8, 9]. However, due to its high cost and the difficulty in analyzing and interpreting results, this method is currently limited to research purposes.

The procedure consists in the oral administration of a defined quantity of stable isotopes ($^2H_2$ and $^{18}O$), incorporated in water molecules. Subsequently, the concentration of these molecules in body fluids, progressively decreasing, is assessed by their dosage in organic fluids (urine). Carbon dioxide production can be determined by the differential rates at which $^2H_2$ (lost in urine) and $^{18}O$ (also expired with $CO_2$) concentrations are reduced. From the production of $CO_2$, an average total energy expenditure (usually over a period of 2 weeks) can be calculated, through the same principles of indirect calorimetry.

Accelerometers represent a smart approach for assessing EE [10]. This technology is not expensive and user friendly, but data analyzed across studies indicate that activity-related energy expenditure (AEE) needs to be interpreted cautiously because based on multiple assumptions [11].

## 11.3 The Role of Indirect Calorimetry (IC) in Weight-Reduction Interventions

Worldwide prevalence of overweight (body mass index, BMI $\geq$ 25 kg/m$^2$) and obesity (BMI $\geq$ 30 kg/m$^2$) has dramatically increased in the last decades, bringing the number of affected individuals to approximately 2.1 billion [12]. This phenomenon is of concern, as excess weight gain results in an increased risk for several diseases, and most notably cardiovascular diseases, type 2 diabetes mellitus, and cancer [13].

Both overweight and obesity are the result of a prolonged imbalance between energy expenditure (EE) and energy intake (EI), with a predominance of the latter. State-of-the-art approaches in the treatment of overweight and obesity consist of a hypocaloric healthy meal plan combined with a physical activity program incorporating both aerobic and resistance exercises [14]. For this approach to be successful, it is essential to balance adequate nutrient intake with the individual's total energy expenditure (TEE), thus subject's TEE must be evaluated.

As previously mentioned, resting energy expenditure (REE) is the major component of total energy expenditure, other than being its less modifiable component. For these reasons, REE is crucial in weight-reduction interventions. Resting energy expenditure can be estimated with the use of predictive equations or measured by a number of methods, as discussed above. Despite being easier to apply and more commonly used to estimate REE, predictive equations are characterized by a lower degree of precision compared to measured values, especially in patients affected by pathological conditions that could affect basal metabolism [15, 16].

Hence, the effective measurement of REE, as opposed to its mere prediction, should be a routine procedure in all clinical weight reduction interventions. As mentioned above, currently, the gold standard procedure for the measurement of REE in clinical practice is the indirect calorimetry (IC).

A large retrospective observational study involving 467 overweight and obese patients who underwent dietary intervention for weight control was conducted.

Patients were divided into two groups: subjects who followed a diet formulated on REE measured by IC (IC group) and subjects who followed a diet based on REE predicted by the Harris–Benedict formula (NO-IC group). In 47.7% of patients in the IC group, the measured value was not adequate to the predicted value, indicating that it is not uncommon to have a non-adequate to predicted REE, specifically in obese population. However, the primary aim of the study was to compare body weight and BMI variations in the two groups: a decrease in weight and BMI was observed in all subjects, but the IC group showed a greater weight loss compared to the NO-IC group. The two-way interaction time by treatment (IC vs. NO-IC) was significant for both end points ($0.805 \pm 0.163$ for BMI and $2.143 \pm 0.445$ for weight, $p < 0.001$). Moreover, analyzing metabolic parameters, a statistically significant difference between the two groups was found in triglycerides, which decreased faster in the IC group (Fig. 11.1) [17].

A study demonstrating the utility of IC in clinical practice is the tight calorie control study (TICACOS). It was a prospective, randomized, controlled trial, involving 112 mechanically ventilated patients undergoing enteral or parenteral nutrition.

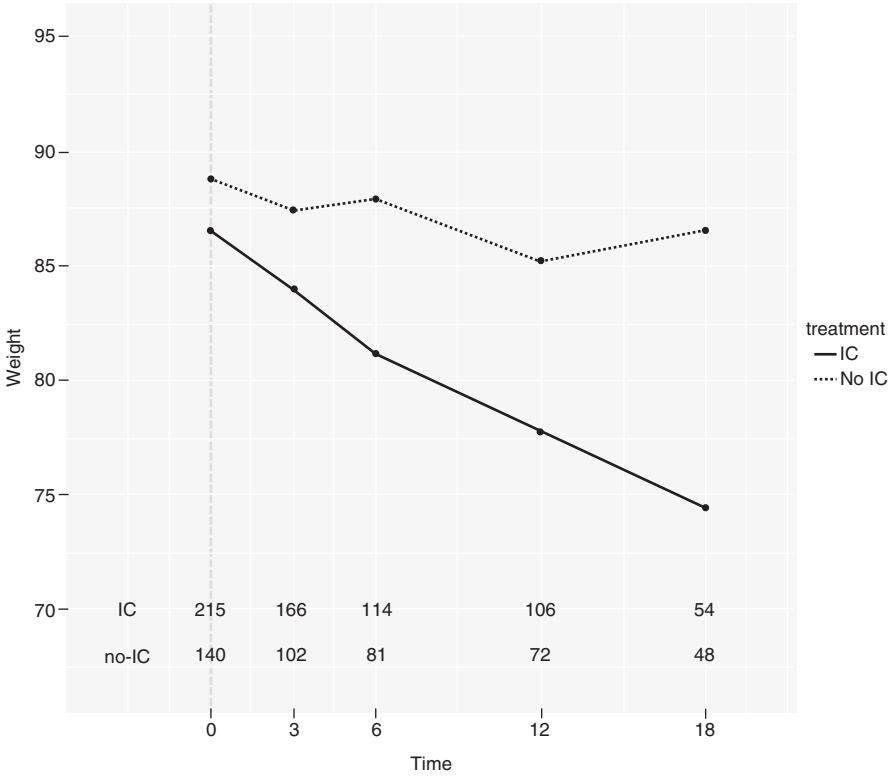


**Fig. 11.1** Average weight at baseline, after 3, 6, 12, and 18 months since the first clinical visit by groups (IC group and NO-IC group). For each group and for each follow-up time, the number of available measurements is reported at the bottom of the figure

A reduction in mortality was observed in the group whose nutrient intake was based on the IC, probably due to an improved energy balance [18].

Based on these evidences, we can assume that the precise assessment of REE by IC is fundamental in clinical dietetic practice in order to maximize the benefits of nutrition therapy, particularly in subjects with potential abnormalities in basal metabolism due to thyroid dysfunction. Thus, it should be a routine procedure in all clinical weight reduction interventions [17].

## 11.4 Thyroid Hormones and Energy Expenditure

Among the pathological conditions that can alter energy expenditure, overt thyroid diseases are some of the most relevant.

It is well known that thyroid hormones (THs) regulate growth and development in children and regulate metabolism in adults [19–21]. Indeed, THs correlate with body weight and resting energy expenditure (REE) [22–24].

Although the role of THs on EE has been known for over a century [25, 26], the specific mechanisms underlying this in humans need to be fully clarified [27].

The mechanisms through which THs modulate EE can be genomic or non-genomic. Genomic activities of TH consist of the transcriptional regulation of hundreds of genes that code for proteins that are involved in carbohydrate, lipid and protein metabolism, energy metabolism, as well as tissue biogenesis, cell cycle, and apoptosis [28]. This action is mediated by nuclear TH receptors (THRs) [29], which bind to TH-responsive elements (TREs) located in the promoter of TH-target genes. Since THs have abrogated effect on EE in the absence of THRs [30], these are certainly involved in mediating TH metabolic activity.

These genomic actions are complemented by non-genomic activities [31] that started on the plasma membrane, cytoplasm, or organelles, and whose principal mediators are the protein kinase signaling cascades [32]. Nongenomic actions include regulation of ion channels and oxidative phosphorylation [28]. Genomic and nongenomic actions may modulate each other and converge at the same targets, and their relative contribution varies based on the context [33].

The effects of THs on EE can be both direct or indirect [34].

Direct effects are referred to TH actions that inherently increase ATP utilization, via metabolic cycles and ion leaks.

Metabolic cycles, also known as futile cycles, consist of opposing metabolic reactions, catalyzed by distinct opposing enzymes, that operate simultaneously without generating net product, but resulting in net ATP hydrolysis [33]. The hexokinase/glucose-6-phosphatase or the phosphofructokinase/fructose 1,6-diphosphatase pairs are examples of futile cycles that consist of two opposing reactions [35]. However, futile cycles may also comprise opposing metabolic pathways, such as glycolysis/gluconeogenesis, lipogenesis/fatty acid oxidation, lipolysis/fatty acid re-esterification or protein turnover, rather than two opposing discrete reactions [36].

Several studies have shown an increased endogenous production and utilization of glucose in hyperthyroid rats and humans [37]. Similarly, Cori-cycles and the glucose/glucose-6-phosphate and fructose-6-phosphate/fructose-1,6-diphosphate substrate cycles are increased in hyperthyroidism and decreased in hypothyroidism [38, 39], suggesting a TH-induced futile cycling of glucose production and utilization. The quantitative contribution of these cycles to TH-induced thermogenesis has been estimated at 2% for humans [40].

Indeed, THs induce lipogenesis by enhancing the expression of the enzymes involved in fatty acid synthesis (e.g., acetyl-CoA carboxylase, fatty acid synthase) [41], as well as those responsible for generating the necessary reducing equivalents (e.g., glucose-6-phosphate dehydrogenase) [42] while on the other hand stimulating the beta-oxidation of fatty acids by increasing the activity of carnitine palmitoyl transferase [43, 44]. This results in futile cycling of long-chain fatty acids biosynthesis and degradation, which is estimated to contribute to TH-induced thermogenesis at 3–4% [45]. Moreover, THs activate adipose tissue lipolysis by increasing its sensitivity to catecholamines [46, 47] and most of the resulting free fatty acids are re-esterified back into adipose or liver triglycerides. This futile cycle of adipose fat lipolysis and fatty acid re-esterification has been estimated at 15% of the TH-induced thermogenesis in humans [48].

Moreover, THs have a more generalized stimulatory effect on total RNA synthesis in liver and muscle [49], resulting in an overall increase in protein synthesis; on the other hand, TH activates muscle protein degradation, implying futile protein turnover [50], which is responsible for 5–10% of TH-induced thermogenesis [40].

TH-induced futile ATP consumption is also due to ion leaks [33]. THs promote ion leakage by increasing the permeability of the cellular membrane to ions. In order to re-establish the physiological intra- and extracellular ion concentrations, ATP must be consumed. THs induce the expression of the $Na^+/K^+$ ATPase [51, 52] as well as its translocation to the plasma membrane [53, 54], resulting in an increased leak of sodium and potassium across the plasma membrane [55], hence futile ion pumping. Other than at the plasma membrane level, futile ion pumping also happens at the intracellular level, in the form of $Ca^{2+}$ transport. THs stimulate the expression of SERCA [56] that mediates ATP-dependent $Ca^{2+}$ pumping in the ER, while concomitantly inducing the expression of IP3R [57] and ryanodine receptors [58] that mediate $Ca^{2+}$ efflux from the ER to the cytosol. Overall, the energy cost of futile ion pumping has been estimated at 5–10% of TH-induced thermogenesis [40, 59].

Both metabolic cycling and ion leakage are mechanisms that decrease metabolic efficiency at the stage of ATP utilization. These mechanisms are certainly important, but have a minor impact on EE compared to indirect effects [40].

Indirect effects are referred to TH actions that increase EE mainly through uncoupling mechanisms and mitochondrial biogenesis (Fig. 11.2) [34].

The main mechanism for converting the chemical-bond energy of substrates in the expendable form of ATP is mitochondrial oxidative phosphorylation. Energetic substrates are first oxidized to produce reduced NADH and FADH, which are then re-oxidized by yielding electrons to the electron transport chain (ETC) of the inner

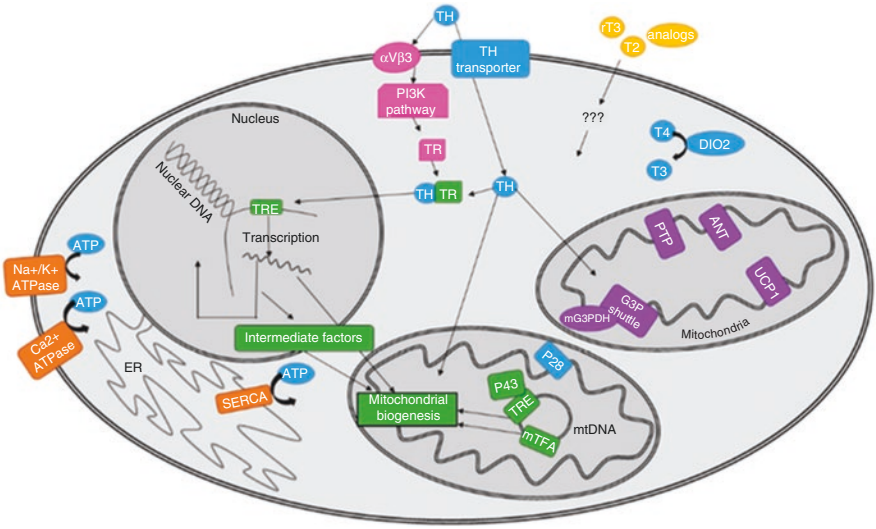


**Fig. 11.2** Summaryof the mechanisms by which thyroid hormone (TH) modulates energy expenditure (EE) on the cellular level. Orange: ion leaks. Pink: non-genomic pathways. Green: mitochondrial biogenesis resulting from nuclear, intermediate, and mitochondrial-specific pathways. Purple: uncoupling mechanisms. Yellow: rT3, T2, TH analogs. Blue: TH, ATP, and intermediate steps in TH metabolism and signaling

mitochondrial membrane (IMM). The electron transfer from donors to acceptors via redox reactions in the ETC, which culminates in the reduction of $O_2$ to $H_2O$, is coupled with the creation of an electrochemical proton gradient that drives ATP synthesis. Coupling electron transport to ATP synthesis is due to the IMM being impermeable to protons [60]. However, if the proton gradient is dissipated as heat bypassing the ATP synthase, the efficiency of mitochondrial ATP synthesis is reduced. Ninety-five percent of mitochondrial proton leak in intact mitochondria is mediated by proteins located in the inner mitochondrial membrane, such as adenine nucleotide translocase (ANT), uncoupling proteins (UCPs), and the mitochondrial permeability transition pore (PTP). Uncoupling mechanisms underlie non-shivering thermogenesis, a process, crucial in homeothermic animals, that converts chemical energy in heat by dissipating the protein-gradient generated by respiration complexes in the mitochondria [61]. This occurs primarily in brown adipose tissue (BAT), due to uncoupling protein 1 (UCP1). In addition to UCP1, other uncoupling proteins (UCP2 and UCP3) exert the same action in other tissues [62, 63]. UCPs act either allowing proton flow according to gradient or transporting protonated carboxylic acids into the mitochondrial matrix and carboxylate anions in the opposite direction [64]. THs enhance the expression of UCP-coding genes that have TREs in their promoters [65]. Adaptive thermogenesis by BAT is modulated by both TH and adrenergic stimulation, which stimulate hyperplasia, UCP1 expression, and substrate availability for mitochondrial oxidation [66]. Because long-chain fatty acids are the main substrate being oxidized in this process, THs induce lipogenesis and

lipolysis of BAT triglycerides [45, 67, 68]. However, because of the limited presence of BAT in humans, the impact of TH-induced BAT thermogenesis on total energy expenditure is unclear [69]. In contrast to UCP1, UCP2 is ubiquitously expressed and may allow proton flow according to gradient when activated by ROS or lipid peroxidation products. UCP3, instead, is tissue-specific and abundant in skeletal muscle, while less in BAT and heart [70]. However, TH modulation of these proteins is not clear. In tissues different from BAT, THs stimulate mitochondrial uncoupling by modulating the opening of the PTP, via regulation of Bcl2-family proteins and of the expression of mitochondrial PTP components [57]. Because mitochondrial PTP is ubiquitously distributed, the TH-induced increase in total energy expenditure may be a reflection of PTP gating in various tissues, mostly skeletal muscle and liver [71]. In light of the 40-fold difference in organ mass between BAT and skeletal muscle, the latter may be of greater contribution to total body uncoupling capacity [57].

While futile cycles and ion leaks decrease metabolic efficiency at the stage of ATP utilization, uncoupling mechanisms decrease metabolic efficiency at the stage of ATP production. A decrease in metabolic efficiency implies an increase in substrate utilization, which, in turn, requires increase in mitochondrial capacity. THs stimulate mitochondrial biogenesis by interacting with nuclear TH receptors [72], activating mitochondrial transcription [73], and through intermediate factors found both in the nucleus and in the mitochondria [28].

The combination of mitochondrial biogenesis and uncoupling mechanisms results in an augmented capacity for non-shivering thermogenesis. This is also achieved through TH-mediated adipocyte differentiation in white adipose tissue, resulting in “beige” adipocytes that are metabolically similar to brown adipocytes and express UCP-1, contributing to non-shivering thermogenesis [74].

In conclusion, we can state that THs modulate metabolic efficiency as the proportion of work ($\Delta G$) vs. heat ($\Delta S$) derived from a given change in enthalpy ($\Delta H$), both at the mitochondrial and at the extra-mitochondrial level. Hypothyroidism results in an increase in metabolic efficiency (decreased energy expenditure and heat production), whereas hyperthyroidism results in a decrease in metabolic efficiency, accompanied by thermogenesis and weight loss despite increased energy intake.

## 11.5 The Role of Indirect Calorimetry (IC) in the Treatment of Overt Thyroid Dysfunction

The prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world, and it is similar in Europe and the United States (0.7% vs. 0.5%) [75–77].

Hypothyroidism is common throughout the world and is particularly common in the UK. Iodine deficiency and autoimmune disease (Hashimoto thyroiditis)

represents the vast majority of cases of primary hypothyroidism [75, 78]. The prevalence of overt hypothyroidism in the general population ranges from 0.2% to 5.3% in Europe [79, 80] and 0.3% to 3.7% in the USA [81].

Given the role of thyroid hormones in modulating energy expenditure, its measurement has historically been used as the gold standard for the clinical assessment of TH activity, until the advent of the immunoassays for TSH and THs [82]. The first approach, in conjunction with the latter, may still be valid: in fact, it is believed that minimal changes in TH signaling can cause a significant perturbation in TEE, even in the absence of abnormalities in the TSH or TH levels [83, 84]. Thus, directly measuring REE by IC would allow the dosage of drug therapy to be assessed in patients with overt thyroid dysfunction. Furthermore, it could help evaluate the possibility of a pharmacological intervention in subjects with subclinical hypo- or hyperthyroidism.

In the current clinical practice, levothyroxine ($LT_4$) replacement therapy is used to achieve euthyroidism in hypothyroid patients. While the clinical manifestations of overt thyroid dysfunction are evident, it is unclear whether variations in thyroid status within or near the reference range affect energy expenditure, body mass, or body composition.

Different levothyroxine dosages have a diverse impact on REE. One cross-sectional study compared the effects of chronic $LT_4$ suppressive therapy on energy balance and body composition in women to two matched groups of euthyroid women either receiving replacement doses of $LT_4$, or with no history of thyroid disease [85]. REE was 6% lower in the $LT_4$-replaced compared with the $LT_4$-suppressed group and was 4% lower in the $LT_4$-replaced compared with the healthy control group, although this did not reach statistical significance ($p = 0.13$). However, despite the lower REE, $LT_4$ euthyroid women had similar BMI and body composition compared to healthy controls and $LT_4$-suppressed women.

In a prospective study, Al-Adsani et al. [86] analyzed the effect of slightly varying $LT_4$ dosage on REE in nine patients in chronic treatment with this hormone was examined. Changes in the thyroxine dose induced significant variations in TSH levels in all patients, while the effect on the concentrations of $T_4$ and $T_3$ was smaller. In each individual, TSH decreased as the dose of $T_4$ increased, and REE decreased as serum TSH levels increased. The results showed a variation of 5–10% in REE when TSH moved around the normal range: this is physiologically relevant, as it could result in significant changes in weight and adiposity.

In a more recent prospective study conducted by Samuels et al. [87], 138 hypothyroid subjects treated with replacement doses of $LT_4$ underwent dosage adjustment over 6 months to achieve one of three TSH ranges (low-normal, high-normal, or mildly elevated). When the $LT_4$ doses increased, direct correlations between increasing thyroid status and greater REE/LBM were found; however, no statistically significant differences in metabolic functions or body composition were shown. It is possible that compensations in non-REE metabolism might maintain daily TEE, preventing weight loss or improvements in body composition; alternatively, the 6-month duration of the study might not have been long enough to see these effects.

Collectively, these findings indicate that variations in $LT_4$ dosage within the normal TSH range may not be sufficient to generate major variations in TEE, body weight or body composition, but can be associated with significant variations in REE.

Given that overt hypo- or hyperthyroidism has a profound impact on EE and that even small variations in TH activity and $LT_4$ dosage seem to have an effect in varying REE, the effective measurement of REE by IC could be of use in monitoring patients with overt thyroid dysfunction undergoing pharmacological treatment, evaluating its efficacy and assessing optimal dosage.

Moreover, a retrospective observational study focusing on patients with chronic thyroiditis ($n = 38$) and currently undergoing $LT_4$ replacement therapy, accepted as poster presentation [88], was conducted. Patients were divided in two groups: subjects who followed a diet formulated on REE measured by IC (IC group) and subjects who followed a diet based on REE predicted by the Harris–Benedict formula (NO-IC group). Subjects in the IC group ($n = 23$) showed a significant weight reduction after 6 months ($-2.13 \pm 0.04\%$, $p = 0.007$), while those in the NO-IC group ($n = 14$) did not ($-0.11 \pm 0.01\%$, $p = 0.7$). Furthermore, patients in the IC group showed a significant reduction in TSH levels ($-7.38 \pm 0.06\%$, $p = 0.05$), while those in the NO-IC group did not ($17.15 \pm 1.5\%$, $p = 0.7$). Neither one of the two groups showed a significant difference from baseline in $FT_4$ levels [88]. These results suggest the importance of directly measuring REE, as opposed its prediction, in patients with thyroid dysfunction, where REE is commonly altered. Direct measurement of REE by IC also resulted in an improved efficacy of $LT_4$ replacement therapy, lowering TSH levels.

## 11.6 The Role of Indirect Calorimetry (IC) in the Treatment of Subclinical Thyroid Disease

Abnormalities in thyroid function are not always as pronounced as in overt hypo- or hyperthyroidism, but may be milder, such as in subclinical hypo- or hyperthyroidism. Subclinical hyperthyroidism (SHT) is defined by serum thyrotropin (TSH) levels that are under the reference range (0.45–4.5 mIU/L), while serum-free thyroxine ($T_4$) and/or triiodothyronine ($T_3$) levels are normal. Subclinical hypothyroidism (SH), in contrast, represents a state with values of TSH that are above the reference range, while values of $T_4$ and $T_3$ are normal [89].

Subclinical hypothyroidism occurs in 4–20% of the adult population [90]: such wide range is a result of differences in age, sex, BMI, race, iodine intake, and cut-off TSH values used to define the condition. The prevalence of subclinical hypothyroidism in the US adult population ranges from 4% to 8.5% in those without known thyroid disease [77, 81]. The prevalence increases with age, and in women older than 60 years, SH is present in up to 20% [91, 92].

Approximately 2–6% patients per year progress to overt hypothyroidism [93].

Subclinical hyperthyroidism, in contrast, is much less common, as only 3.2% of the US population is defined as having subclinical hyperthyroidism [77]. However, SHT is common in subjects undergoing $LT_4$ treatment, being present in 14–21% of such patients [94].

Some studies have suggested that patients with SHT may develop overt hyperthyroidism (OHT) at a rate of 1–5%/year [95], while other suggested they revert to normal after diagnosis [94].

One of the major controversies in subclinical hypo- and hyperthyroidism is to treat or not these pathological conditions, and if so, what are the recommended daily dose?

Besides the risk of evolving into clinically overt hypothyroidism, some studies have shown that subclinical hypothyroidism could be associated with increased risk of cardiovascular disease, mood disorders, and cognitive dysfunction as well as impaired neuromuscular function [96].

Subclinical hypothyroidism is usually asymptomatic, but in some patients appear symptoms that would indicate hypothyroidism. A cross-sectional study including 25,862 participants [81] reported that hypothyroid symptoms were more prevalent in subjects with SH than in euthyroid subjects, but less prevalent than in overtly hypothyroid individuals. These symptoms are usually milder than those in patients with overt hypothyroidism and tend to increase with higher thyrotropin levels.

Furthermore, baseline data from a double-blind, placebo-controlled trial [97] showed that individuals with SH had an increased prevalence of hypothyroid symptoms when compared to healthy subjects. The same study reported significant improvement in symptomatic patients with subclinical hypothyroidism treated with levothyroxine compared with placebo-treated controls.

In a meta-analysis including 11 prospective cohort studies, for a total of 55,000 participants, the risk of fatal and nonfatal events of coronary heart disease increased with higher baseline thyrotropin levels [98]. In similar meta-analysis, subclinical hypothyroidism has also been associated with increased risk of congestive heart failure [99] and fatal stroke [100]. The cardiovascular effects may be due to alterations in lipid metabolism, such as increased total and LDL-cholesterol levels [101].

The goal of treatment for subclinical hypothyroidism is to restore the thyrotropin levels to within the reference range [96], and oral levothyroxine treatment is the treatment of choice.

However, the efficacy of levothyroxine treatment in subclinical hypothyroidism is debated. A large, randomized controlled trial [102] investigated the effects of treatment with levothyroxine on patients older than 65 years of age, showing no benefit of treatment. A smaller randomized controlled trial [103] involving 66 women with more pronounced subclinical hypothyroidism showed a significant improvement in symptoms specifically in the subgroup of patients with TSH levels >12 mIU/L. Another randomized study involving 100 participants (mean TSH level 6.6 mIU/L) suggested a benefit of treatment with levothyroxine for some symptoms, but a reduction in tiredness was the only symptom for which a significant difference between treatment and placebo groups was reported [104].

These data suggest that levothyroxine treatment is unlikely to reduce symptoms in persons with modest elevations in thyrotropin levels and with minimal symptoms at baseline, but such treatment may have benefit in symptomatic patients, particularly in those who have a serum thyrotropin level above 10–12 mIU/L [93].

Current guidelines suggest treatment for persons 70 years of age or younger who have thyrotropin levels of 10 mIU/L or higher. For persons older than 70 years of age or for persons who have a thyrotropin level of less than 10 mIU/L, treatment decisions should be guided by individual patient factors, including the extent, of thyrotropin elevation and whether the patient has symptoms of hypothyroidism, antibodies to, thyroid peroxidase, goiter, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors [96].

Also, despite levothyroxine replacement therapy is usually associated with a considerable improvement of the lipid profile in hypothyroid patients [105], there are studies that suggest a possible cardiotoxic effect of this drug. Subjects with treated hypothyroidism showed no increase in all-cause mortality compared with healthy subjects; however, these patients revealed an increased risk of cardiovascular morbidity, such as nonfatal ischemic heart disease and dysrhythmias [106]. Moreover, a preliminary study analyzing overweight and normal weight subjects with chronic thyroiditis showed that patients treated with a higher dose of levothyroxine had increased cardiovascular risk and excess of fat mass compared to those treated with a lower dose [107]. These findings may be taken into account when evaluating treatment. Also for this reason, direct measurement of REE by IC could be useful in evaluating the need and dosage of a pharmacological intervention.

Subclinical hyperthyroidism, as well, can be associated with a number of risks and symptoms. These may be of cardiovascular nature, such as an increased average heart rate, atrial arrhythmias and heart failure, left ventricular mass and diastolic dysfunction, and reduced heart rate variability [108]. Among patients older than 65 years old, those with subclinical hyperthyroidism had a higher rate of cardiovascular events compared with euthyroid subjects [109].

Subclinical hyperthyroidism may also exert similar effects on bone metabolism in postmenopausal women to those associated with overt hyperthyroidism, such as increased bone turnover, decreased bone density and increased risk of fractures; however, there is little evidence that the same effects occur in men or premenopausal women [110].

The American Thyroid Association (ATA) recommends treating patients with TSH levels persistently less than 0.1 mIU/L if they are: (1) 65 years or older; (2) younger than 65 years with heart disease, osteoporosis, or symptoms of hyperthyroidism; (3) postmenopausal, younger than 65 years, and not taking estrogen or bisphosphonates [111].

In conclusion, subclinical thyroid dysfunctions can impact on patient's health, other than enhance overt thyroid dysfunction. Since a number of studies showed a significative variation of REE in association with TSH levels, effective measurement of REE by IC, in conjunction with immunoassays for THS and THs, could help to evaluate the possibility of a pharmacological intervention in subjects with

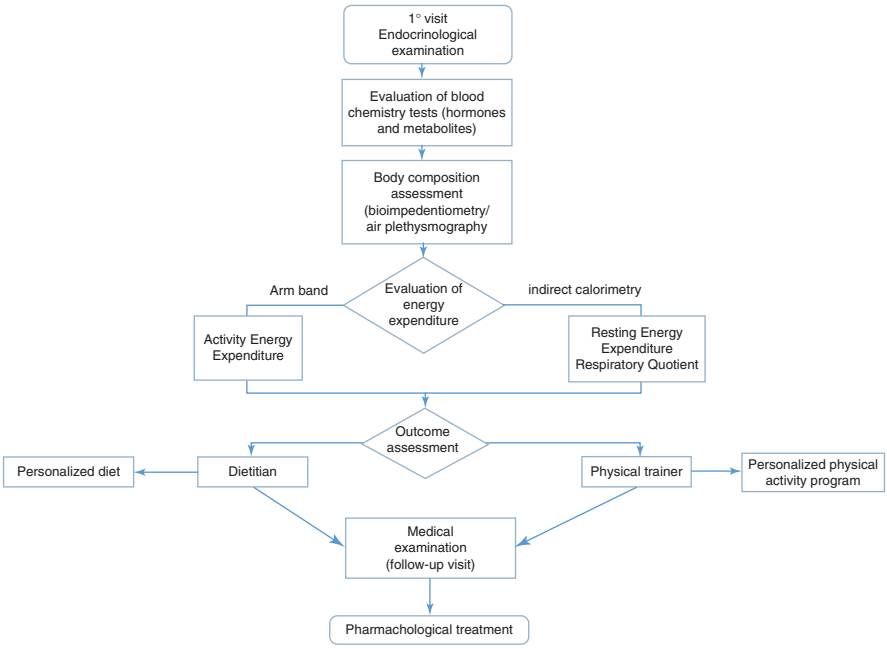


**Fig. 11.3** The Diagnostic–Therapeutic Protocol for patients with thyroid function alteration at MultiMedica Hospital Group

subclinical thyroid dysfunctions. Figure 11.3 represents the Diagnostic–Therapeutic Protocol for patients with thyroid function alteration at MultiMedica Hospital Group.

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# Chapter 12
# Muscle Tissue in Hypothyroidism and Hyperthyroidism

**Ileana Terruzzi**

Skeletal muscle (SM) represents the largest component tissue (40–50%) of the total body mass. SM wide distribution makes it one of the tissues most involved in body energy consumption, glucose and lipid homeostasis [1].

SM metabolism is strictly controlled by both thyroid hormones and insulin action; accordingly, muscle metabolism, differentiation, repair, and contractile activity are dramatically impaired by insulin resistance condition and thyroid dysfunction [2].

Therefore, before considering the consequence of hypothyroidism and hyperthyroidism on skeletal muscle, it is useful briefly to highlight some points of skeletal muscle physiology.

## 12.1 Skeletal Muscle Physiology

Skeletal muscle is a very heterogeneous tissue consisting of different post-mitotic polynucleated fibers that develop following the fusion of many embryonic muscle cells (myoblasts) and group together to generate body movement.

Based on distinct contractile and metabolic properties, muscle fibers are divided into type I (also known as slow) having oxidative metabolism, IIA (also known as fast) having intermediate metabolic properties, and IIx (also known as fastest) having glycolytic metabolism. Their different properties are a result of an adaptive mechanism which allows the muscle to respond to different metabolic and mechanical demands [3].

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Skeletal muscle shows significant plasticity in response to a multiplicity of stimuli.

Fiber type switching is a common response to an increase of exercise training or physical inactivity [4], and skeletal muscle mass changes through hypertrophic or atrophic processes [5]. In particular, skeletal muscle has a remarkable ability to regenerate after a damage [6].

The nuclei present in the muscle fibers are unable to replicate since they have irreversibly escaped the cell cycle and are in a permanent postmitotic state. It follows that these terminally differentiated cells are not able to repair any loss of tissue, which may occur due to trauma or degenerative diseases, not being able to restore the mitotic activity of its nuclei.

On the other hand, the tissue repair takes place thanks to the presence of a small population (1–6% of total muscle nuclei) of resident, undifferentiated cells that retain the ability to self-renew and differentiate, referred to as satellite cells (SCs) [7].

Mononuclear satellite cells, residing between the basal lamina and the sarcolemma of the mature muscle fibers, are normally quiescent. Following the loss or degeneration of muscle fibers, the satellite cells are stimulated to replicate by forming a progeny of cells destined to fuse together, repeating a myogenic process similar to that of the embryonic muscle myoblasts (Fig. 12.1). The syncytial structures

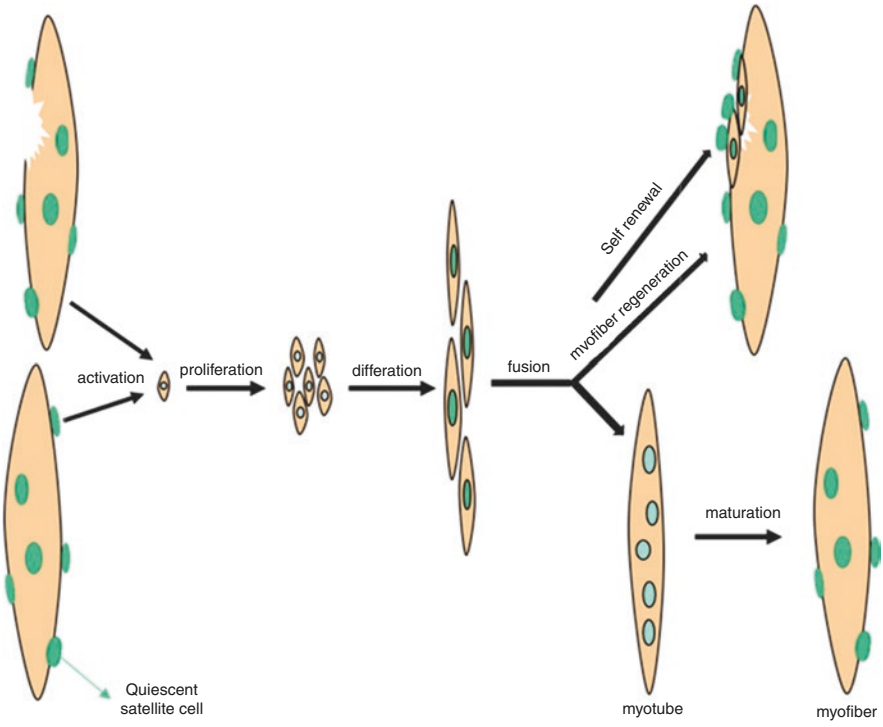


**Fig. 12.1** Muscle stem cells in mature muscle fibers are in a quiescence state until homeostatic stimuli, i.e., hormones, cytokines, or injury, induce their self-activation, re-enter into the cell cycle and consequently their proliferation in order to promote differentiation process

originated by the program of proliferation, fusion, and differentiation restore both the integrity of the muscle tissue and the pool of muscle stem cells.

During postnatal life, the activation of quiescent SCs promotes muscle fiber growth and maturation. Indeed, SC depletion produces an abnormal skeletal muscle development: myofiber size is significantly reduced at the same manner as muscle mass.

The crucial role of SCs in muscle regeneration has been extensively demonstrated [8]. Skeletal muscle injury induces the activation of a multi-step process that coordinates the SC cell cycle re-enter, proliferation and differentiation, aimed at complete tissue repair.

Muscle differentiation is orchestrated by four skeletal muscle-specific myogenic regulatory factors (MRFs): MyoD, myogenin, MYF-5, and MRF4.

Myogenic regulators represent nuclear phosphoproteins that bind to DNA at similar sites, activating the transcription of muscle-specific genes [9].

Several studies have proven that the transcription factor paired box 7 (Pax7) is an absolute requirement for the normal function [10] of SCs and represents a marker of quiescent satellite stem cells ($Pax7^{+}$) in skeletal muscle. Pax7 is essential for the survival of the satellite cells and for the transcriptional activation of the myogenic gene *MyoD*; *MyoD* plays a critical role in satellite cell biogenesis, survival, and self-renewal and represents the earliest and crucial expression marker of SC activation [10].

Posttrauma, a marked increase in Pax-7 expression near the injury zone, has been described. The event would indicate an increase in the recruitment of satellite stem cells and the activation of the skeletal muscle regeneration cascade near the lesion area [11].

MYF5 protein levels are high during quiescence, whereas MyoD levels are negligible [12].

When satellite cells are activated rapidly induce expression of MyoD.

In proliferating SCs, MYF5 and MyoD drive transcription of genes that facilitate cell cycle progression, and regulate timely myogenic progression during regeneration. MyoD induces myogenin expression and simultaneously downregulates Myf5 expression.

MyoD and Myogenin cooperate in enhancing the expression of these genes which rapidly drive cell cycle output [13].

Moreover, MyoD and myogenin enhance MRF4 expression and other specific genes of late muscle differentiation, leading to the formation of mature myofibers. In myofibers, MRF4 together with heavy myosin chain protein (MyHC) are highly expressed and represent the main markers of mature differentiated muscle, whereas MyoD and myogenin are downregulated [13] (Fig. 12.2).

Based on the molecular markers, two proliferation models have been developed providing myoblasts that fuse with damaged myofibers to repair them or that fuse together to generate new myofibers, and new self-renewed satellite cells to maintain their own population.

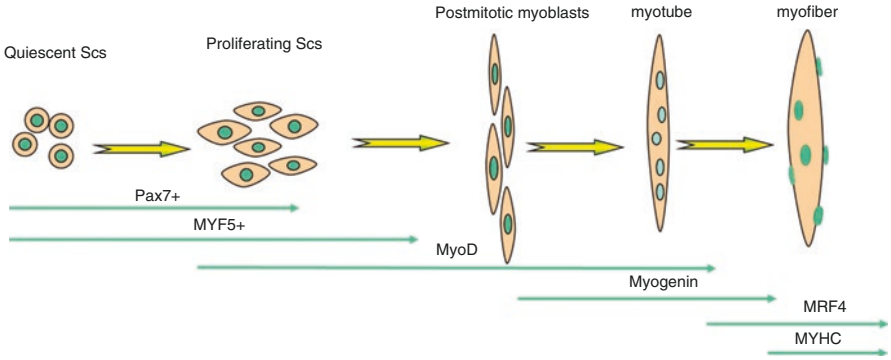


**Fig. 12.2** Adult activated satellite cells initially express MyoD or Myf5 or both myogenic factors. Subsequently, the proliferating myoblasts express MyoD and Myf5. MyoD induces the expression of myogenin, the downregulation of Myf5 and the production of MRF4, the main marker, together with MRF4, of mature differentiated myofibers

1. Following muscle damage, the quiescent $Pax7^+$ satellite cells coexpress the MyoD factor. After proliferating as myoblasts derived from $Pax7^+$ and $MyoD^+$ cells, most of the cells continue to express MyoD while inhibiting Pax7 in order to differentiate for myonucleus replacement.

   The other progeny, on the other hand, loses the expression of MyoD but retains that of Pax7 and contributes to the renewal of the satellite cells themselves.
2. Two types of $Pax7^+$ satellite cells exist, depending on whether or not they express the MYF5 marker ($Pax7^+/MYF5^+$ and $Pax7^+/MYF5^-$).

In relationship with aging, there is a functional decline of the SCs: their capacity of activation and differentiation decreases, leading to a decline in the regenerative function [14]. Aged muscle SCs respond to injury with limited expansion and differentiation capacity, contributing to the decline in muscle regenerative potential.

Although the intervention of SCs in muscle regeneration is recognized, their role in the processes of atrophy (loss of muscle mass) and hypertrophy (increase in muscle mass) in response to external stimuli, intrinsic factors, or physical activity is not yet clear [15, 16].

Muscle tissue plasticity implies a series of mass fluctuations: muscle subjected to resistance exercise becomes hypertrophic, mass and strength increase, but drastically decrease following atrophy due to immobilization, sepsis, cachexia, etc.

The consequences of atrophy have obvious health implications. Muscle weakness is an important factor for both mortality and morbidity and is associated with an increased risk of all causes of death [17]. Indeed, reducing muscle atrophy in cancer cachexia can significantly prolong life [18]. Additionally, many older individuals suffer from sarcopenia, a prolonged muscle wasting disorder that typically begins after the age of 50 years and results in a loss of approximately 1% of muscle mass per year [19]. This means that by the age of 80 years, sarcopenic individuals have lost about 40% of their muscle mass, a key factor in falls, frailty, and nursing

home admissions. Consequently, understanding the mechanisms and potential therapeutic responses to atrophy is of broad clinical and basic interest.

The syncytial nature of the muscle cells and their large number of nuclei represent a unique feature that allows the muscle fibers to reach enormous lengths (up to 600 mm) and the nuclei to produce adequate amounts of mRNA to generate and maintain muscle mass.

In the past, the plastic nature of muscle and its syncytial organization have led to formulate the "myonuclear domain hypothesis" which identifies SCs as fundamental in the processes of hypertrophy and atrophy [20]. "Myonuclear domain hypothesis" was developed on the basis of "sphere of influence" concept postulated at the end of the nineteenth century by Strassburger [21] that each nucleus is able to support a limited volume of cytoplasm, thus defining the size limit of the cell. The syncytial nature allows the muscle fiber to greatly increase its size, but during hypertrophy or atrophy, new nuclei are added or lost to preserve the right ratio of nuclei/cytoplasm.

Although some controversy remains, substantial data has shown that during the hypertrophy process, the number of nuclei increases [22, 23]. The muscle fiber inherits the supernumerary nuclei from the satellite cells which, stimulated by anabolic steroids or focal lesions following resistance exercises, proliferate and finally merge with the muscle fiber, facilitating both repair and growth.

However, an interesting study, performed using an animal model characterized by a conditional depletion of SCs, has shown that SCs are not necessary to induce hypertrophic response to overload at short time [24]. However, the same authors have shown that long-term SC ablation affects muscle hypertrophy [24].

Following the myonuclear domain hypothesis, if hypertrophy involves the addition of new nuclei, atrophy implies their loss. Although numerous apoptotic cells appear within the atrophic tissue, several authors have shown that the atrophic process involves a reduction in the volume of muscle fibers, but no loss of myonuclei [25, 26]. Contrasting the myonuclear domain hypothesis, it appears that the myonuclei acquired by the fibers persist even when the muscle becomes atrophic.

## 12.2 Thyroid Hormones and Muscle Tissue

Thyroid plays an important regulatory function of metabolism, contractile function, process of formation, and repair of muscle tissue.

The influence of the thyroid gland on muscle is mediated not only by the blood concentration of thyroid hormones (TH: thyroxine or $T_4$ and triiodothyronine or $T_3$) but also by the local tissue levels of TH, consequent to the efficiency of TH transporters, TH receptors, and the activity of the enzyme deiodinase (DIO).

The intracellular availability of TH depends on the efficiency of the facilitated transport of TH across the plasma membrane, mediated by primary monocarboxylate transporters MCT10 and MCT8 [27].

Type 2 (DIO2) and 3 (DIO3) iodothyronine deiodases also contribute to the control of intracellular TH levels: production and inactivation of $T_3$ are closely related to DIO2 and DIO3 activities [28].

DIO2 increases the availability and effect of $T_3$ by converting $T_4$ to $T_3$, while DIO3 conversely reduces them by converting $T_4$ to reverse $T_3$ ($rT_3$) and $T_3$ to diiodothyronine ($T_2$), unable to interact with TH receptors.

$T_3$ is transported and concentrated in the cell nucleus where it is bound by specific free receptors α and β (TRA mainly present in SM and TRB). Each receptor has a binding site for DNA and a distinct site for binding $T_3$. The $T_3$-TR complex, after dimerization of the receptor and interaction with transcription factors, binds to DNA and promotes the interaction with TH response elements (TREs), activating the transcription of target genes and therefore the synthesis of proteins necessary for the physiological effect of $T_3$ in the muscle cell occurs [2, 29].

Consequently, the intramuscular levels of $T_3$, their link with TRs, and the consequent effects depend on the balance of activity between DIO2 and DIO3.

In this scenario, thyroid exerts a control over the myogenic progression of activated satellite cells, in a spatial- and temporal-regulated manner, showing an important impact on the proliferation and differentiation balance of muscle stem cells.

The expression of D3 and D2 is finely regulated during the different stages of myogenesis within SCs. D3 is expressed only in the proliferative and therefore early phase of myogenesis, while D2 is expressed in the late phase, playing an essential role in the differentiation process [30].

It is conceivable that the early expression of D3 is aimed at keeping the TH signal inactive to allow proliferation and prevent the differentiation of stem cells. In fact, both D3-depletion and TH treatment induce the expression of pro-apoptotic genes in muscle stem cells.

In this context, D3 supports the proliferation of myoblasts and is essential for the stem cell activation program.

At the end of the proliferation phase, the activated myoblasts undergo the differentiation process, fusing to form the muscle fibers. The production of $T_3$ by DIO2 plays a critical role in this process. $T_3$ production contributes to the induction of myogenic factors such as MyoD, the main regulator of the myogenic development and regeneration program [31] (Fig. 12.3).

## 12.3 Hypothyroidism and Muscle Tissue

Most patients with hypothyroidism mention various muscle pains, from stiffness to cramps.

Muscle symptoms are often underestimated without considering that they can represent an important manifestation of hypothyroidism. Sometimes the muscular symptoms dominate the clinical picture or even can present themselves as the only onset manifestation of hypothyroidism, so the differential diagnosis with other causes of myopathy becomes difficult.

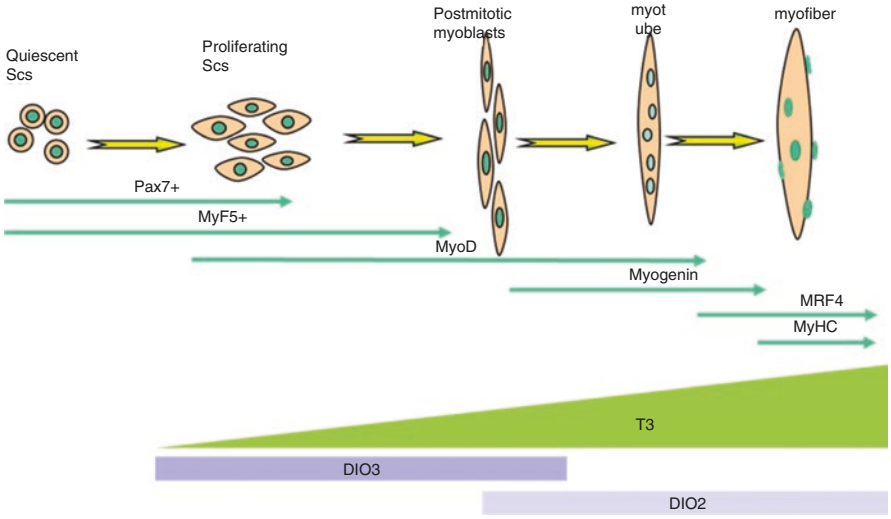


**Fig. 12.3** Differential expression of DIO3 and DIO2 determines the increase of active thyroid hormone $T_3$ destined to induce and complete the myogenesis process

The severity of muscle pain correlates with the duration and extent of thyroid hormone deficiency [2, 32].

Hypothyroid myopathy represents the most important clinical problem [33]. This muscle pathology includes four different subtypes: (1) myasthenic syndrome, beginning in childhood and usually causes mobility loss in aging [34], (2) Kocher–Debre–Semelaigne syndrome, which in children causes severe muscle atrophy [35], (3) Hoffmann syndrome, usually associated with primary hypothyroidism in adults that often report painful spasms, slow movements, and proximal muscle weakness [36], and (4) severe muscle atrophy. In rare cases, hypothyroid myopathy evolves into rhabdomyolysis [37].

Increased level of creatine kinase and other muscle enzymes, such as lactic dehydrogenase, are typical biochemical alterations of hypothyroid myopathy [33, 37], and recently other markers, i.e. titin and desmin, are proposed to evaluate skeletal muscle damage associated with thyroid dysfunction [38].

At cellular level, mitochondrial dysfunction is the main feature of hypothyroid-induced muscle impairment. Hypothyroidism induces a metabolic myopathy, with a reduction of the energetic production and mitochondrial metabolism, due to an inhibition of the main oxidative pathways and the respiratory chain. $T_3$ influences mitochondrial activity by modulating the expression of proteins encoded by both the nuclear and mitochondrial genome.

This metabolic modification is associated with fiber switch: hypothyroidism causes the loss of fast muscle fibers. Skeletal muscles of hypothyroid patients are primarily constituted by slow fibers having numerous fibrotic depots that aggravate inflammation condition [33, 39]. As known, $T_3$ plays a crucial role in the metabolism of the connective tissue, and its deficiency is associated with an altered increase

in the synthesis of glycosaminoglycans as demonstrated by an increased urinary excretion of glycosaminoglycans in hypothyroid patients [33, 40]. Moreover, slow muscle fibers are characterized by an internal area called "core-like areas," not having enzymatic activity and intermyofibrillar material [41]. The loss of muscle morphology and activity is corroborated by high abnormal expression of vimentin, desmin, fetal, and neonatal MyHC isoforms, the latter marker of muscle regeneration process [33].

In addition, hypertrophy, typical compensatory response observed in hypothyroid muscle, is insufficient [33], and hypothyroid patients have a reduced capacity to perform exercise training [34] due to mitochondrial dysfunction that causes abnormal accumulation of protons and ions, in particular $Ca^{2+}$ the main regulator of actin–myosin interaction, membrane excitability, and glucose metabolism [35]. Moreover, thyroid hormone loss promotes glycogen accumulation in muscle, but mitochondrial oxidative pathway impairment causes defective utilization of glycogen and simultaneously activates anaerobic metabolism that exacerbates the risk of cramps and fatigue [42]. Considering the peculiar interconnection between hypothyroidism and obesity, the reduced ability to exercise creates a vicious circle that further exacerbates the metabolic condition of patients with hypothyroidism.

In addition, different works have demonstrated how in hypothyroid rats skeletal muscle show a less response to insulin, and in general, insulin impairment action in hypothyroid skeletal muscle causes leads to insulin resistance in hypothyroid patients [43].

Finally, it is important to note that hypothyroidism causes not only muscle damage but also peripheral nervous system impairment, and then muscle damage induced by hypothyroidism should be seen from a neuromuscular perspective.

## 12.4 Hyperthyroidism and Muscle Tissue

The only muscle clinical manifestation in common between patients with hypothyroidism and hyperthyroidism is represented by muscle weakness, comprising both the upper and lower extremities, and exacerbation of muscle fatigue and exercise intolerance [44].

Different authors have proposed that these muscle alterations are caused by weight loss because rarely hyperthyroid patients refer only muscle weakness as only symptom of their pathology. In contrast to hypothyroid myopathy, biochemical markers, such as creatine kinase, have normal levels in hyperthyroid patients [45].

Hyperthyroidism is associated with Grave's ophthalmopathy disease, characterized by severe damage of muscles that control movement of the eyelids and eye leading to vision loss, and with thyrotoxic periodic paralysis, characterized by overproduction of TH and a simultaneous hypokalemia, not due to altered intake of potassium but due to a sudden intracellular intake.

Thyrotoxic periodic paralysis is a rare complication of hyperthyroidism which causes complete momentaneous immobility that involves not only proximal and

distal limb muscles but also respiratory musculature. Moreover, cardiovascular alterations are important and typical manifestations of thyrotoxic periodic paralysis, and to avoid serious cardiopulmonary complications, it is fundamental to restore immediately optimal potassium concentration [46, 47].

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# Chapter 13
# Thyroid Function and Effects on Cardiovascular System


**Cesare C. F. Berra and Mariluce Barrasso**

## 13.1 Introduction

Heart and thyroid are known for many years to share close interactions: as early as 1802, Giuseppe Flajani [1] reported the case of a woman patient aged 22 years having a "tumor in the anterior part of the neck, protrusion of the eyes" and "extraordinary palpitation in the region of the heart."

In 1825, Sir Caleb Parry was the first to report some cases of serious heart failure (HF) in the presence of goiter [2]. The patient, a 37-year-old woman, was described as having "eyes protruded from their sockets" and palpitations in which "each systole of the heart shook the whole trunk of the body."

Robert James Graves described in 1835 three cases of women with goiter and palpitations [3], at the same time, Carl Adolph von Basedow [4] reported the association between goiter, exophthalmos, and palpitations.

In the early years of the nineteenth century, other academics have been involved in studying the effects of thyroid hormones (THs) on the vascular system, specifically White and Aub [5] observed, as effect of thyroid disease on the heart, hypertension, tachycardia, tremors, and also changes of the T-wave, tachycardia, and paroxysms of auricular fibrillation.

Hamilton described cases of adenomatous goiter complicated with congestive HF [6], and in 1930, studies showed that thyroidectomy, some patients with HF or

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angina pectoris refractory to clinical treatments led to an improvement in the clinical situation after thyroidectomy [7].

Some years later, MacKenzie [8] published experimental studies showing the effectiveness of chemical compounds in inhibiting the thyroid gland. In the same year, Williams [9] reported the first clinical study on the use of thiouracil to treat thyrotoxicosis.

In the middle of the twentieth century, it was known that heart damage in hyperthyroidism depended on both increased metabolism and oxygen consumption. The accumulation of metabolite caused peripheral vasodilatation, and tachycardia was seen as a compensatory mechanism [10].

The effect of TH on the heart function would result, according to Tata et al., from the action of TH at the cell level that would cause increase in protein synthesis ($Na^+$/$K^+$-activated ATPase, $Na^+$/$Ca^{++}$ exchanger) with consequent effect on myocardial contractility [11].

Some years earlier, autoptic cardiovascular alterations in middle woman with myxedema, the presence of serous effusion in the pericardium, and large heart with the arteries everywhere thickened were reported [12].

The first link between myxedema and the heart could be derived from the postmortem examination of the two patients described by Ord [12], in whom large-sized hearts were found due mainly to an enlarged left ventricle, left auricle slightly dilated, fairly healthy right side of the heart, and great vessels extremely atheromatous with thickened and prominent patches of atheroma of gelatinous appearance.

It could be seen as the first pathophysiological substrate for the heart alterations which would later be associated with myxedema [13].

Nowadays, it is known that thyroid hormone receptors (THs) are present in myocardium and vascular endothelial tissues, and patients who are overt hypo or hyperthyroid show cardiovascular (CV) and hematologic manifestations that are well-documented, and both can, if left untreated, accelerate the onset of symptomatic CV disease.

Minor changes in TH concentration may have an adverse impact on the CV system, and subclinical thyroid dysfunction has been associated with a 20%–80% increase in vascular morbidity and mortality risk [14–16].

TH gives an important contribution to the regulation of metabolic processes and CV risk factors, as demonstrated by analysis Health Study Nord-Trøndelag (HUNT Study) that showed more TSH level correlated with mortality from coronary heart disease, especially in women [17].

The most frequent CV risk factors associated with thyroid diseases are explained below.

## 13.2 TH and Hyperlipidemia

Hyperthyroidism reduces cholesterol levels while hypothyroidism is associated with an increase in lipid parameters [18], in particular, an elevation of low-density lipoproteins (LDLs) by reducing both hepatic LDL receptor expression, biliary

excretion and activity of cholesterol 7α hydroxylase [19]. LDL levels represent a potent marker of atherogenesis that decreases with TH replacement [20, 21].

### 13.2.1 TH, Vasculature, and Blood Pressure

Hyperthyroidism is characterized by increased cardiac contractility and heart rate, increased preload, and decreased systemic vascular resistance (SVR), resulting in significantly increased cardiac output. Moreover, hyperthyroidism can increase systolic blood pressure [22, 23]. The relationship between subclinical hyperthyroidism (SHyper) and blood pressure is less clear. Most observational studies does not find any significant correlation; however, others have shown a positive association [24, 25].

Furthermore, in one study, restoration of euthyroidism after treatment of overt hyperthyroidism results in a reduction in systolic blood pressure [26].

OHypo and SHypo are associated with diastolic hypertension, impaired vascular function, and increased carotid intima hyperplasia [27]. Endothelial-dependent vasodilation is lower in OHypo and SHypo patients [28] and improves with levothyroxine treatment, as does pulse wave velocity, a surrogate measure of arterial stiffness [29, 30].

Several factors could likely contribute to arterial stiffness and endothelial dysfunction in SHypo and OHypo, including hyperlipidemia and a proinflammatory state [31]. Thus, in the Rotterdam Study, aortic calcification and the prevalence of myocardial infarction were higher in patients with SHypo who were positive for thyroid autoantibodies than in those with SHypo alone [32]. Both hyperlipidemia and thyroid antibodies are thought to reduce expression of endothelial nitric oxide synthase, thereby impairing vasodilation [33]. In addition, increased arterial stiffness and a low renin state are contributory factors leading to blood pressure and vascular dysregulation due to the lack of the normal vasodilatory effects of $T_3$ [14, 22, 29].

### 13.2.2 TH and Thrombogenesis

OHyper and SHyper have been associated with cerebrovascular events related to increased markers of thrombogenesis (fibrinogen and factor X levels) [34, 35]. Hyperthyroid patients may also have higher von Willebrand antigen levels compared with euthyroid patients, leading to enhanced platelet plug formation, which decreases after treatment [36].

In SHypo, factor VII activity and the factor VII activity to factor VII antigen ratio were significantly increased in women with SHypo compared with controls [37]. Another study showed decreased antithrombin III activity and increased levels of fibrinogen, factor VII, and plasminogen activator inhibitor antigen in SHypo patients assuming a potential hypercoagulable state [38].

Studies investigating coagulation in OHypo have conflicting results, with two studies showing hypercoagulability [39, 40] and one study showing increased fibrinolysis [41]. Interestingly, a study comparing moderate and severely hypothyroid patients with euthyroid controls found that patients with moderate hypothyroidism had decreased fibrinolytic activity and were more susceptible to clot formation, whereas patients with severe hypothyroidism had increased fibrinolysis and lower tissue plasminogen activator antigen [42].

The effects of TH on platelet function are unclear [36]. A study using the Badimon chamber, a surrogate ex vivo model of plaque rupture in a moderately stenosed coronary artery, showed increased thrombus formation in patients with SHypo 7–10 days post-non-ST-segment elevation myocardial infarction compared with euthyroid patients, despite dual antiplatelet therapy [43].

This thrombogenic state may, in part, explain the higher CV risk seen in patients with SHypo. In summary, both TH deficiency and excess can affect the coagulation pathway, although the precise clinical relevance of this finding is unclear.

## 13.3 Molecular and Cellular Mechanisms of Thyroid Hormone Action

The action of THs on cardiovascular system is mediated through different signaling pathways:

- Responses dependent on $T_3$ binding to thyroid receptors (TRs) localized in the nucleus.
- (*genomic effects*)
- Signaling through TRs localized in the cytoplasm or associated with the plasma membrane (*non-genomic effects impacting on transmembrane and intracellular ion flux*).

Many of these pathways are described below and depicted schematically in Fig. 13.1.

### *13.3.1 Responses Dependent on $T_3$ Binding to Thyroid Receptors (TRs) Localized in the Nucleus (Genomic Effects)*

The two main iodate THs are $T_4$ and triiodothyronine ($T_3$), both have biological effects. However, $T_3$ is considered the active and more potent hormone. Cardiac tissue does not appreciably convert $T_4$ to $T_3$; therefore, the heart is dependent on available serum $T_3$.

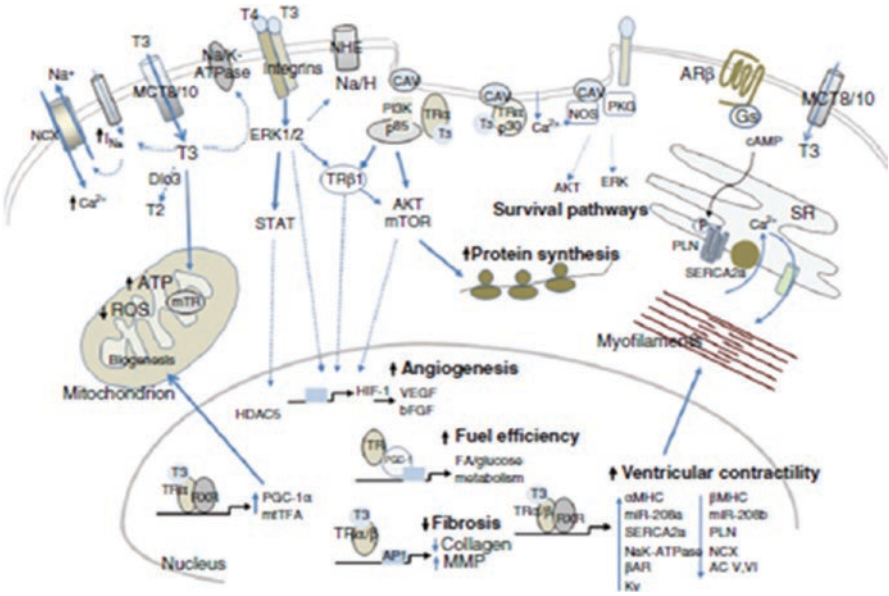


**Fig. 13.1** Thyroid hormone signaling pathways (*From Gerdes AM and Ojamaa K Thyroid Hormone and Cardioprotection. Compr Physiol. 2016; 6 (3): 1199–219*)

Unlike steroid hormones, $T_3$ is not lipid-soluble and must be transported into the cytoplasm of TH-responsive cells. Several families of TH transporters have been identified, including the monocarboxylate transporters (MCTs) 8 and 10, which are highly specific for iodothyronines.

MCT10 has a greater affinity for $T_3$ than $T_4$, and an even greater capacity to transport $T_3$ than MCT8 [44]. The cardiac myocyte TH-responsive genes are expressed as a function of serum $T_3$, and not $T_4$, implying that $T_4$ is neither transported across the myocyte sarcolemma nor deiodinated into $T_3$. Therefore, optimal myocyte gene expression remains dependent on serum $T_3$ levels, and despite the TSH and $T_4$ levels being normal, the heart will express a hypothyroid phenotype when serum $T_3$ levels are low.

The genomic effects of THs are mediated by TRs. The nuclear-localized TR function acts as transcription factors that bind to specific DNA sequence, known as thyroid hormone response elements (TREs), located in the regulatory regions of target genes. In general, binding of $T_3$ to these TREs activates transcription by recruiting coactivator complexes, while TRs bound to TREs in the absence of $T_3$ repress transcription through their interactions with corepressor complexes that control histone acetylation, methylation, and chromatin remodeling [45–47].

In mammals, these receptor proteins exist in two isoforms, α and β (TRα and TRβ), and bind to TH response elements in the promoter regions of TH-responsive genes. TRα and TRβ activate expression of positively regulated genes in the

presence of $T_3$ and repress expression in its absence. The TRα1 isoform has been shown to play an important role in the regulation of cardiac genes.

They are regulated by encoding the contractile proteins, α-myosin heavy chain (α-MHC) and β-MHC, the sodium calcium exchanger (NCX1), the sarcoplasmic reticulum calcium ATPase (SERCA2), phospholamban, and the b adrenergic receptor. The net effect of these alterations in gene expression is to alter cardiac contractility, calcium cycling, and diastolic relaxation of the myocardium.

The myofibrillar proteins, myosin heavy chains (MHC) α and β that constitute the thick filament, were among the first cardiac genes identified as being regulated by $T_3$.

α-MHC, the fast myosin, is positively regulated by thyroid hormone, whereas the slow myosin ATPase, β-MHC, is negatively regulated [48, 49].

Other $T_3$ positively regulated proteins are the $Na^+/K^+$-ATPase, especially the α2 and β1 subunits, two voltage-gated potassium channel isoforms (Kv4.2 and Kv4.3) and the sodium/calcium ion ($Na^+/Ca^{2+}$) exchanger (NCX1).

Cardiac contractility is further regulated by several cardiac proteins, including the sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2) and its inhibiting counterpart phospholamban (PLB). SERCA2 functions to pump calcium ions ($Ca^{2+}$) back into the sarcoplasmic reticulum in the relaxation phase of myofilament contraction. SERCA2 is positively regulated by $T_3$, whereas PLB is negatively regulated. Together, they are responsible for the kinetics of calcium ion influx into (and subsequent efflux from) the sarcoplasmic reticulum (SR) [50, 51].

The cardiac contractile cycle depends on rapid calcium release from intracellular stores during systole followed by calcium reuptake using an energy requiring process during diastole. In response to membrane depolarization, calcium enters through sarcolemma voltage-gated L-type calcium channels (LTCC) and induces calcium release (known as calcium-induced calcium release CICR) from SR through ryanodine receptors (RyR2) [52].

Diastole requires calcium reuptake into the SR by a calcium-ATPase (SERCA2), a process that regulates PLN, and extrusion of calcium by the sodium–calcium exchanger (NCX) [53, 54].

TH regulation of the β1 adrenergic receptor (AR) gene has been documented [55].

Adrenergic regulation of cardiac function occurs through G protein-coupled receptors and activation of kinase signaling cascades increasing phosphorylation of PLN that reduces its inhibition of SERCA2 and increases calcium reuptake.

THs have an important role in angiogenesis and vascular remodeling. THs have been shown to bind to the extracellular domain of integrins and activate intracellular mitogen-activated protein kinase (MAPK) signaling cascades or protein kinase D and histone deacetylase 5 (HDAC5), resulting in increased expression of angiogenetic proteins, bFGF and VEGF, possibly through induction of hypoxia-inducible factor-1α (HIF1-α) [56, 57].

**Table 13.1** $T_3$-regulated cardiac genes

| Positively $T_3$ regulated | Negatively $T_3$ regulated |
|---|---|
| α-MCH | β-MCH |
| Voltage-gated $K^+$ channels (Kv 1.5, Kv 4.2) | $Na^+/Ca^{2+}$ exchanger (NCX1) |
| SERCA2 | Phospholamban |
| $Na^+/K^+$ ATPase | Adenylyl cyclase types V, VI |
| β1-adrenergic receptor | Thyroid hormone receptor α1 |
| Adenine nucleotide translocase (ANT1) | Thyroid hormone transporters (MCT8, 10) |
| Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel | L-type $Ca^{2+}$ channel |
| Vascular endothelial growth factor (VEGF) | |
| Vasodilator stimulated phosphoprotein (VASP) | |
| mtTFA (mitochondrial transcription factor) | |

$T_3$-regulated cardiac genes are reported in Table 13.1.

### *13.3.2 Signaling through TRs Localized in the Cytoplasm or Associated with the Plasma Membrane (Non-genomic Effects Impacting on Transmembrane and Intracellular Ion Flux)*

Many effects on biological processes are activated by TRs localized outside the nucleus and acts through activation of the PI3K/Akt signaling pathway that causes activation of endothelial nitric oxide synthase [58].

The production of endothelial nitric oxide leads to a reduction in systematic vascular resistance acting on vascular smooth muscle cells and resulting in vasodilation of the blood vessels [16, 59].

Rapid molecular responses to THs have been reported, including effects on transmembrane and intracellular ion flux such as voltage-gated potassium channels, sodium channels, and sodium-potassium ATPase [60].

Electrophysiological studies using isolated atrial and ventricular myocytes have shown that pacemaker activity, repolarizing currents, and intracellular calcium transients were altered quickly in response to $T_3$ treatment, thus excluding transcriptional mechanisms of action [61].

Whole-cell recordings of atrial myocytes showed that $T_3$ treatment increased sodium flux and increased intracellular calcium by stimulating reverse-mode sodium–calcium exchange resulting in enhanced contractility [62]. $T_3$ rapidly increased L-type calcium current in ventricular myocytes by activation of adenylyl cyclase pathways [63].

## 13.4 Cardiovascular Consequences of Overt Hyperthyroidism (OHyper) and Subclinical Hyperthyroidism (SHyper)

OHyper or thyrotoxicosis is the clinical condition resulting from chronic exposure to high concentrations of thyroid hormones. The most frequent causes are autoimmune hyperthyroidism (Flajani–Basedow's disease, toxic multinodular goiter, toxic adenomas (Plummer's disease), the hyperthyroid phase of Hashimoto's thyroiditis (Hashitoxicosis), silent subacute thyroiditis (transient thyrotoxicosis)) [64, 65]. Less common causes of OHyper due to iodine- and drug-induced thyroid dysfunction and secondary hyperthyroidism of pituitary origin [66]. The prevalence is 0.5% in iodine-replete communities, and it is 5–10 times higher in women than in men [67].

The clinical manifestations of OHyper include weight loss with maintenance of appetite, reduced heat tolerance, sweating, easy fatigue, asthenia, insomnia, nervousness, psychomotor agitation, palpitations, tendency to diarrheal alvo or increased frequency of the alvo, reduced glucose tolerance, and hypercholesterolemia.

Cardiovascular symptoms contribute largely to the clinical feature of thyrotoxicosis. In young subjects, neuropsychic manifestations are mainly present while cardiovascular symptoms are more modest and often limited to heart rate, tachycardia, dyspnea. In the elderly cardiac symptoms are prevalent and related to heart failure, supraventricular arrhythmias (TPSV, FA), and angina [68]. Hyperkinetic circle frequently presents with a wide pulse, and often a short and intense systolic murmur occurs in the left marginosternal area. The apical ichthy is accentuated often visible. Peripheral vasodilation involves diastolic hypotension and is associated with systolic hypertension.

OHyper has been associated with 16% increased risk of major CV events, mainly due to higher incidence of HF events [69]. TH excess increases cardiac output by affecting stroke volume and heart rate [70] that are associated with pulmonary arterial hypertension and also causes cardiac hypertrophy initially of a concentric type, followed subsequently by progressive dilation of the left ventricle.

The ejection fraction (EF) is elevated in resting conditions and does not present the physiological increase during physical activity, so long-lasting hyperthyroidism can lead to heart failure even in non-cardiac patients and will have the characteristics of high-flow HF essentially due to an excessive peripheral demand and not to a primitive reduction of the capacity of the heart.

Clinical features are pleural effusion, hepatic congestion, and fluid retention, which can improve with diuretic agents and beta-blockers [71].

OHyper is linked to increased supraventricular ectopic activity. The onset of atrial fibrillation (AF) may increase CV morbidity and mortality, resulting from severe HF and stroke. $T_3$ increases systolic depolarization and diastolic repolarization and decreases the action potential duration, refractory period of the atrial myocardium, and atrial/ventricular nodal refractory period. Reduced interatrial potential

duration facilitates the occurrence of AF by enhancing the spreading of ectopic activity from the left atrium [72].

Increased oxygen consumption induced by OHyper can cause an aggravation of or preexisting angina. In fact, the increased oxygen consumption is associated with a reduction in the coronary reserve since the coronary circulation is already basically dilated.

Advanced age and the presence of associated CV risk factors (history of HF, hypertension, diabetes mellitus, previous thromboembolism, left atrial enlargement, and left ventricular dysfunction) can further elevate the embolic risk [73].

### *13.4.1 SHyper*

SHyper is defined as a subnormal serum TSH level along with serum-free $T_4$ and $T_3$ concentrations within the normal reference ranges [74].

The frequency of SHyper progressively increases with aging, reaching 15.4% in persons older than 75 years and is more frequent in individuals with nodular goiter. SHyper is more frequent in iodine deficient compared to an iodine replete area [75, 76]. According to its severity, SHyper is classified into two categories: grade 1, with mildly low but detectable serum TSH (0.1–0.40 mIU/L), and grade 2, with suppressed serum TSH levels (below 0.1 mIU/L). The etiology of SHyper may be exogenous or endogenous. Exogenous (iatrogenic) suppression of TSH may be due to thyroid hormone overtreatment, intentionally (in patients with thyroid carcinoma), unintentionally (in patients with hypothyroidism), or surreptitiously. Major endogenous causes are similar to OHyper and include mild Graves' disease, multinodular goiter, and autonomous functioning thyroid nodule. Patients with SHyper appear to be associated with an increased risk of CV disease and dysrhythmia [77, 78].

Cardiac sympathetic predominance and parasympathetic withdrawal are evident in patients with SHyper [79]. SHyper is associated with increased risks of total and CV mortality, and incident AF with highest risks incurred in patients with severe SHyper (TSH < 0.10 mIU/L). The mechanisms involved in the increased CV risk conferred by SHyper are numerous and comprise effects on cardiac morphology and function, probably from long exposure of the heart to a mild excess of thyroid hormones. Enhanced systolic left ventricular function and impaired diastolic left ventricular function, due to slowed myocardial relaxation, may cause increased left ventricular mass in these individuals [80], together with increased heart rate and arrhythmias, such as AF [81], as it happens in OHyper.

An unfavorable metabolic profile including insulin resistance, as well as endothelial dysfunction and a prothrombotic effect, is reflected by decreased fibrinolytic activity, hypercoagulability, and increased levels of interleukin (IL)-6, IL-12, and IL-18 [82].

The rate of HF and risks of HF events are higher for SHyper compared with euthyroidism, particularly for TSH levels <0.1 mIU/L. SHyper appears to be an

independent predictor for increased risk of all-cause and HF mortality in HF patients.

SHyper does not appear to be associated with incident hypertension and no significant alterations in the lipid levels.

### *13.4.2 Treatment of OHyper and SHyper*

In patients with cardiovascular (CV) diseases, OHyper or SHyper, the collaboration between cardiologist and endocrinologist is mandatory.

Once a stratification of the cardiopathic patient has been performed using ECG Holter for arrhythmias, ergometric test for the evaluation of the coronary reserve, and echocardiography for the study of morphology and cardiac function, the aim of the cardiologist is to reduce the risk of damage due to hyperdynamic circulation, alterations of the heart rhythm, and possible reduction of the cardiac and coronary reserve.

The most effective drugs in this regard are beta-blockers by blocking the interaction of THs with the adrenergic system, reducing heart rate (HR), and also peripheral and myocardial oxygen consumption. Calcium antagonists are also used to control HR but only in cases of contraindication to the use of beta-blockers.

Correction of thyrotoxicosis is achieved by the administration of antithyroid drugs. The commonly used drug is methimazole, but propylthiouracil is equally effective. In this phase, association with beta-blockers (propranolol) is recommended to control cardiovascular manifestations and to reduce the conversion peripheral of $T_4$ into $T_3$. For more refractory cases, radiometabolic option or surgical procedures may be necessary to control the OHyper [83].

Treatment of SHyper has been recommended for elderly (>65 years) patients, for postmenopausal patients or for younger (<65) patients with CV disease or CV risk factors, with undetectable serum TSH (<0.1 mU/L) for the increased risk of AF, osteoporosis, and bone fractures and for the higher risk of progression to overt disease. When TSH is persistently below the lower value (e.g., <0.5 mU/L) but ≥0.1 mU/L, treatment of SHyper should be considered in individuals ≥65 years and in patients with CV disease or symptoms of OHyper [84, 85].

## 13.5 Cardiovascular Consequences of Overt Hypothyroidism (OHypo) and Subclinical Hypothyroidism (SHypo)

Overt hypothyroidism (OH) is diagnosed when serum TSH is elevated and circulating THs are low. The prevalence varies from 0.2% to 2% of nonpregnant adults. SHypo is diagnosed when serum THs are within their reference range in the presence of raised serum TSH concentrations. SHypo can be classified as grade 1 (TSH >4.0 or 4.5, but <10 mU/l) or grade 2 (TSH >10 mU/l).

Most (at least 80%) patients with hypothyroidism have SHypo [18].

Manifestations of hypothyroidism depend on the degree of hypothyroidism and the age of onset. The extent of hypothyroidism varies from subclinical pictures detectable only with laboratory investigations (subclinical hypothyroidism) to full-blown pictures (myxedema) and to extremely serious situations such as coma (Coma Mixedematoso).

The main symptoms of hypothyroidism are dry and fragile hair, reduced sweating, and a sense of cold, weight gain, dyspnea, accumulation of mucopolysaccharides in the dermis (myxedema), sleepiness, slowing of osteotendinous reflexes, bradycardia, and sometimes low-range HF [86].

OHypo has several cardiac manifestations, including a reduction in cardiac output, a decrease in HR, and an increase in peripheral vascular resistance and diastolic dysfunction. There are also significant changes in modifiable atherosclerotic risk factors, including hypercholesterolemia, diastolic hypertension, increased carotid intimal-media thickness, and reduced endothelial nitric oxide [87].

In OHypo, clinically relevant cardiovascular manifestations occur only in the presence of severe and prolonged thyroid insufficiency. The most common target finding is sinus bradycardia. Other findings are weak and late pulse, blood pressure is often modestly increased, especially diastolic [88]. Sometimes there are weak cardiac tones, paraphonic due to the presence of pericardial effusion.

In chronic, severe myxedema, various cardiovascular alterations are found, including dilation of the left ventricle associated with turgor, myofibrillary edema, and interstitial fibrosis.

In myxedema, pulmonary stasis and expansion of plasma volume are absent, central venous pressure, left ventricular pulmonary, and end-diastolic pressure are normal, and the response to digital and diuretic treatment is poor. In hypothyroidism, the cardiac output increases during effort. The electrocardiographic examination beyond the sinus bradycardia shows flattening or inversion of the T wave and diffuse reduction of the voltages, anomalies of AV, and intraventricular conduction, rarely BAV. The ultrasound examination shows that all the cardiac contractility parameters are reduced and often allows to highlight pericardial effusion.

The coronary reserve is reduced mainly because the myxedematous infiltration of the myocardium makes diastolic coronary filling difficult. Anginous manifestations, however, are scarce also because in myxedema there is a reduced request for oxygen [89]. In addition, the coronary arteries show a worsening of atherosclerosis due to alteration of the lipid metabolism caused by the deficiency of thyroid hormones that causes hypercholesterolemia and hypertriglyceridemia [90].

### *13.5.1 SHypo*

Prevalence of SHypo in the general, adult population is 4–20%, and this range is a result of differences in age, sex, body mass index, race, dietary iodine intake, and the cut-off concentrations of serum TSH that are used to define the condition [14]. Prevalence of raised serum TSH concentrations is higher in white than in black

populations. Estimations indicate that at least 10% of old women (aged >60 years) have SHypo [18, 91].

The most frequent cardiac abnormality observed in SHypo is diastolic dysfunction due to impaired ventricular filling and relaxation [92, 93]. SHypo can also impair relaxation of vascular smooth muscle cells, inducing increases in SVR and arterial stiffness, as well as changes in endothelial function by reduction of nitric oxide availability, without apparent clinical significance [94].

SHypo is associated with increased prevalence of coronary artery disease (CAD) and myocardial infarction (MI), greater total and CAD-related mortality, particularly in those with a TSH concentration of ≥10 mIU/L, and this association seems to be independent of standard CV risk factors, which also appear to be more prevalent in SHypo. Treatment of SHypo with levothyroxine appears to attenuate CAD-related morbidity and mortality. The mechanisms involved in the increased CV risk may include conventional risk factors (hypertension, dyslipidemia, insulin resistance) observed more commonly in these patients, but also factors probably related to raised TSH levels, such as low-grade inflammation, oxidative stress, endothelial dysfunction, and increased thrombogenicity [95].

### *13.5.2 Treatment of OHypo and SHypo*

The need to treat OHypo is universally accepted. The difference between beneficial effects and negative consequences on cardiovascular situation of the patient depends on the dose and especially on the modality of administration of L-thyroxine. It is necessary to start with very low doses (12.5–25 μm/day) and proceed with gradual increments every 4 weeks.

Replacement treatment with L-thyroxine in a patient with manifest hypothyroidism and coronary artery disease makes some additional evaluations.

If the patient is "at low coronary risk," it is suggested to proceed as described above. In the presence of "high coronary risk," it is necessary to establish preventively if revascularization is indicated. In these cases, vascularization should be performed before undertaking hormone replacement therapy. In hypothyroid patients undergoing coronary revascularization, an increase in perioperative mortality was not observed [96]. However, they have reported an increased incidence of intraoperative hypotension and perioperative heart failure. For percutaneous transluminal angioplasty, both the success rate and the risk of complications are comparable in hypothyroid and euthyroid patients, although the risk of hematomas is higher in the group of hypothyroid patients [97].

Several studies in patients with SHypo showed similar results of improved cardiac function with levothyroxine therapy [92].

In an observational study including 3093 patients with raised serum TSH, patients aged <70 years treated with levothyroxine fewer cardiovascular events were described than untreated patients. However, in individuals aged >70 years ($n$ = 1642), levothyroxine treatment had no benefit [98]. Interestingly, a small,

interventional trial in patients with subclinical hypothyroidism showed improvement in cardiac mitochondrial function with levothyroxine treatment. This study provides a novel insight at the subcellular level of the action of THs in cardiac tissue [99].

According to the recommendations from the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA), treatment of SHypo is reasonable in patients with serum TSH >10 mU/L for the increased risk for HF and CV mortality [100]. Treatment for the milder form of SHypo remains controversial; it may be considered for patients <75 years [101], otherwise it should be individualized [14]. The AACE and ATA recommend treatment based on individual factors for patients with lower TSH levels (4.5–10 mIU/L) to be considered particularly if patients have symptoms suggestive of hypothyroidism, positive antimicrosomal/thyroid peroxidase antibodies (TPOAb), or evidence of atherosclerotic CV disease, HF, or associated CV risk factors [74]. When treatment with levothyroxine is undertaken, a goal serum TSH concentration of 0.5–2.5 mU/L in the young and middle-aged patients is recommended and possibly higher values (4–6 mU/L) in elderly patients [102].

## 13.6 TH and Cardiovascular Consequences of Heart Failure (Low $T_3$ Syndrome)

HF is a complex clinical condition that results from impaired efficiency of the heart as a pump. The most common cause of HF is coronary artery disease, and many patients have a history of MI [103].

HF is characterized by increased atrial pressure and inadequate blood volume, which is compensated by the activation of the renin–angiotensin aldosterone system (RAAS) and systemic nervous system to preserve blood volume and pressure. A low $T_3$ syndrome can develop in this phase of HF and could represent an adaptive process to reduce energy expenditure and metabolic demand. Subsequently, the progression of HF is characterized by a persistent neuroendocrine activation, which is associated with an increase in hormonal response (enhanced levels of RAAS, vasopressin, cortisol, insulin, atrial natriuretic peptide, and BNP and reduced levels of growth hormone) and in inflammatory and immunologic mediators (cytokines, such as interleukin 6 and tumor necrosis factor). All these changes are responsible for an increased cardiac overload and myocardial fibrosis with a negative cardiac remodeling and a progressive deterioration and apoptosis of myocytes and endothelial function.

In this advanced stage of HF, the administration of β-adrenergic blocking drugs, digitalis, angiotensin-converting enzyme inhibitors, diuretics, and aldosterone antagonists can improve symptoms. Therefore, the persistent activation of the hormonal and inflammatory system and the persistent low $T_3$ syndrome represent a maladaptive mechanism inducing cellular, functional, and morphologic negative CV changes with a negative cardiac remodeling [104].

The hypoxia and the inflammatory response to HF are able to reduce the type 2 deiodinase activity in the cardiomyocytes, which results in a decrease of intracellular $T_3$ bioavailability [105].

Hypoxia is also able to induce the expression of D3 in cardiomyocytes. The induction of D3 in the cardiomyocytes is associated with a decrease in the $T_3$ concentrations in the tissue and in the $T_3$-dependent gene expression with TRα 1 overexpression [106, 107].

All these findings suggest that $T_3$ has an important role in regulating myocyte transverse shape and wall stress and could play a key role during the progression of HF in patients with low $T_3$ syndrome [108].

Hypothyroid cardiac alterations in HF can be reversible with TH replacement therapy.

The $T_3$ supplementation in the culture of neonatal cardiomyocytes was associated with a positive change in the myocyte shape, with an increase in the synthesis of a-MHC, normalized the SERCA2 contents of cardiomyocytes, improving systolic and diastolic functions and heart performance [109, 110].

This opinion is supported by the evidence that $T_3$ has positive effects on the CV function, and even mild TH deficiency is associated with a worse outcome in patients with HF. Moreover, low $T_3$ syndrome bring to negative impact on cardiac dysfunction and this improved after TH administration.

The suggested substitutive dose of $T_3$ should not exceed 0.2–0.4 μg/kg per day (i.e., 15–30 μg per day, divided into two or three administrations) and about 1 μg/kg per day for levothyroxine (i.e., 50–100 μg once daily).

In conclusion, THs have a role in cardioprotection due to activation of cytoprotective mechanisms, stimulation of cell growth, neoangiogenesis, and metabolic adaptations.

This results in a reduction in myocardial damage and positive reverse left ventricular remodeling, resulting in a delay or absence of evolution toward post-ischemic irreversible HF.

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# Chapter 14
# Obesity, Adipokines and Thyroid Dysfunction


**Cristina Parrino**

## 14.1 Obesity and Adipose Tissue

Obesity is a multifactorial chronic metabolic disease characterised by an increase of body fat stores [1]. Adipose tissue is a complex organ including several cells among which adipocytes, immune cells, fibroblasts, blood vessels and collagen fibres. Previously its role was underestimated, but later Spiegelman's group described that it acts as an important active endocrine organ [2]. Over the past decade, there has been a paradigm shift recognising that adipose tissue has additional important functions other than energy storage as it secretes a variety of endocrine, paracrine and autocrine hormones, cytokines and growth factors able to influence local adipose tissue and different organs and tissues [3]. The adipose tissue forms a large organ with discrete anatomy, specific vascular and nerve supplies, complex cytology and high physiological plasticity [4]. The adipose tissue depots are located in the area below the skin (subcutaneous depots) and in the trunk (visceral depots), allowing the definition of "multi-depot" organ [4].

Two main types of adipocytes represent the parenchymal cells: white adipocytes and brown adipocytes [4]. White adipocytes are spherical cells with a single cytoplasmic lipid droplet and a nucleus with leptin- and S100-B-immunoreactivity [4]. They store energy for the metabolic needs of the organism and are present in subcutaneous depots (mainly large adipocytes) and visceral depots (mainly small adipocytes). White adipose tissue represents the predominant type, and it is commonly called "fat" in mammals [3, 5]. The largest white adipose tissue depots are found in the subcutaneous region and around viscera, and those provide a limitless capacity for triglyceride storage [5]. Brown adipocytes are polygonal cells with a roundish nucleus and several cytoplasmic lipid droplets and are rich in mitochondria marked by the expression of uncoupling protein 1 (UCP1), a protein that uncouples

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oxidative phosphorylation from ATP synthesis. They burn energy for thermogenesis and are mainly located near the aorta and in the interscapular brown adipose organ [4, 6]. Brown adipose tissue is less represented and usually regresses after birth [3, 5]. In addition to white and brown adipocytes, scientists have also identified and studied "beige", "brite" (brown in white) and pink adipocytes. Beige and brown-in-white adipocytes are thermogenic adipocytes primarily found in subcutaneous white adipose tissue after adrenergic stimulation [6, 7]. They play a key role in the process of adaptive thermogenesis and participate in the promotion of non-shivering thermogenesis [7]. Pink adipose tissue, instead, has been observed in female mice. A reversible conversion from white subcutaneous adipose tissue to milk-secreting epithelial glands during pregnancy and lactation has been described. In addition, after lactation, pink adipocytes appeared able not only to reconvert to white adipocytes but also to convert to brown adipocytes [8]. The adipose organ exhibits highly plastic properties as adipocytes are able to reprogram and transdifferentiate into cells with a different morphology and physiology [4].

Adipose tissue is able to adapt to different environmental factors as it happens in response to overnutrition and positive energy balance or during calorie restriction. In overnutrition, mature adipocytes accumulate more fat and undergo cellular hypertrophy, secreting in turn paracrine factors (hormones and cytokines), which facilitate preadipocyte recruitment and promote their differentiation into mature adipocytes. Dynamic mechanisms within the tissue regulate the number and size of mature adipocytes (hypertrophy), and precursor cells are recruited and committed towards the adipocyte lineage (hyperplasia) [9]. This process of "adipose tissue remodelling" is usually well regulated, but the rapid expansion of adipose tissue in obesity could cause adipocyte death, hypoxia and mechanical stress that might trigger an inflammatory response and induce the dysregulation of adipose tissue secreted cytokines [9]. In addition, in obesity the white adipose tissue may become severely dysfunctional and not expand properly to store the energy excess, inducing in turn ectopic fat deposition in other tissues. This process, defined "lipotoxicity", can lead to alterations in glucose homeostasis, insulin resistance and increased risk of cardiovascular diseases [9].

## 14.2 Adipokines

We define adipokines as all the molecules produced and secreted by the adipose tissue. Adipokines have a variety of functions and can exert local (autocrine and paracrine action) and systemic effects (endocrine). They have crucial roles in appetite control, thermogenesis, energy homeostasis, glucose and lipid metabolism, immune response, reproductive and neuroendocrine functions [3, 5, 10, 11]. Unfortunately, they also participate in the pathogenesis of obesity in humans and contribute to the development of dyslipidaemia, type 2 diabetes (T2D), hypertension and cardiovascular complications, by promoting a process of low-grade inflammation [3].

The list of molecules newly identified as adipokines is constantly growing, and it includes hormones, cytokines, chemokines, lipid metabolism regulators, glucose metabolism regulators, growth factors, complement factors, vascular homeostasis and blood pressure-regulating proteins, angiogenetic factors, inflammatory proteins, stress–response factors and extracellular matrix components. Adipokines can be classified according to their structure or their function. Their production is strictly regulated, and in conditions such as obesity, it is profoundly affected with observed increased levels of leptin and interleukin-6 (IL-6) and reduced levels of adipsin and adiponectin [10]. The following paragraphs will provide a brief description of specific adipokines with a potential role in the pathogenesis of thyroid dysfunctions. Leptin, adiponectin, resistin, vaspin and visfatin will be presented, and their effects on thyroid axis will be highlighted.

### *14.2.1 Leptin*

Leptin is a 167-amino acid pluripotent adipocyte-derived cytokine, produced by the ob gene on chromosome 7 [12, 13]. It reflects the amount of body fat, and it is considered a pro-inflammatory adipokine [14]. Leptin exhibits anorexigenic effects regulating energy homeostasis and food intake in the hypothalamus [12, 15]. It is produced by white adipose tissue mainly, but also by ovary, mammary epithelia cells, placenta, pituitary gland, stomach and liver [16]. Leptin acts through its central and peripheral receptors, which belong to the class I cytokine receptor superfamily, and it is coded by the db gene [13, 15]. Receptors are predominantly expressed centrally in the hypothalamus [15]. This adipokine has a key role in complex processes such as immune response, haematopoiesis, fertility, bone remodelling, glucose metabolism, T2D, cardiovascular diseases, angiogenesis and cancer [11, 14, 15, 17, 18]. Genetic leptin or leptin receptor deficiency can cause severe obesity, diabetes and infertility in humans [15, 19].

Several reports indicate that leptin can regulate thyroid function at a central level acting on the hypothalamus and the pituitary gland [14] and indicate also a direct stimulatory effect on hormone release from the thyroid gland [13]. Leptin is critical for the regulation of the thyrotropin-releasing hormone (TRH) gene expression in the paraventricular nucleus of the hypothalamus and thus for the normal functioning of the thyroid axis [20]. It is also able to regulate the activity of central and peripheral iodothyronine deiodinase and the conversion of $T_4$ to $T_3$ [13]. A role in the pathogenesis of the euthyroid sick syndrome has also been hypothesised [13]. Leptin and its receptors may have a role in the pathogenesis of thyroid cancer, but this topic will be extensively explored in the next chapter.

Leptin has not only direct effects on the thyroid axis but may also affect thyroid metabolism by indirect effects [13]. On the other hand, the thyroid axis can influence leptin secretion by a direct effect on adipocytes, probably via TSH receptors on the surface of adipocytes [21], explaining the observed positive association between leptin and TSH, caused by this direct effect of TSH on leptin secretion by adipocytes [21].

### 14.2.2 Adiponectin

Adiponectin is a 244-amino acid adipocyte-derived hormone [22] inversely related to the degree of adiposity [14]. Patients with obesity, metabolic syndrome, insulin resistance and T2D show lower adiponectin levels [23–27]. It has anti-inflammatory, anti-atherosclerotic and anti-diabetic properties [22, 28]. Adiponectin binds two different types of specific receptors AdipoR1, expressed primarily in muscles, and AdipoR2, expressed primarily in the liver [29]. Three different circulating forms, with different biological effects, have been identified: trimer, hexamer and high molecular weight multimers [29]. The high molecular weight multimers are the most active forms. Adiponectin regulates body temperature and basal metabolic rate, controls glucose and lipid metabolism and has anti-apoptotic and immunoregulatory properties [24, 25, 30]. It also seems to have a role in endocrine malignancies [31].

Adiponectin and thyroid hormones have similar action on thermogenesis and lipid oxidation so it has been hypothesised an interaction with the thyroid axis [3, 14]. This adipokine may increase free thyroxine synthesis ($FT_4$), as its C-terminal globular structure can interact with a receptor in the mitochondria of thyroid cells [3]. The changes of adiponectin levels in thyroid dysfunction have been studied, and available data are conflicting showing sometimes contrary results [3]. Adiponectin and its receptors may also have a role in the pathogenesis of thyroid cancer [31], but this topic will be extensively explored in the next chapter.

### 14.2.3 Resistin

Resistin is a 114-amino acid polypeptide synthesised by adipose tissue, muscles, pancreas and macrophages [10, 13]. It is a pro-inflammatory adipokine and has a role in insulin resistance, in obesity and obesity-associated low-grade inflammation [10, 14, 32]. The modulation of glucose metabolism is linked to its ability to interfere with insulin signalling in adipocytes and it has been observed in animal models [10]. In humans, instead, its pro-inflammatory effects are clear as it stimulates the production of IL-6 and tumour necrosis factor and counteracts adiponectin's action. The effect of resistin on thyroid axis is not well known. A study showed positive correlation between resistin levels and free triiodothyronine ($FT_3$) and $FT_4$ and negative correlation with the thyroid-stimulating hormone (TSH) [33]. The positive association between serum resistin and $FT_4$ levels has been confirmed also in patients with anorexia nervosa [34]. The changes in resistin levels in thyroid dysfunction are interpreted as adaptive mechanisms [13]. A role of other adipokines on resistin levels has also been considered [13].

### *14.2.4 Vaspin*

Vaspin is a serine protease inhibitor derived from visceral adipose tissue. It was first identified in rats affected with obesity and diabetes and its administration resulted in improvement in glucose tolerance and insulin sensitivity [3]. In humans, vaspin expression has been reported in several tissues including subcutaneous adipose tissue, skin, stomach and skeletal muscle [35]. Vaspin expression in subcutaneous and visceral adipose tissue increases from overweight to obesity and is not detectable in subjects with body mass index (BMI) <25 kg/m$^2$. It is more frequently detected in patients with T2D [36]. In healthy volunteers circulating vaspin levels were higher in women than in men, highlighting a sexual dimorphism, but a major role in insulin sensitivity was not observed [37]. Animal studies demonstrated a possible relationship between vaspin levels and thyroid functions [3], but a few data are available in humans. On the other hand, controversial results on the role of thyroid hormones in the regulation of vaspin in rats with hypothyroidism and hyperthyroidism have been reported [38].

### *14.2.5 Visfatin*

Visfatin is a 52-kDa cytokine [3] mainly produced by the visceral adipose tissue, but also expressed in skeletal muscle [3, 10]. It shows insulin mimicking-sensitising and pro-inflammatory effects [10, 35, 39]. Visfatin levels positively correlated with fat mass and obesity [3, 10] and increased serum visfatin concentrations have been observed in T2D, polycystic ovary syndrome, and non-alcoholic fatty liver disease [39]. Only a few studies have investigated the relationship between visfatin and thyroid hormones. It has been reported that $T_3$ could either increase or decrease visfatin levels acting on adipocytes [3]. It is also likely that visfatin release from adipose tissue may be affected directly or indirectly via pro-inflammatory cytokines involving it in thyroid dysfunction [3].

## 14.3 Adipokines and Thyroid Dysfunction in Humans

Thyroid dysfunctions are classified as secondary causes of obesity [1], and the effects of thyroid hormones on tissue growth, thermogenesis and metabolism have been clearly elucidated in the past [40]. Thyroid hormones act on multiple aspects of metabolic and energy homeostasis and have a strong influence on body weight and lipolysis in adipose tissue [14, 40].

A link between thyroid and obesity has been identified, showing that thyroid dysfunction can cause metabolic alterations and obesity. A growing interest in the effects of white adipose tissue adipokines on thyroid axis has emerged. Adipokines

are biologically active with multiple effects and act on several tissues linked to energy metabolism [14]. A possible bidirectional link between adipose depots and the thyroid gland has been revealed.

The thyroid system is regulated at multiple levels: the hypothalamus, the pituitary gland, the thyroid and the periphery [20]. The thyrotropin-releasing hormone (TRH) is produced in the paraventricular nucleus of the hypothalamus and acts on the pituitary gland releasing TSH, which in turn stimulates the thyroid gland to synthesise and release the thyroid hormones $T_4$ and $T_3$. Another important step takes place in periphery as a family of deiodinases metabolise the $T_4$ to the biologically active $T_3$ or to the inactive reverse $T_3$ [20]. The system is also regulated through negative feedbacks acting on the hypothalamus and the pituitary gland [40]. All the above-mentioned systems could represent potential target for the adipokines, which are able to modulate organs and tissues.

Recent studies have identified adipokines as possible causative or protective factors in the development of thyroid dysfunctions [3, 13]. Clinical data in patients with thyroiditis, hypothyroidism and hyperthyroidism are still controversial [3], and additional studies are needed to clarify the effects of adipokines on thyroid.

In the following paragraphs, available data on leptin, adiponectin, resistin, vaspin and visfatin and their possible role in thyroid axis regulation, thyroid autoimmune diseases, hypothyroidism and hyperthyroidism in humans are presented.

### *14.3.1 Thyroiditis*

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is an organ-specific autoimmune disease characterised by the presence of goitre, lymphocytic infiltration and serum thyroid autoantibodies [41]. The role of adipokines in thyroid autoimmunity is complex and debated. Adipokines have a role in the regulation of the immune system [3, 5, 10] and show either pro-inflammatory or anti-inflammatory properties [5, 10, 22, 28, 35].

Studies available in literature evaluated leptin, adiponectin, resistin levels in different clinical conditions of thyroid autoimmunity. A study enrolling patients with HT and healthy controls has suggested a possible involvement of leptin in this autoimmune thyroid diseases [42]. A modest increase in leptin plasma levels and significantly higher leptin from culture of CD4+ T cells in patients with HT compared to healthy controls were detected [42].

The contribution of leptin in the pathogenesis of postpartum thyroiditis has been suggested by a control-matched retrospective study examining serum leptin levels in patients developing postpartum thyroiditis. Four weeks after partum patients with positive autoantibodies showed higher leptin levels. In addition, patients with positive antibodies and experiencing one or more episodes of thyroid dysfunctions maintained significantly higher leptin values and leptin/BMI ratio compared to healthy women at 6-month follow-up [43].

In a large postmenopausal euthyroid women group with HT, instead, higher levels of IL-6 compared to healthy controls were observed in the presence of similar leptin and adiponectin concentrations. The authors concluded that in that specific population HT is characterised by an increased production of IL-6, but does not have an influence on adipokine levels such as leptin and adiponectin [44].

Different data are reported in children and adolescents. In a study investigating serum leptin, adiponectin and resistin levels in children and adolescents with autoimmune thyroid disorders, patients with HT showed lower adiponectin, higher resistin and similar leptin levels compared to patients with untreated Grave's diseases and simple euthyroid goitre [45].

### *14.3.2 Hypothyroidism*

Hypothyroidism is defined by increased TSH levels and low $FT_4$ circulating levels, while subclinical hypothyroidism is defined by increased TSH levels and normal $FT_4$ circulating levels [41]. Several adipokines have the ability to modulate the thyroid axis at central and peripheral levels and could have a direct and indirect role in hypothyroidism pathogenesis [3, 13]. In literature data on leptin, adiponectin, resistin, vaspin and visfatin levels in subjects with hypothyroidism are available.

A study carried out in India, in patients with non-autoimmune hypothyroidism and control subjects, showed significantly higher fasting leptin levels and significantly lower fasting adiponectin levels in patients affected with hypothyroidism. Patients with hypothyroidism also exhibited a more pronounced insulin resistance and an unfavourable adipokines balance (high leptin levels and low adiponectin levels) [46].

A similar adipokine profile is reported by another study investigating leptin, adiponectin and resistin levels in women with hypothyroidism. Increased leptin and resistin and reduced adiponectin concentrations were detected in patients with hypothyroidism along with android fat distribution, insulin resistance and atherogenic dyslipidaemia [47]. Another study reported comparable serum resistin levels in patients with hypothyroidism and in euthyroid subjects [14].

Even though some studies showed similar trends with lower adiponectin levels in hypothyroidism [46–48], other studies describe unchanged adiponectin levels [49–52].

Contrasting data on baseline adipokine levels are reported by studies conducted in patients with subclinical hypothyroidism. A study reported similar baseline leptin and adiponectin levels in women with and without subclinical hypothyroidism [53] and another described significantly higher leptin and resistin levels in patients with subclinical hypothyroidism [54]. Consistent results are showed with levo-thyroxin treatment, with decreased leptin levels and increased adiponectin levels independent of body fat change in the first study [53] and decreased leptin and resistin levels in the second study [54].

Interestingly, no significant short-term changes in leptin, adiponectin and resistin levels were observed in patients with thyroidectomy-induced hypothyroidism compared to euthyroid subjects [55].

Vaspin levels did not appear altered in subclinical and overt hypothyroidism in one report [3]. No effects on vaspin levels were observed after normalisation of thyroid hormones, and there was no correlation between vaspin levels and TSH [3].

Another group described different findings observing higher vaspin levels in women with obesity and subclinical hypothyroidism than in women with and without obesity and normal thyroid function. They also report a positive correlation between TSH and vaspin levels [38].

Visfatin levels appeared higher in patients with hypothyroidism than in patients with hyperthyroidism and decrease significantly after treatment with levothyroxin [56].

### *14.3.3 Hyperthyroidism*

Hyperthyroidism is defined by reduced TSH levels and high $FT_4$ circulating levels [41]. Adipokines may be involved in the pathogenesis of hyperthyroidism as they have a direct role on hormone release from the thyroid gland, can modulate peripheral conversion of $T_4$ to $T_3$ and have a role in the immune response [3, 10, 13]. Available data on leptin, adiponectin, resistin and visfatin levels in subjects with hyperthyroidism are reported.

A study investigating the changes in leptin, adiponectin and resistin and in patients with Graves' disease before and after hyperthyroidism treatment showed higher concentrations of serum adiponectin and resistin in the hyperthyroid state than in the hypothyroid state and unchanged leptin levels. A strong positive correlation of both adiponectin and resistin with thyroid hormones was noted [33].

Conflicting data on adiponectin levels in hyperthyroidism have been reported showing higher [14, 33, 49, 57, 58] or unchanged concentrations [50–52]. A reduction in adiponectin levels after normalisation of thyroid state is also reported [33, 59].

Visfatin levels were found lower in patients with hyperthyroidism and increased after treatment [3, 56], with a negative correlation between visfatin and $fT_3$ and $fT_4$ levels and a positive correlation between visfatin levels and TSH [3]. On the other hand, elevated plasma visfatin concentrations in hyperthyroidism have been observed in different studies [60–62].

## 14.4 Conclusions

Clinical studies in humans illustrate a complex interaction between adipose tissue, adipokines, and the thyroid gland. Thyroid can influence adipokine production by adipose tissue, and adipose tissue, in turn, can produce pro-inflammatory and

anti-inflammatory adipokines, which could play a key role in thyroid disease pathogenesis. The changes in adipokine secretion may also represent an adaptive mechanism to diverse energy expenditure and metabolic substrates in thyroid dysfunctions. The current knowledge of the adipose tissue–thyroid axis does not allow disentangling a precise cause–effect relationship between the two organs. A bidirectional link clearly exists, but the regulation of the systems is not yet well understood. Altered levels of adipokines such as leptin, adiponectin, resistin, vaspin, and visfatin are reported in thyroiditis, hypothyroidism, hyperthyroidism, and thyroid malignancies (see next chapter). An additional level of complexity is represented by obesity, a metabolic chronic disease, in which the adipose tissue may become dysfunctional and secrete altered adipokines profiles. Controversial results on the role of adipokines in thyroid dysfunctions are very often described, and it is not possible to draw conclusions. Different results observed can be explained by multiple variables among which patients' characteristics (anthropometric parameters, body composition, gender, age), thyroid disease (disease pathogenesis, disease duration, severity, treatment), concomitant comorbidities (insulin-resistance, T2D, other autoimmune diseases, renal or hepatic impairment), balance between different adipokines (stimulation or inhibition of specific adipokines), role of unknown adipokines and regulating factors, analytic methods used to assess adipokines' concentrations, small sample size and inclusion criteria in clinical studies. A better understanding of the mechanisms regulating the interaction between adipose tissue and thyroid could represent an opportunity to gain insights into obesity and thyroid disease pathogenesis and also to develop potential new treatments for patients.

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# Chapter 15
# Adipokines and Thyroid Malignancies

**Carla Colombo and Laura Fugazzola**

## 15.1 Thyroid Cancer

### *15.1.1 Epidemiology, Histological Classification, and Molecular Alterations*

Thyroid cancer (TC) is the most frequent endocrine tumor and its incidence is increasing worldwide: thyroid cancer incidence tripled in the last 35 years, rising from 4.9 to 14.3/100,000 in 2009 in the United States [1, 2]. Since the increase in TC incidence is mostly due to microcarcinomas, especially of the papillary histotype, which have a good prognosis, TC-related mortality has remained stable over the last decades. The high prevalence of microcarcinomas can be attributed to various factors, but, above all, the greater use and better diagnostic accuracy of ultrasound and cytological examination by means of fine needle aspiration (FNAC) (Fig. 15.1).

There are several known risk factors for thyroid cancer (Fig. 15.1). Exposure to ionizing radiation, especially during childhood, is the best-established, and it is known that radiation-induced papillary thyroid carcinomas are molecularly characterized by the presence of fusion oncogenes, usually involving the RET gene. Other risk factors are race (lower incidence in black than white Americans), gender (higher incidence in women), a first-degree relative with familial thyroid carcinoma or thyroid cancer syndrome, history of thyroid disease. Iodine deficiency has been proposed as a risk factor, but data are still controversial on this issue.

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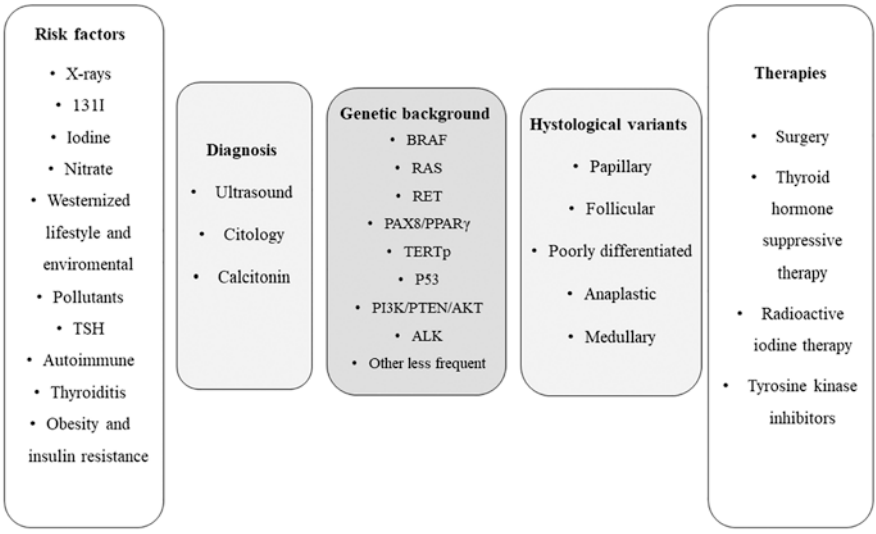


**Fig. 15.1** Characteristics of thyroid carcinomas. The boxes show the risk factors, the diagnostic techniques, the underlying molecular alterations, the different histological variants, and the main treatments used

Thyroid cancer may arise from endodermal-derived thyroid follicular cell, responsible for differentiated thyroid cancer (DTC), or from neural crest-derived thyroid C cell, responsible for medullary thyroid cancer.

The most important DTC histotypes are (Fig. 15.1):

– Papillary thyroid carcinoma (PTC)*:* It represents about 85% of all TCs, and it is composed of epithelial cells arranged in papillae; PTC nuclei are clear, with a typical ground glass appearance; calcifications (psammoma bodies) are often present and characteristic of this histotype.

  Several PTC subtypes have been identified: The classic variant, the most frequent one, the follicular variant, and the more aggressive tall cell, columnar cell, hobnail, solid, and diffuse sclerosing variants.
– Follicular thyroid carcinoma (FTC): It represents 5–10% of all thyroid carcinomas and may be limited to the thyroid or minimally or widely invasive, the last harboring the worst prognosis.
– Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): The new histopathological terminology proposed this term for the encapsulated follicular variant of papillary thyroid carcinoma without evidence of capsular and/or lymphovascular invasion. This lesion is now classified as nonmalignant.

DTC prognosis is excellent in the majority of cases, with a 10-year overall relative survival rates of 93% and 85% for papillary and follicular carcinoma, respectively.

Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) are rare, arise from follicular thyroid cells, and have an aggressive behavior and a poor prognosis.

Medullary thyroid cancer (MTC): It represents the third most common TC, representing about 3% of all cases and originate from the parafollicular cells (C cells), which produce calcitonin.

PTC is characterized by molecular alterations of genes encoding effectors of the mitogen-activated protein kinase (MAPK) pathway: $BRAF^{V600E}$ is the most frequent genetic alteration, followed by *RAS* and *TERT* promoter mutations and by chromosomal rearrangements of receptor tyrosine kinases, such as *RET*, *NTRK*, and *ALK* (Fig. 15.1) [3, 4].

*RET* mutations have been recorded in 97% of MTC associated with type 2 multiple endocrine neoplasia syndromes (MEN 2), in 87% of familial MTC (FMTC) and also in 50% of sporadic MTC [5].

### *15.1.2 Diagnosis, Treatments, and Follow-Up*

Surgery is the first therapeutic step for thyroid cancer: total thyroidectomy or lobectomy (in tumors <1 cm and limited to the thyroid) can be chosen. Moreover, prophylactic central-compartment neck dissection should be considered in patients with thyroid carcinoma who have advanced primary tumors or clinically involved lateral neck nodes.

In MTC, thyroidectomy should be total and prophylactic central neck lymphadenectomy must be performed even if there is no evidence of neck lymph node and distant metastases.

As a consequence of the impressive increase in the incidence of papillary microcarcinomas, which have an excellent prognosis in virtually all cases, in recent years some experts suggested the possibility to perform just an active surveillance for selected patients with small PTCs.

After surgery, all patients have started on levothyroxine therapy: Patients with a structural incomplete response to initial treatment should receive TSH-suppressive doses (goal TSH <0.1 mU/L), patients with a biochemical incomplete or indeterminate response should have serum TSH levels 0.1–0.5 mU/L, while in patients with an excellent response TSH should be 0.5–2.0 mU/L. MTC cases should undergo thyroxine therapy at replacement doses since this tumor is not responsive to TSH suppression.

Following thyroidectomy, radioactive iodine (RAI) is administered in DTC cases in order to ablate the thyroid residue and possible regional or distant metastases. According to International Guidelines [6, 7], only patients with tumors <1 cm without extrathyroidal extension do not have any indication to receive RAI treatment after total thyroidectomy. RAI treatment is effectively used, after surgery and residue ablation, for regional and distant metastases able to uptake the radioisotope, too. The vast majority of patients will be cured after thyroidectomy and RAI

ablation. Patients with stable or minimally progressive and asymptomatic disease are usually followed up by monitoring the tumor biomarkers (thyroglobulin and anti-thyroglobulin antibodies for DTC and calcitonin and CEA for MTC) and by neck ultrasound evaluation.

Patients with rapidly progressive disease or symptomatic (not responsive to RAI treatment for DTC cases) had no effective therapeutic options available until few years ago since external beam radiation and chemotherapy are scarcely effective in these tumors.

In recent years, some molecular-targeted agents, able to inhibit tyrosine kinase receptors (TKI), cell proliferation, and angiogenesis, have been developed. In particular, four of them have been approved by the Food and Drug Administration (FDA) and the European Medical Agency (EMA): lenvatinib and sorafenib for the treatment of progressive RAI-refractory differentiated and poorly differentiated TC and vandetanib and cabozantinib for advanced MTC [8].

## 15.2 Thyroid Cancer: Association with Adipokines and Metabolism

The increased incidence rates of TCs recorded in many countries over the last decades parallel to the increased incidences in obesity and metabolic disorders. Transversal studies suggested an epidemiological link between metabolic derangement associated with excess body weight and TCs, and these data were subsequently confirmed in meta-analyses and prospective studies.

There are some epidemiological data to support that obesity is independently associated with an increased incidence of various solid tumors, including TC [9–13]. Some hypotheses have been formulated to suggest potential mechanisms for this link, implicating factors such as inflammation and adipokines, obesity, hyperinsulinemia, and insulin resistance, but the data are still scanty and controversial (Fig. 15.2).

### *15.2.1 Insulin*

Through its own receptor (IR), it regulates cellular metabolism and stimulates cell growth; many cancers, including TC, overexpress the A isoform of IR (IR-A), which has a mitogenic effect and binds insulin and IGF-2 [14]. Therefore, insulin could potentially act as an oncogene by stimulating cell signaling, and increasing cell growth factor-dependent proliferation [15]. In TC, the overactivation of IR-A and IGF2 has been associated with stem-like features and refractoriness to some targeted therapies. Moreover, molecular mechanisms have been described by which IR isoforms are deregulated and become able to crosstalk with other molecules and

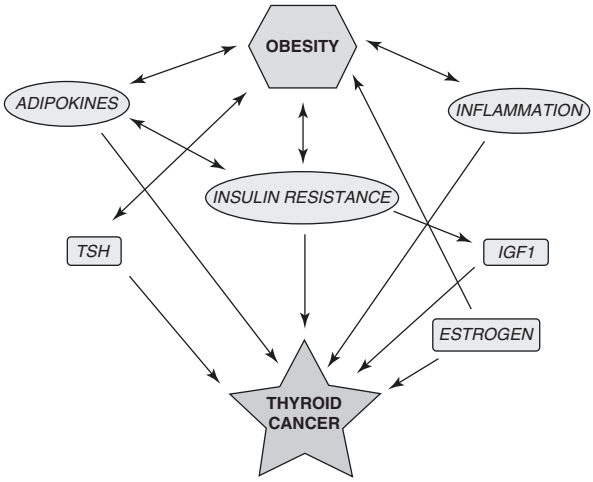


**Fig. 15.2** Hypothesized mechanisms underlying the correlation between obesity and development of thyroid cancer

signaling pathways, thus contributing to thyroid carcinogenesis, progression, and resistance to conventional treatments.

### *15.2.2 Adipokines*

The adipokines, cytokines secreted by the adipose tissue, include several proteins. Indeed, the adipose tissue is an endocrine/paracrine/autocrine organ with a significant role in the physiopathology of several inflammatory diseases (mostly in obesity and in autoimmune diseases) [16]. Leptin was the first adipokine to be discovered in 1994 and, since that time, other hundreds of factors including chemokines, growth factors, complement system molecules, acute phase reactants, and hormones have been discovered: adiponectin, apelin, chemerin, interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4), tumor necrosis factor-alpha (TNFα), and many others. For leptin and adiponectin, a potential role in thyroid tumorigenesis has been proposed:

(a) In addition to the known role in the regulation of appetite and metabolism, **leptin** can also stimulate angiogenesis and cell proliferation, and elevated serum leptin levels have been associated with a higher risk for some tumors [17, 18]. Indeed, leptin modulates growth and proliferation of cancer cells via the activation of various growth and survival signaling pathways including JAK/STAT, PI3-kinase/AKT and/or Map kinases (Fig. 15.3).
(b) **Adiponectin** is able to improve insulin sensitivity and has been shown to influence cell proliferation and to regulate the balance between pro- and anti-inflammatory mediators that influence local and systemic inflammation.

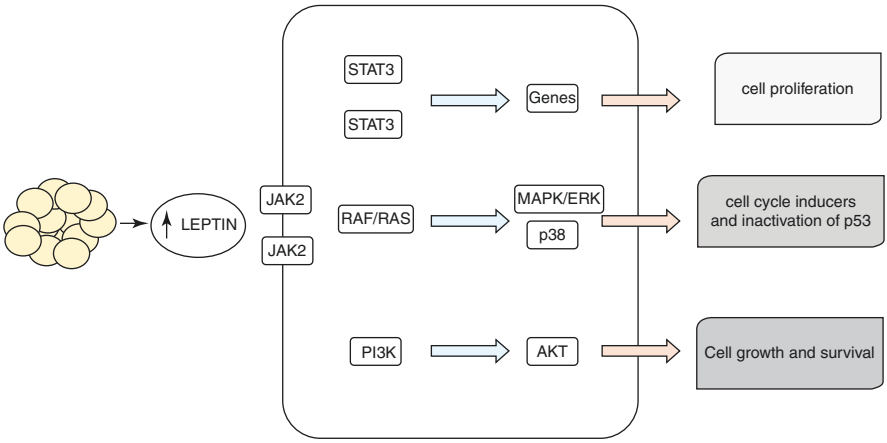


**Fig. 15.3** Mechanisms by which elevated leptin levels increase the activation of several intracellular signaling cascades, responsible for the increase of cell proliferation possibly underlying the development of malignant tumors

Some recent studies showed lower circulating adiponectin levels in patients with TC with respect to unaffected controls, suggesting a potential protective effect of adiponectin against the development of this tumor [19]. The pathogenic mechanisms underlying this role are still unknown but could be related to the pro-apoptotic activity through the caspase pathway in neoplastic cells, or to a role in preventing the development of insulin resistance, a possible pro-cancerous factor.

*In vitro* studies have shown that malignant cell lines, including PTC cells, express leptin receptors and are responsive to the administration of leptin [20]. Moreover, it has been shown that the prolonged exposure to high concentration of leptin mildly contributes to increase the aggressive phenotype of PTC cells, by stimulating the PI3K/AKT signaling pathway [21].

Finally, it is also worth of mention that PTC tissues have been shown to express **ghrelin**, an orexigenic hormone capable of GH secretagogue activity, and **obestatin**, which is encoded by the same gene that encodes ghrelin but shows opposite effects on GH secretion and appetite. Scanty and controversial data are available on the tissue expression and serum levels of these hormones and their possible role in tumorigenesis and/or tumor aggressiveness.

The whole of the above-reported evidences show that a correlation between obesity, insulin resistance, adipokines, and development of TC could exist, but more *in vitro* and epidemiological studies are needed to draw definite conclusions on this topic.

Finally, recent data show that ghrelin and leptin levels display significant variations in patients with advanced TC during TKIs treatment. In these patients, a severe weight reduction is observed particularly during the first year of treatment. Leptin levels have been found to be parallel to progressive loss of fat mass, whereas the

opposite increase in ghrelin levels is thought to stimulate food intake, leading to the following stabilization of the body weight [22].

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# Part IV
# Clinical Cases

# Chapter 16
# Clinical Cases

**Claudio Cusini**

## 16.1 Clinical Case 1

A 28-year-old woman complained about excess weight since the late adolescence.

During the last medical examination, she was overweight (height 158 cm, weight 64.5 kg, BMI 25.8 kg/m$^2$).

She suffered from chronic autoimmune thyroiditis with hypothyroidism treated with levothyroxine (50 μg/day, 0.74 μg/kg/day). Thyroid function, recently evaluated, was adequate: TSH 1.8 mU/L (n.v. 0.45–4.5), $FT_4$ 1.1 ng/dL (n.v. 0.9–1.8), $FT_3$ 2.8 pg/mL (n.v. 2.3–4.2).

In the past 10 years, she went on many hypocaloric diets (1200 Cal/day), both self-made and prescribed by a nutritionist, who used the Harris–Benedict equation to estimate her resting energy expenditure (REE) = 1430 Cal.

She attended the gym twice weekly; she denied night eating, emotional eating, or binge eating.

She obtained repeated loss and regain of body weight (weight cycling).

The endocrinologist prescribed a measurement of energy expenditure through indirect calorimetry. Measured REE was 1201 Cal (84% of predicted REE). The nutritionist optimized the dietary program with a low-calorie diet (1000 Cal/day).

She was evaluated at 6 months since baseline: height 158 cm, weight 62.1 kg (−3.6%), BMI 24.9 kg/m$^2$ (−3.87%). Taking the same dosage of levothyroxine (50 μg/day, 0.80 μg/kg/day), thyroid function was still adequate: TSH 1.6 mcU/mL (−12.1% since baseline), $FT_4$ 1.4 ng/dL (+21.5% since baseline), $FT_3$ 3.1 pg/mL (+9.7% since baseline).

**Comment**. Thyroid hormones play crucial roles in the control of energy homoeostasis, acting both peripheral (adipose tissue) and in the brain [1]. Triiodothyronine

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($T_3$) is responsible for approximately 30% of REE [2]. Not only overt thyroid dysfunctions are associated with changes in basal metabolism, but also in euthyroid subjects, thyroid hormones levels can influence body composition and insulin resistance [3]. In patients with potential REE abnormalities due to thyroid dysfunction, prescription of an hypocaloric diet based on predictive equations of REE may be unsuccessful in the treatment of overweight/obesity. Especially in these patients, a weight reduction program based on measured REE is more effective in promoting weight loss than a dietary program based on estimated REE [4]. Indirect calorimetry is the gold standard in measuring energy expenditure in clinical settings [5].

## 16.2 Clinical Case 2

A 48-year-old man, non-smoker, living a sedentary lifestyle and suffering from obesity (height 178 cm, weight 98 kg, BMI 30.9 kg/m$^2$), was recently diagnosed with type 2 diabetes.

Blood tests: Fasting plasma glucose 246 mg/dL (13.6 mmol/L), glycated haemoglobin 73 mmol/mol (8.8%), insulin 15 mcU/mL, HOMA-IR 9.1, C-peptide 3.4 ng/mL (n.v. 0.5–3.2), anti-glutamic acid decarboxylase (anti-GAD) and anti-insulin antibodies: negative, total cholesterol 218 mg/dL, HDL 39 mg/dL, triglycerides 190 mg/dL, LDL cholesterol 141 mg/dL, ACR 2 mg/L, creatinine 0.87 mg/dL.

He underwent indirect calorimetry to measure the resting energy expenditure (REE): 1580 Cal (84% of predicted REE). His endocrinologist prescribed hypocaloric (1400 Cal/day) and lipid-lowering diet, an aerobic physical activity program, meftormin 1000 mg bid, and dulaglutide 1.5 mg qw.

The patient was revaluated after 3 months. Despite weight loss (height 178 cm, weight 93.5 kg [−4.6%], BMI 29.5 kg/m$^2$) and the improvement of the glycemic control, total and LDL cholesterol were still high: fasting plasma glucose 136 mg/dL (7.5 mmol/L), glycated hemoglobin 51 mmol/mol (6.8%), total cholesterol 203 mg/dL, HDL 42 mg/dL, triglycerides 140 mg/dL, LDL cholesterol 133 mg/dL (total cardiovascular risk score = moderate-risk patient because of T2DM, 10-year risk of fatal CVD: 1–5%, LDL-C target <100 mg/dL or 2.6 mmol/L).

Thyroid function was investigated: TSH 8.9 mU/L (n.v. 0.45–4.5), $FT_4$ 0.9 ng/dL (n.v. 0.9–1.8), $FT_3$ 2.7 pg/mL (n.v. 2.3–4.2), thyroperoxidase and thyroglobulin antibodies: negative. Thyroid ultrasonography showed small bilateral cystic nodules, 7 mm in the right lobe, 5 mm in the left lobe.

Levothyroxine treatment was started (dose titration up to 75 μg qd, 0.8 μg/kg/day). After 3 months, thyroid function and lipid profile were revaluated: TSH 3.7 mU/L, $FT_4$ 1.1 ng/dL, $FT_3$ 2.9 pg/mL, total cholesterol 187 mg/dL, HDL 44 mg/dL, triglycerides 126 mg/dL, LDL cholesterol 117 mg/dL.

Lipid-lowering therapy was prescribed (simvastatin 20 mg qd).

**Comment**. Lifestyle modifications (quit smoking, healthy diet low in saturated fat, moderately vigorous physical activity) are the first-line therapy in the treatment of dyslipidemia, especially in case of metabolic syndrome, when dyslipidemia

represents a cluster of lipid and lipoprotein abnormalities. There is considerable individual variability in the LDL cholesterol response to dietary treatment. If therapeutic lifestyle changes are not sufficient to reduce the total cardiovascular risk by reaching the designated goals for total cholesterol and LDL cholesterol, a lipid-lowering drug may be necessary, especially in individuals at moderate to very-high cardiovascular risk [6].

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy [7].

Thyroid hormones have different effects on the regulation of lipid metabolism. Changes are directly related to the magnitude of hormonal deficit. Overt hypothyroidism significantly affects the lipid profile. Hypercholesterolemia is characterized by increased total and low-density lipoprotein (LDL) cholesterol and depends on reduced biosynthesis and hepatic degradation, rather than on increased production. Triglyceride increase is moderate and depends on reduced plasma lipoprotein lipase activity. Overall, changes in lipid profile are atherogenic and promote cardiovascular disease [8]. Treatment of overt hypothyroidism with levothyroxine restores lipid metabolism.

Also subclinical hypothyroidism is associated with atherogenic changes in lipid profile, that is, the increase in total cholesterol, LDL cholesterol, apolipoprotein B, and lipoprotein (a) [Lp(a)]. Levothyroxine treatment results in a significant decrease of both total and LDL cholesterol concentrations [9].

## 16.3 Clinical Case 3

In March 2020, a 45-year-old woman complained neck pain, without fever, insomnia, or palpitation. She experienced a respiratory tract infection with cough treated with antibiotic therapy, a couple of weeks before the raise of neck pain.

Thyroid function tests showed thyrotoxicosis: TSH 0.08 mcU/mL (n.v. 0.45–4.5), $FT_4$ 1.48 ng/dL (n.v. 0.9–1.8), $FT_3$ 4.24 pg/mL (n.v. 2.3–4.2); erythrocyte sedimentation rate and C-reactive protein were elevated; thyroperoxidase and TSH receptor antibodies were negative, thyroglobulin antibodies were slightly positive; thyroid ultrasound showed an inhomogeneous gland with bilateral ill-defined hypoechoic areas, the greatest measuring 2 cm in the right lobe.

Biochemical, hormonal, and ultrasound features suggested the diagnosis of de Quervain's subacute thyroiditis. In consideration of the widespread diffusion of SARS-CoV-2 infection in Northern Italy during the first months of 2020, serologic test to detect SARS-CoV-2 antibodies was performed: IgM and IgG were positive; reverse transcriptase-PCR by nasopharyngeal swab was negative for SARS-CoV-2. She received oral prednisone that was slowly tapered over 12 weeks.

After 8 weeks, inflammatory markers were normal. Thyroid dysfunction had a typical course: after 8 weeks, thyrotoxicosis was followed by mild hypothyroidism (TSH 9.1 mcU/mL, $FT_4$ 1.1 ng/dL), after 12 weeks, prednisone was withdrawn,

mild hypothyroidism was still present (TSH 5.8 mcU/mL, $FT_4$ 1.0 ng/dL), thyroid ultrasound showed a 7-mm hypoechoic pseudonodular area in the right lobe, and color Doppler sonography showed increased flow; after 16 weeks, euthyroidism was restored (TSH 3.8 mcU/mL, $FT_4$ 1.1 ng/dL).

**Comment**. Subacute thyroiditis (also known as granulomatous thyroiditis or de Quervain's thyroiditis) is a self-limiting inflammatory thyroid disorder, sometimes relapsing, with a typical course of few weeks or few months. Subacute thyroiditis is an uncommon condition, with an incidence rate of 2–4.9 cases per 100,000/year, occurs more commonly in women than men (sex ratio between 3:1 and 7:1), with a peak incidence in the fourth to fifth decades.

The pathogenesis of the condition is still not fully understood, but generally is caused by a viral infection or a post-viral inflammatory process in a genetically predisposed individual. The hypothesized mechanism is that a viral infection provides an antigen, the resulting antigen-HLA complex is recognized by cytolytic T cells that then damage thyroid follicular cells because of molecular mimicry. The post-viral etiology is supported by clusters of the disease occurring during outbreaks of viral infection, and the tendency for the disease to have an antecedent history of an upper respiratory tract infection, fever, malaise, or myalgia. Viruses most associated with subacute thyroiditis are coxsackievirus, echovirus, adenovirus, paramixovirus, enterovirus, influenza, Epstein–Barr virus, and rubivirus. The incidence is higher in individuals with specific major histocompatibility antigen status, i.e., HLA-B35, HLA-B67.

The onset of the disease is characterized by neck pain (monolateral or bilateral, limited to the thyroid or radiated to upper neck, jaw, ears) and systemic symptoms (fever, arthralgia/myalgia, fatigue) that progress over 1–2 weeks and continue with fluctuating intensity over weeks (usually 3–6 weeks). They are associated with thyrotoxicosis due to follicular disruption and thyroid hormone release. Thyroid dysfunction typically has a triphasic course: thyrotoxicosis, usually mild but symptomatic in more than 60% of patients, generally resolves over weeks to months and is followed by an hypothyroid phase (30–60%), usually mild and asymptomatic. Eventually, around 90–95% of patients recover normal thyroid function.

Subacute thyroiditis is primarily a clinical diagnosis. Laboratory tests showed increased ESR, CRP, and mild neutrophilic leukocytosis. Thyroid function tests vary through the different phases of the disease: in the acute phase, most patients have thyrotoxicosis with elevated serum thyroglobulin, $T_3$ and $T_4$ and suppressed TSH; in the hypothyroid phase, mostly patients have subclinical or mild overt hypothyroidism. Thyroperoxidase and thyroglobulin antibodies are usually absent, although transient low-titer antibodies may be found.

Thyroid ultrasound showed thyroid enlargement and ill-defined hypoechogenic areas ("map like"). During the acute phase, color Doppler sonography shows low flow and radionuclide thyroid scanning shows reduced or absent uptake.

Treatment aims at relieving pain and symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually all that is required in mild to moderate thyroiditis. Beta-adrenergic blockers may be used for control of hyperthyroid symptoms; levothyroxine is rarely needed in the early hypothyroid phase. In more severe cases,

glucocorticoid therapy may be employed once acute suppurative thyroiditis has been excluded (oral prednisolone 30–50 mg daily with tapering doses over 2–3 months). ESR and CRP are sensitive markers of the course of the disease. A relapse rate of 10–35% is described with tapering or cessation of glucocorticoids [10, 11].

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), there were increasing reports of extrapulmonary clinical features of the disease. To date (*November 2020*), some cases of subacute thyroiditis has been described, and a review of the literature comparing the clinical and diagnostic findings has been published [12].

All cases of subacute thyroiditis due to COVID-19 occurred in women with no (or minor) medical comorbidities. Two patients had concurrent diagnoses of COVID-19 and thyroiditis [13, 14]; two patients reported symptoms occurring after 2 weeks of infection with SARS-CoV-2 [12, 15]; one patient had symptoms 6 weeks after infection [16]. All patients had laboratory findings of thyrotoxicosis and ultrasound findings suggestive of subacute thyroiditis. All patients responded favorably to anti-inflammatory and corticosteroid therapy. Pathogenic mechanisms already noted with SARS virus have been hypothesized: host inflammatory response, direct viral replication, interactions with ACE2 receptor, central mechanism (hypothalamus–pituitary dysfunction). Endocrinologist must be aware of the possibility of subacute thyroiditis after COVID-19 infection due to SARS-CoV-2.

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