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Thyroid disease and autoimmunity in obese patients: a narrative review

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Abstract

Introduction: The high prevalence of obesity and thyroid diseases worldwide justifies *di per se* their simultaneous coexistence. In recent decades, there has been a parallel and significant rise in obesity and thyroid diseases in industrialised countries, although the underlying mechanisms are complex and not well known.

Material and methods: The authors accomplished a comprehensive literature search of original articles concerning obesity and thyroid status. Original papers exploring the association between these two morbidities in children and adults were included.

Results: A total of 79 articles were included in the present analysis. A total of 12% of obese children (mean age 10.9 ± 1.4 years) showed a thyroid disease, and they were younger than healthy obese children (10.9 ± 1.2 *vs.* 11.0 ± 0.4 years, $p < 0.001$). Isolated hyperthyrotropinaemia was the most frequent finding in children (10.1%). Autoimmune thyroid disease was more frequent in puberal age. Thyroid antibodies and subclinical hypothyroidism were more frequent in obese that in non-obese patients (7% *vs.* 3%, $p < 0.001$; 10% *vs.* 6%, $p < 0.001$). Among obese adults, 62.2% displayed a thyroid disease; those affected were younger (35.3 ± 6.8 *vs.* 41.0 ± 1.9 years, $p < 0.001$), heavier [body mass index (BMI): 39.4 ± 6.3 *vs.* 36.1 ± 2.3 kg/m^2, $p < 0.001$], and more frequently female (13% *vs.* 8%, $p < 0.001$). The most frequent disease was overt hypothyroidism (29.9%). BMI appears to be correlated with TSH levels in obese adults. Overt hypothyroidism was significantly more frequent in obese patients (7% *vs.* 3%, $p < 0.005$), but no difference was found in thyroid antibodies (15% *vs.* 14%, $p = 0.178$).

Conclusions: An undeniable relationship between obesity and thyroid impairments exists. Isolated hyperthyrotropinaemia is frequently seen in obese children, often followed by spontaneous resolution. Subclinical hypothyroidism should never be treated in children or adults with the aim of reducing body weight. **(Endokrynol Pol 2023; 74 (6): 576–590)**

Key words: *obesity; thyroid; hypothyroidism; hyperthyroidism; autoimmune thyroid diseases*

Introduction

Excess weight and obesity are defined as an abnormal or excessive fat accumulation representing a risk to health [1]. They are classified by calculating body mass index (BMI), with overweight classified as a BMI between 25.0 and 29.9 kg/m^2 and obese as a BMI ≥ 30 kg/m^2. The obese category is subdivided into class I (BMI 30.0 to 34.9 kg/m^2), class II (BMI 35.0 to 39.9 kg/m^2), and class III (BMI ≥ 40 kg/m^2), the latter also referred to as severe or massive obesity [1].

The issue has grown to epidemic proportions both in adults and in children. In the last 40 years, the prevalence of overweight or obese subjects has increased from 4% to 18% worldwide [1]. Many comorbidities are related to this condition, such as type 2 diabetes mellitus, cardiovascular and immune-mediated diseases, and some malignancies [2]. Moreover, more than 4 million people die from obesity complications every year [3].

Thyroid dysfunctions are quite common in the general population. In community surveys, subclinical and overt hypo- and hyperthyroidism have a prevalence ranging from 0.1% to 12.4% and from 0.2% to 10% in adults, respectively [4–9]. The most frequent cause is autoimmune thyroid diseases (AITDs) that are T cell-mediated, organ-specific disorders [10, 11]. Graves' disease and Hashimoto thyroiditis are the most frequent, both characterised by lymphocytic infiltration, although clinically different [12]. The former is characterized by the presence of thyroid-stimulating hormone receptor antibodies (TRAb) that activate the follicular cell receptor, thereby stimulating thyroid hormone synthesis and secretion [13]. The latter shows antibod-

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ies to thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) that are correlated with the active phase of disease leading to hypothyroidism [14–17].

The high prevalence of obesity and thyroid diseases worldwide justifies *di per se* their simultaneous coexistence. Indeed, in recent decades, there has been a parallel and significant rise in obesity and autoimmune disorders, including thyroid diseases, in industrialised countries, although the underlying mechanisms are complex and not well known [18–20].

For these reasons, we performed a literature review with the aim of assessing the prevalence of thyroid dysfunction, focusing on thyroid autoimmunity with or without hypo- and hyperthyroidism, both in obese children and in adults.

Material and methods

The review was conducted according to the PRISMA statement, and the checklist is reported in Supplementary File.
A PubMed/MEDLINE, Web of Science, and Scopus search was performed for free-text words and terms related to "obesity", "obese", "overweight", "thyroid autoimmunity", "Hashimoto's thyroiditis", "Graves' disease", "Graves hyperthyroidism", "hyperthyroidism", "hypothyroidism", "thyroid peroxidase antibody", "TPOAb", "thyroglobulin antibody", "thyroglobulin antibodies", "TgAb", "thyroiditis", and "thyrotoxicosis". Original studies and reviews in English published online up to 30 April 2023 were selected and reviewed. The final reference list was defined based on the relevance of each paper to the scope of this review.
Three authors extracted data from all the included studies in the full text, tables, and figures concerning general study information (authors, publication year, country, study design, and funding sources) and patient characteristics (i.e. sample size, age, sex ratio, and clinical setting).
The selected method used for assessing the risk of bias in individual studies and the applicability to the review question was QUADAS-2, a tool for evaluating quality in diagnostic test accuracy studies [21]. Three reviewers assessed the studies' grades in the systematic review in four domains (patient selection, index test, reference standard, and flow and timing) concerning the risk of bias and in three fields regarding the applicability (patient selection, index test, and reference standard).

Results

In the preliminary search, 9742 articles were identified, and 6901 remained after removing duplicates. A total of 458 full-text publications were retrieved after further careful review of abstracts. A total of 143 studies were eligible for full-text and 79 articles were included in the present analysis. A PRISMA flow diagram of the screening and selection process can be found in Figure 1.

Taking advantage of the data reported in each study, the Authors assessed the risk of bias and concerns about the applicability of the included papers based on the QUADAS-2 instruments. The results of the quality assessment are reported in Figure 2.

Post hoc, the studies were divided by the age of the subjects. In detail, 24 studies involved children (10 cross-sectional studies, 7 case controls, and 7 cohort studies) and 55 involved adults (42 cross-sectional studies, 4 case controls, and 9 cohort studies) (Tab. 1 and 2).

Thyroid disease in obese children

A total of 9784 obese children were evaluated and enrolled in this review. Among them, 1174 (12%) children (mean age 10.9 ± 1.4 years) showed thyroid autoantibodies and/or hypo-hyperthyroidism (Tab. 1 and 3). Based on the available data, no difference in sex distribution was observed among obese children with (415/343 F/M) or without thyroid dysfunctions (3452/3288, F/M) ($p = 0.065$) [22, 23], whereas a significant difference in age was identified (10.9 ± 1.2 *vs*. 11.0 ± 0.4 years, respectively; $p < 0.001$) [26, 28, 29, 31, 34–36].

Autoimmune thyroiditis was found in 86/9784 children (0.9%) [22, 23, 25, 31, 35, 37, 38], whereas thyroid disfunction was found in 1088 (11%) [22–44]. In more detail, 988 (10.1%) children showed subclinical hypothyroidism [22–30, 32–36, 38, 39], 96 (1%) overt hypothyroidism [22, 39, 44, 45], and 4 (0.04%) hyperthyroidism [44].

Data on sex distribution within each thyroid disease category were only available for a few articles, mainly regarding subclinical hypothyroidism [22–30, 32, 33, 41, 45], which showed that 439/788 (55.7%) obese children suffering from this condition were female [22–30, 32, 33, 41]. In addition, the onset of this condition was observed during puberty for 179/788 (23%) children: 113 (63%) experienced it in prepubertal age [26, 28].

Conversely, Dursun et al. showed, in a small number of patients, the presence of anti-peroxidase and/or thyroglobulin antibodies mainly post puberty (81%) rather than in prepubertal age [31].

Regarding the possible differences in the prevalence of thyroid antibodies between obese and non-obese patients, four studies evaluated 2317 subjects [22, 23, 37, 38]. The data revealed a significantly higher prevalence among obese compared to non-obese children (7% *vs*. 3%, respectively, $p < 0.001$). Nine studies, for a total of 9667 subjects, investigated the prevalence of subclinical hypothyroidism; again, the prevalence was higher in obese as compared to non-obese children (10% *vs*. 6%, $p < 0.001$) [22–25, 27, 32, 35, 38, 40, 42]. Only one study, conducted in a large cohort of children (6165 subjects), investigated the prevalence of overt hypothyroidism and hyperthyroidism. An equal distribution was found between obese and non-obese children (5% *vs*. 7%, respectively, $p = 0.101$), whereas hyperthyroidism was associated more with non-obese subjects (1% *vs*. 3%, respectively, $p < 0.001$) [44].

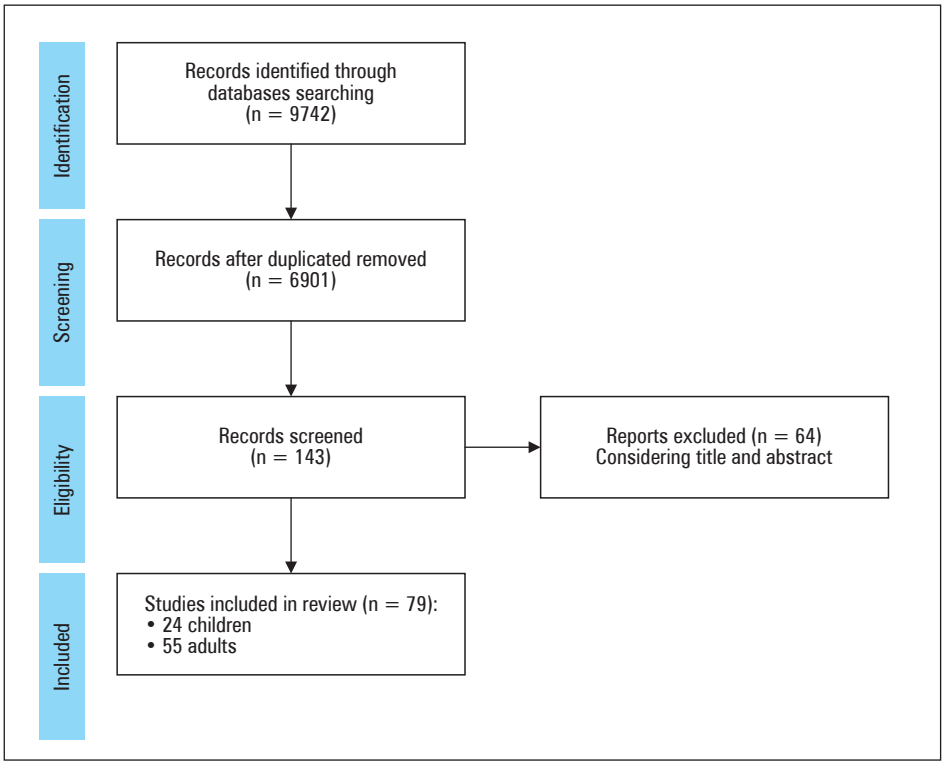

Figure 1. *PRISMA flowchart*

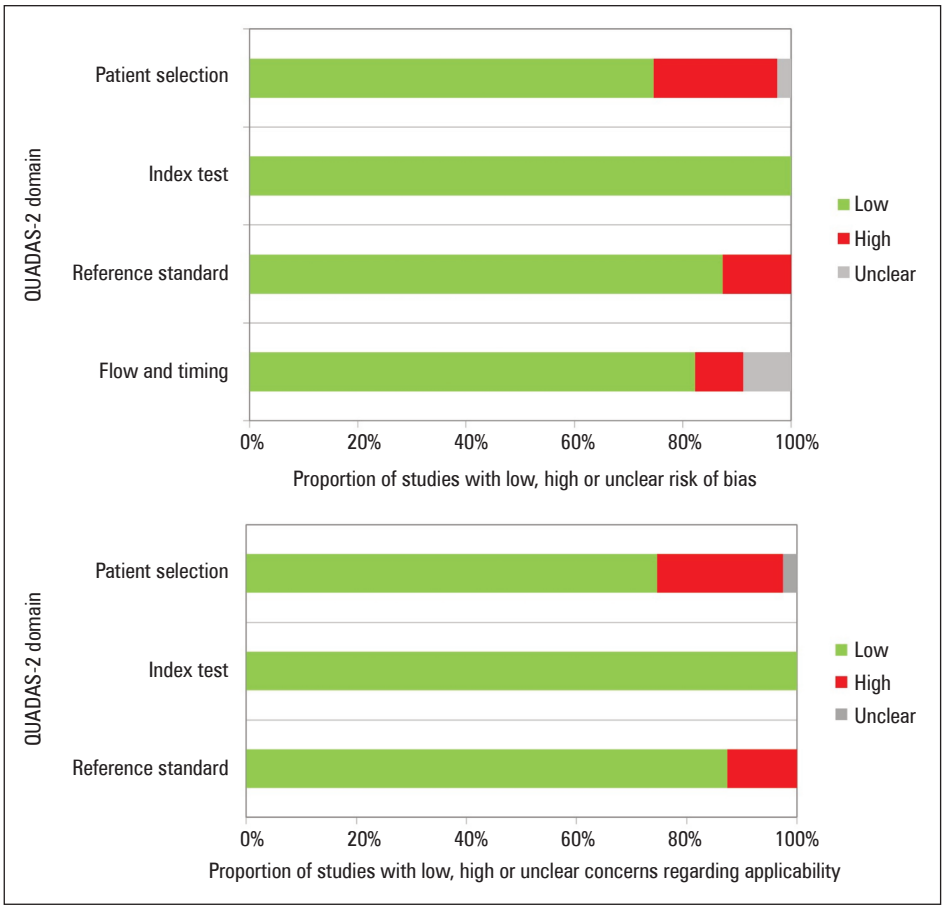

Figure 2. *Quality assessment according to the QUADAS-2 tool*

Table 1. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese children*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Stichel et al., 2000 [22]	Retrospective case-control	290	AITD	10 (3.4%)	The prevalence of AITD increased in obese children, mostly in those with elevated TSH
			Subclinical hypothyroidism	22 (7.6%), 14/8	
			Hypothyroidism	1 (0.3%)	
Eliakim et al., 2006 [29]	Prospective cohort	196	Subclinical hypothyroidism	41 (20.9%), 20/21	No beneficial effects on body weight, body mass index, linear growth, and body lipids were found in treated obese subjects, suggesting that thyroid substitution is not necessary in most cases
Bhowmick et al., 2007 [23]	Retrospective case-control	308	AITD	5 (1.6%), 1/4	A higher prevalence of TSH elevation was observed in the obese group
			Subclinical hypothyroidism	36 (11.7%), 14/22	
Dekelbab et al., 2010 [35]	Retrospective case-control	191	AITD	6 (3.1%)	Mild elevation of TSH values in the absence of AITD is not uncommon in obese children, but no special characteristics was found
			Subclinical hypothyroidism	20 (10.8%)	
Grandone et al., 2010 [28]	Prospective cohort	938	Subclinical hypothyroidism	120 (20.8%), 58/62	A moderate elevation of TSH concentrations is frequent in obese children, it is not associated to metabolic risk factors, it is reversible after weight loss, and it should not be treated
Marras et al., 2010 [27]	Prospective cohort	468	Subclinical hypothyroidism	15 (3.2%), 6/9	An increased fT3 concentration is the most frequent abnormality. Serum fT3 and TSH correlate with BMI. Moderate weight loss frequently restores abnormalities
Ong et al., 2012 [134]	Prospective cohort	264	AITD/ hypothyroidism	NA	Childhood weight gain and childhood overweight conferred an increased susceptibility to later hypothyroidism and AITD, particularly in females
Ittermann et al., 2013 [44]	Retrospective case-control	563	Hypothyroidism	29 (5.1%)	Active and passive smoking may mediate the association between thyroid function and BMI in adolescents
			Hyperthyroidism	4 (0.7%)	
Marwaha et al., 2013 [24]	Retrospective cross-sectional	488	Subclinical hypothyroidism	48 (9.8%), 26/22	Serum fT3 and TSH were positively while fT4 was negatively associated with BMI in apparently healthy euthyroid children
Bouglè et al., 2014 [34]	Prospective cohort	528	Subclinical hypothyroidism	69 (13.1%)	Increased TSH may be predictive of a decrease in insulin resistance, fT4 was associated with a low metabolic risk. Changes in thyroid function could protect against the occurrence of obesity-associated metabolic diseases
Ghergherehchi et al., 2015 [25]	Retrospective case-control	190	AITD	28 (14.7%), 11/17	TSH and fT4 levels are increased in obese children, but the incidence of AITD is lower
			Subclinical hypothyroidism	20 (10.7%)	
Krause et al., 2015 [42]	Retrospective case-control	572	Subclinical hypothyroidism	28 (4.9%)	Paediatric obesity is associated with higher TSH and lower FT4 concentrations and with a greater prevalence of abnormally high TSH
Matusik et al., 2015 [41]	Prospective cohort	NA	Subclinical hypothyroidism	51, 20/31	In obese children with sHT dietary-behavioural management intervention contributed to reduction of body mass index, irrespective of levothyroxine use. Moderately elevated levels of TSH are a consequence rather than cause of overweight, and pharmacological treatment should be avoided
Garcia-Garcia et al., 2016 [38]	Retrospective cross-sectional	129	AITD	4 (5.6%)	Obese children and adolescents had higher levels of TSH, and among them the prevalence of AITD is higher
			Subclinical hypothyroidism	11 (14.4%)	
Dahl et al., 2018 [32]	Retrospective case-control	1796	Subclinical hypothyroidism	186 (10.4%), 121/142	The prevalence of SH was higher among overweight/obese study participants. TSH and fT4 are positively correlated with WHtR

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Table 1. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese children*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Jin, 2018 [40]	Retrospective cross-sectional	111	Subclinical hypothyroidism	27 (24.3%)	SCH is common in obese children; TSH levels were linked with the lipid profile
Dursun et al., 2019 [31]	Retrospective cross-sectional	218	AITD	16 (7.3%), 13/3	Obese adolescents with non-autoimmune thyroiditis had a higher incidence of insulin resistance
Kumar et al., 2019 [45]	Prospective cohort	162	Hypothyroidism	51 (31.4%), 17/34	The addition of levothyroxine to the weight reduction program did not show beneficial effects on body weight, BMI, and thyroid profiles in obese children with isolated hyperthyrotropinaemia
Ruszała et al., 2019 [33]	Retrospective cross-sectional	100	Subclinical hypothyroidism	20 (20.9%), 7/13	Isolated increased TSH level is common in obese adolescents, there is no correlation between TSH, fT3, and fT4 levels and BMI SDS value. Autoimmune thyroiditis in obese adolescents is more common than in the general population.
Thiagarajan et al., 2019 [39]	Prospective cross-sectional	102	Hypothyroidism	15 (14.7%)	No correlation was found between fT4, TSH, and BMI
Özcabı et al., 2021 [37]	Retrospective cross-sectional	56	AITD, TPOAb	13 (23.2%)	An association between central adiposity and TgAb levels was found
			AITD, TgAb	17 (30.4%)	
Patel et al., 2021 [36]	Retrospective cross-sectional	404	Subclinical hypothyroidism	122 (30.2%)	Obesity-related subclinical hypothyroidism predisposes to increased non-alcoholic steatohepatitis independently of severity adiposity
Dündar et al., 2022 [26]	Retrospective cross-sectional	1130	Subclinical hypothyroidism	59 (5.2%), 25/34	Subclinical hypothyroidism can negatively affect the lipid and glucose profile in obese children
Di Sessa et al., 2023 [30]	Retrospective cross-sectional	844	Subclinical hypothyroidism	85 (10.1%), 27/58	Children with obesity and NAFLD presented increased risk of SCH, and vice versa

AITD — autoimmune thyroid disease; TSH — thyroid stimulating hormone; NA — not available; BMI — body mass index; fT3 — free triiodothyronine; fT4 — free thyroxine; TPOAb — anti-thyroid peroxidase antibodies; TGAb — anti-thyroglobulin antibodies; WHtR — waist-height ratio; SCH — subclinical hypothyroidism; BMI SDS — standardised body mass index; NAFLD — non-alcoholic fatty liver disease. (*) if available

Table 2. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese adults*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Rimm et al., 1975 [63]	Retrospective cross-sectional	73532	Hypothyroidism	35950 (48.9%), 0/35950	Obesity is related with a higher risk of hypothyroidism and a decreased risk of Graves' hyperthyroidism
			Hyperthyroidism	35651 (48.5%), 0/35651	
Szomstein et al., 2002 [94]	Retrospective cross-sectional	195	Hypothyroidism	14 (7.2%)	Article included for epidemiological data
Raftopoulos [90] et al., 2004	Retrospective cross-sectional	86	Subclinical hypothyroidism	9 (10.5%)	Article included for epidemiological data
Holm et al., 2005 [135]	Retrospective cohort	NA	NA	68, 0/68	Obesity was associated with a decreased risk of Graves' hyperthyroidism
Knudsen et al., 2005 [136]	Retrospective cross-sectional	NA	NA	NA	Even slightly elevated serum TSH levels were associated with an increase in the occurrence of obesity

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Table 2. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese adults*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Moulin de Moraes et al., 2005 [50]	Retrospective cross-sectional	72	Subclinical hypothyroidism	18 (25.0%), 2/16	Article included for epidemiological data
Chikunguwo et al., 2007 [77]	Retrospective cross-sectional	86	Subclinical hypothyroidism	9 (10.5%)	Article included for epidemiological data
Asvold et al., 2009 [57]	Retrospective cross-sectional	27097	Subclinical hypothyroidism	1804 (6.7%), 451/1353	Hypothyroidism is associated with high BMI, both in current smokers and in never-smokers
			Hypothyroidism	158 (0.6%), 21/137	
			Hyperthyroidism	574 (2.1%), 141/433	
Gniuli et al., 2009 [80]	Retrospective cross-sectional	45	Subclinical hypothyroidism	11 (24.4%)	Article included for epidemiological data
Gopinath et al., 2010 [137]	Prospective cohort	NA	Subclinical hypothyroidism	1.9%	Obesity is a risk factor for SCH and overt hypothyroidism
			Hypothyroidism	6.2%	
Marzullo et al., 2010 [47]	Retrospective cross-sectional	165	AITD	18 (10.9%), 3/15	Obese patients had lower fT3 levels and fT4 levels, greater prevalence of hypothyroidism, and higher prevalence of TPOAb positivity
			Hypothyroidism	17 (10.3%), 4/13	
Somwaru et al., 2011 [138]	Retrospective cohort	NA	Hypothyroidism	1027	Higher BMI was independently associated with greater risk for overt hypothyroidism
Hemminki et al., 2012 [87]	Prospective cohort	29665	Hypothyroidism	83 (0.3%)	The risk of Hashimoto's disease/hypothyroidism was significantly increased; a small but significant increase was also noted for the Graves' disease/hyperthyroidism
			Hyperthyroidism	54 (0.2%)	
Sundaram et al., 2013 [92]	Retrospective cross-sectional	1221	Hypothyroidism	231 (18.9%)	Article included for epidemiological data
Agbaht et al., 2014 [70]	Retrospective cross-sectional	548	AITD	96 (17.5%)	Article included for epidemiological data
			Hypothyroidism	123 (22.4%)	Article included for epidemiological data
Ruiz-Tovar et al., 2014 [81]	Retrospective cross-sectional	60	Subclinical hypothyroidism	10 (16.7%)	Article included for epidemiological data
Han et al., 2015 [58]	Retrospective cross-sectional	90 pregnant women	AITD	21 (23.3%), 0/21	Obesity was associated with increases in the odds of hypothyroidism and TPOAb positivity
			Subclinical hypothyroidism	7 (7.8%), 0/7	
			Hypothyroidism	3 (3.3%), 0/3	
Janssen et al., 2015 [52]	Retrospective cross-sectional	503	Subclinical hypothyroidism	61 (12.1%)	Article included for epidemiological data
Amouzegar et al., 2016 [139]	Prospective cohort	NA	NA	NA	Early diagnosis of SCH and hypothyroidism was significantly associated with obesity
Bedaiwy et al., 2017 [61]	Retrospective cross-sectional	105	Subclinical hypothyroidism	25 (23.8%), 0/25	Article included for epidemiological data
Răcătăianu et al., 2017 [72]	Retrospective cross-sectional	82	Hypothyroidism	12 (14.6%)	Article included for epidemiological data
			Hyperthyroidism	1 (1.2%)	Article included for epidemiological data
			AITD	27 (32.9%)	Article included for epidemiological data

Table 2. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese adults*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Valdes et al., 2017 [75]	Retrospective cross-sectional	1193	Subclinical hypothyroidism	41 (3.4%)	SCH is more prevalent in obese and morbid obese population
Zendel et al., 2017 [84]	Retrospective cross-sectional	1823	Hypothyroidism	93 (5.1%), 8/85	Article included for epidemiological data
Milla Matute et al., 2018 [89]	Retrospective cross-sectional	1581	Hypothyroidism	35 (2.2%)	Article included for epidemiological data
Mousa et al., 2018 [69]	Retrospective cross-sectional	102	AITD	26 (25.5%)	Article included for epidemiological data
Ornaghi et al., 2018 [88]	Retrospective cohort	98 pregnant women	Hypothyroidism	17 (17.3%), 0/17	Obese patients with chronic hypertension showed a 2.4-fold increased risk of developing hypothyroidism during pregnancy versus normal BMI women
Pedro et al., 2018 [83]	Retrospective cross-sectional	1449	Hypothyroidism	106 (7.3%)	Article included for epidemiological data
Răcătăianu et al., 2018 [72]	Retrospective cohort study	158	Hypothyroidism	28 (17.7%)	Article included for epidemiological data
			Hyperthyroidism	1 (0.6%)	Article included for epidemiological data
			AITD	39 (24.7%)	Article included for epidemiological data
Rudnicki et al., 2018 [93]	Retrospective cross-sectional	1756	Hypothyroidism	90 (5.1%), 17/73	Article included for epidemiological data
Sami et al., 2018 [56]	Retrospective cross-sectional	1193	Subclinical hypothyroidism	19 (15.0%), 6/13	Subclinical hypothyroidism is highly prevalent in obese patients
Wang et al., 2018 [59]	Retrospective cross-sectional	310	AITD	33 (10.6%), 15/18	Obese females had higher risk of SCH than non-obese females. No association between obesity and hypothyroidism was observed in male participants
			Subclinical hypothyroidism	37 (11.9%), 14/23	
			Hypothyroidism	39 (10.6%), 15/24	
Zhang et al., 2018 [46]	Retrospective cross-sectional	534	Subclinical hypothyroidism	108 (20.2%), 0/108	Article included for epidemiological data
Abdelbaki et al., 2019 [53]	Retrospective cross-sectional	554	Subclinical hypothyroidism	72 (13.0%), 9/63	Article included for epidemiological data
Almunif et al., 2019 [79]	Retrospective cross-sectional	1480	Subclinical hypothyroidism	106 (7.2%)	Article included for epidemiological data
			Hypothyroidism	160 (10.8%)	Article included for epidemiological data
Dambros Granzotto et al., 2019 [49]	Retrospective cross-sectional	215	Subclinical hypothyroidism	20 (9.3%), 6/14	Article included for epidemiological data
Nayak et al., 2019 [62]	Retrospective cross-sectional	175	Hypothyroidism	37 (21.1%), 0/37	Article included for epidemiological data
Neves et al, 2019 [78]	Retrospective cross-sectional	641	Subclinical hypothyroidism	11 (1.7%)	Article included for epidemiological data
			SubHyper	4 (0.6%)	Article included for epidemiological data
Xia et al, 2019 [51]	Retrospective cross-sectional	101	AITD	12 (11.9%), 7/5	Article included for epidemiological data
Zhu et al., 2019 [48]	Retrospective cross-sectional	88	Subclinical hypothyroidism	28 (31.8%), 11/17	Article included for epidemiological data
Khan et al., 2020 [91]	Retrospective cross-sectional	883	Hypothyroidism	93 (10.5%), 12/81	Article included for epidemiological data

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Table 2. *Summary of clinical studies about thyroid dysfunctions and autoimmunity in obese adults*

Author, date	Study design	Total obese patients	Thyropathy	Patients affected (%), male/female*	Outcome
Makwane et al., 2020 [86]	Retrospective cross-sectional	31	Hypothyroidism	6 (19.0%)	No significant relationship between thyroid hormones and BMI was found in normal or in obese groups
			Hyperthyroidism	1 (3.0%)	
Wu et al., 2020 [74]	Retrospective cross-sectional	NA	AITD	1041	Obesity was positively correlated with the prevalence of positive thyroid autoantibodies in euthyroid subjects
Mahdavi et al., 2021 [55]	Retrospective case-control	1144	AITD	198 (17.3%), 33/165	Higher prevalence of hypothyroidism and TPOAb positivity among obese patients
			Subclinical hypothyroidism	87 (7.6%), 9/78	
			Hypothyroidism	46 (4.0%), 5/41	
			Subclinical hyperthyroidism	31 (2.7%), 11/20	
			Hyperthyroidism	17 (1.5%), 4/13	
Yin et al., 2021 [68]	Retrospective case-control	280	AITD	80 (28.5%)	No significant associations between obesity and TGAb levels. Prevalence of SCH was higher in obese patients, rather than overweight and normal ones, whereas there were no differences in prevalence of hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism between the three groups
			Subclinical hypothyroidism	56 (20,0%)	
			Hypothyroidism	3 (1.0%)	
			Subclinical hyperthyroidism	1 (0.3%)	
			Hyperthyroidism	1 (0.3%)	
Agbaht et al., 2022 [70]	Retrospective cohort study	285	Hypothyroidism	109 (38.2%)	Article included for epidemiological data
			AITD	64 (22.5%)	Article included for epidemiological data
Dewantoro et al., 2022 [82]	Retrospective cross-sectional	887	Hypothyroidism	49 (5.5%)	Article included for epidemiological data
Fierabracci et al., 2022 [64]	Retrospective cross-sectional	749	AITD	135 (18.0%)	Autoimmune thyroiditis is highly prevalent in patients with obesity. TgAb may be associated with hypothyroidism in the absence of TPOAb
			Subclinical hypothyroidism	153 (20.4%)	
			Hypothyroidism	104 (13.8%)	
			Hyperthyroidism	10 (1.3%)	
Walczak et al., 2022 [54]	Retrospective cross-sectional	181	AITD	57 (31.4%), 6/51	BMI is significantly higher in patients with high normal TSH
Zhao et al., 2022 [140]	Prospective cross sectional	764	Subclinical hypothyroidism	66 (8.6%)	Article included for epidemiological data
Yan et al., 2022 [66]	Retrospective cross-sectional	289	AITD	58 (20.7%)	No significant associations between obesity and TPOAb levels. Among patients with positive TgAb and TPOAb, SCH prevalence was significantly higher in obese subjects
			Subclinical hypothyroidism	27 (9.3%)	
Yang et al., 2022 [67]	Retrospective case-control	3697	AITD	870 (23.0%), 358/512	Obesity was a significant independent risk factor for hypothyroidism in males, whereas in females it was not
Sharma et al., 2022 [60]	Retrospective case-control	15	AITD	7 (46.7%), 0/7	Article included for epidemiological data
Alourfi et al., 2023 [141]	Retrospective cross sectional	292	Subclinical hypothyroidism	13 (4.5%)	Article included for epidemiological data
Kang et al., 2023 [76]	Retrospective cross-sectional	51	Subclinical hypothyroidism	42 (82.4%)	Article included for epidemiological data

NA — not available; TSH — thyroid stimulating hormone; BMI — body mass index; SCH — subclinical hypothyroidism; AITD — autoimmune thyroid disease; fT3 — free triiodothyronine; fT4 — free thyroxine; TPOAb — anti-thyroid peroxidase antibodies; TGAb: anti-thyroglobulin antibodies. (*) if available

Table 3. *Summary of data about obese children and adults diagnosed with thyropathies*

Thyropathy	Patients affected (%)	Male/female (OR F/M)*
Children (n = 9784)		
Autoimmune thyroiditis	86 (0.9%)	1/4 (2.5)
Subclinical hypothyroidism	988 (10.1%)	64/81 (1.4)
Overt hypothyroidism	96 (1.0%)	17/34
Hyperthyroidism	4 (0.1%)	NA
Adults (n = 125,958)		
Autoimmune thyroiditis	1741 (1.4%)	415/794 (1.5)
Subclinical hypothyroidism	2752 (2.2%)	480/1474 (1.5)
Overt hypothyroidism	37600 (29.9%)	45/232 (2.5)
Subclinical hyperthyroidism	36 (0.03%)	11/20 (0.8)
Overt hyperthyroidism	36256 (28.8%)	145/36097 (39.3)

NA — not available. (*) if available

REVIEW

Thyroid disease in obese adults

A total of 125,953 obese adults were evaluated and included in this review. Among them, 78,385 (62.2%) patients (43.2 ± 9.1 years old) showed AITDs and/or hypo-hyperthyroidism (Tab. 2 and 3). The available data revealed significant differences in age, BMI, and sex distribution between obese patients with and without thyroid diseases. In detail, those with thyroid diseases were younger (35.3 ± 6.8 *vs*. 41.0 ± 1.9 years, $p < 0.001$) [46–53], heavier (BMI: 39.4 ± 6.3 *vs*. 36.1 ± 2.3 kg/m^2, $p < 0.001$) [46–49, 51, 52], and more frequently female (13% *vs*. 8%, $p < 0.001$) [46–51, 53–62]. These last data were obtained excluding the study by Rimm et al., which enrolled only female patients [63].

Autoimmune thyroiditis was found in 1741/125,953 (1.4%) patients [47, 51, 55, 58–60, 64–47] whereas thyroid dysfunction was found in 76,644 (60.9%) patients. In detail, 2752 (2.2%) subjects showed subclinical hypothyroidism [46, 48–50, 52, 53, 55–59, 61, 64, 66, 69, 75–81], 37,600 (29.9%) overt hypothyroidism [47, 55, 57–59, 62–64, 68, 70–73, 79, 82–94], 36 (0.03%) subclinical hyperthyroidism [55, 68, 78], and 36,256 (28.8%) overt hyperthyroidism [55, 57, 63, 64, 68, 72, 73, 86, 87]. All these conditions were significantly associated with females (Fig. 3). The BMI values according to the patients' thyroid status are reported in Figure 4. In detail, patients with AITDs showed a BMI of 34.6 ± 7.0 kg/m^2 [47, 51, 55, 60, 64–68], those with subclinical hypothyroidism had a BMI of 39.3 ± 7.0 kg/m^2 [46, 48–50, 52, 53, 55, 56, 66, 68, 80], and those with overt hypothyroidism had a BMI of 40.9 ± 8.2 kg/m^2 [47, 55, 64, 68, 71, 82, 84, 86, 88, 90, 91, 93]. Patients affected by subclinical hyperthyroidism showed a BMI of 31.1 ± 0.6 kg/m^2 [55, 68] and those affected by overt hyperthyroidism a BMI of 34.1 ± 4.2 kg/m^2 [55, 64, 68, 86].

Nine studies, including 74,662 patients, compared the prevalence of thyroid autoantibodies in obese compared to non-obese subjects [47, 55, 58–60, 66, 68, 69, 74]. The prevalence was superimposable: 15% of obese and 14% of non-obese patients showed thyroid autoimmunity ($p = 0.178$). Eight studies, including a total of 23,032 subjects, investigated the prevalence of subclinical hypothyroidism, again comparing obese and non-obese subjects [55, 58, 59, 61, 66, 66, 68, 75, 76], and again no difference was observed among the two groups (10% *vs*. 9%, respectively, $p = 0.296$). By contrast, among 16,605 patients, overt hypothyroidism was significantly more frequent in obese patients (7% *vs*. 3%, respectively, $p < 0.005$) [47, 55, 58, 59, 62, 68, 86, 88]. Sub-clinical or overt hyperthyroidism was evaluated in 6162 patients: no difference was observed between obese and non-obese subjects (2% *vs*. 3%, respectively, $p = 0.067$) and (1% *vs*. 2%, respectively, $p = 0.150$) [55, 68, 86].

Discussion

Thyroid impairment and obesity are among the most frequent conditions in the general population [1, 4–9]. Although available data have uncovered an intriguing relationship between these two conditions, the chicken-egg conundrum has not yet been completely solved. Considering the large set of data published on obese adults and obese children, we performed a systematic review with the aim of improving knowledge in this field.

With reference to obese children, thyroid diseases were found to be equally distributed among female and male patients. The large set of data included subjects with a mean age of 10.9 ± 1.4 years, thus mostly prepubertal, and significantly younger than those with-

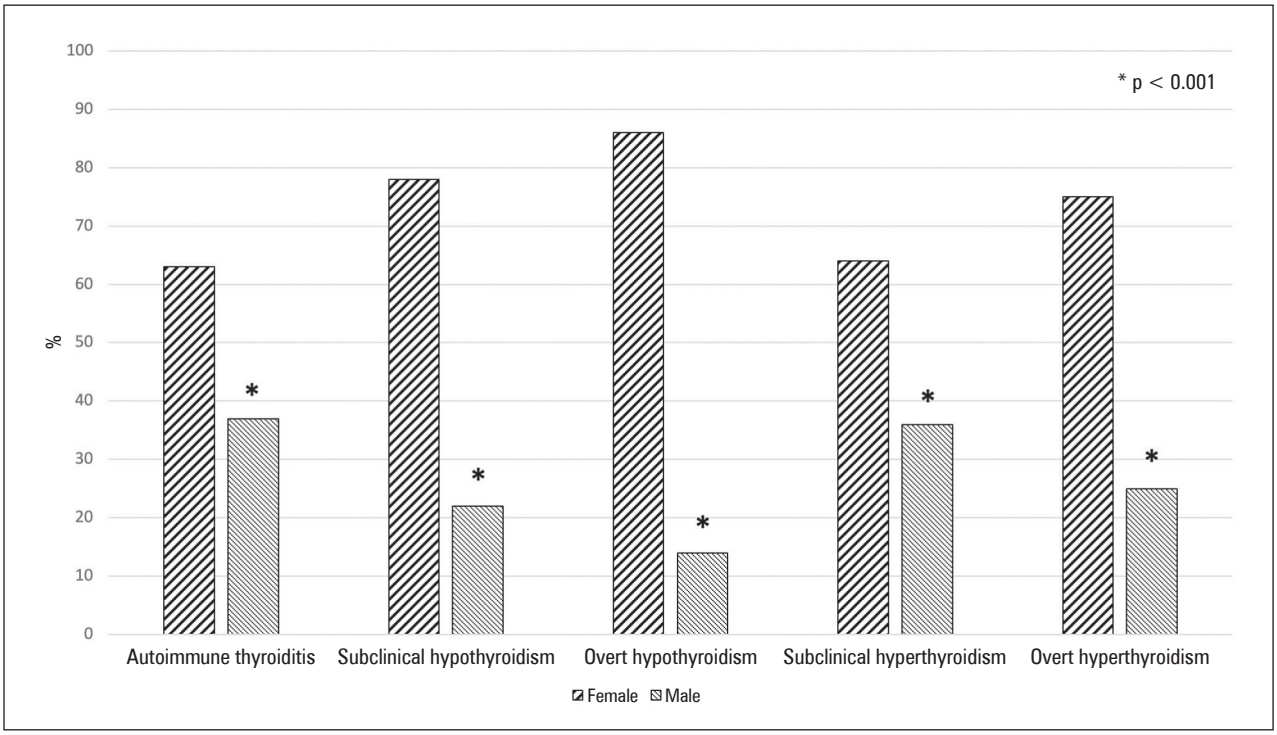

Figure 3. *Sex distribution according to adult patients' thyroid conditions*

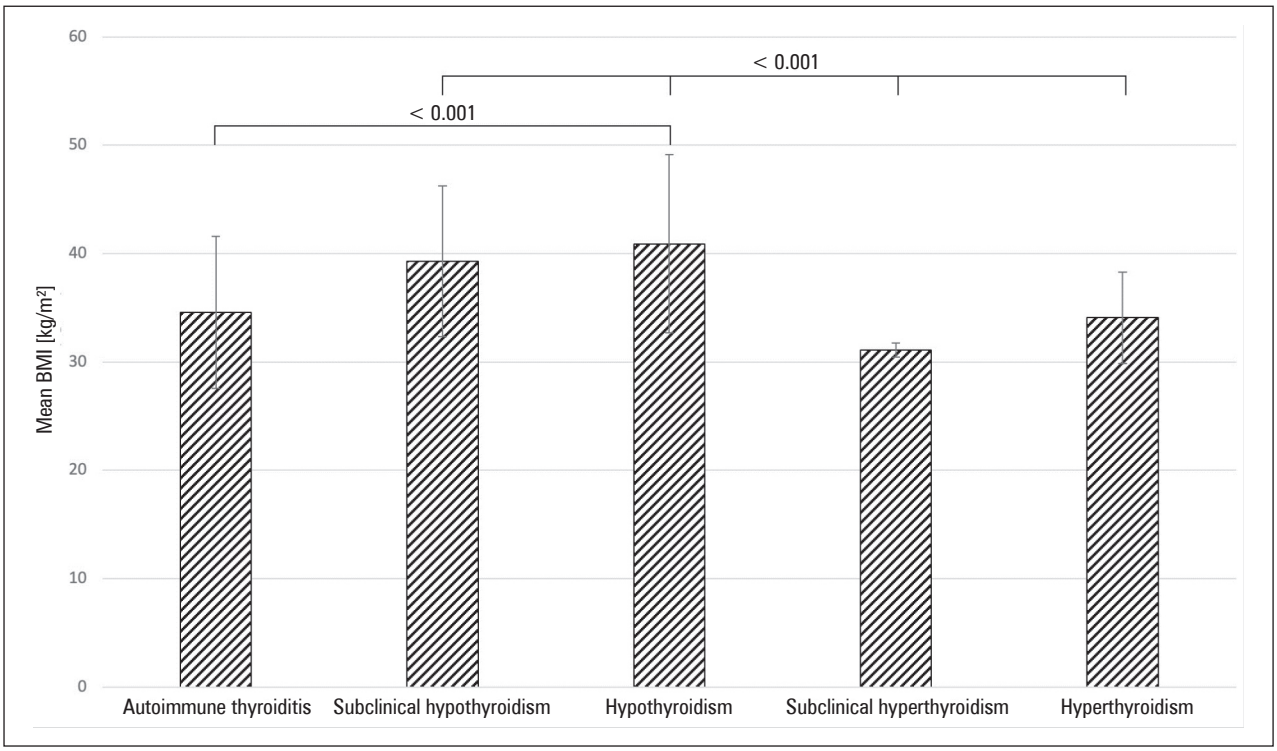

Figure 4. *Body mass index (BMI) values related to adult patients' thyroid condition*

out thyroid impairments (11.0 ± 0.4 years, $p < 0.001$). In addition, the most frequent finding was subclinical hypothyroidism, identified in 988/9784 (10.1%) children. Grandone et al. reported that the mean age is lower for obese children with higher thyroid-stimulating hormone (TSH) levels [28]. Moreover, some authors described a spontaneous reduction in TSH with increasing age both in obese and in non-obese children

[95–97]. In addition, cross-sectional and longitudinal studies demonstrated a positive correlation between obesity and weight status [22, 23, 27, 28, 41, 98–102]. Isolated hyperthyrotropinaemia is commonly reported in obese children. In the paediatric population, risk groups for this condition include children with diabetes mellitus and those with Down syndrome [29]. Elevated TSH levels in childhood obesity may be a direct effect of nutrition or an effect of leptin (which is usually elevated in obesity) on the production of hypothalamic thyrotropin-releasing hormone (TRH), which stimulates pituitary TSH secretion [29, 103–105]. In addition, Burman et al. suggest the presence of thyroid hormone resistance at the pituitary level [106], whereas D'Adamo et al. believed it may be caused by an increase in oxidative stress [107]. Even without any certain cause, it is reasonable to assume that during puberty there is a sexually dimorphic effect with subtle alterations in the hypothalamic-pituitary-thyroid axis [96]. To treat or not to treat patients with hyperthyrotropinaemia with levothyroxine is still debated, even though it is common and accepted practice to treat patients who test negative for thyroid antibodies and display clinical signs or symptoms of hypothyroidism. In obese children, many authors suggest that pharmacological treatment should be avoided, showing that changes in diet, lifestyle, and physical activity lead to a spontaneous restoration of normal TSH values and reduction of body mass index [27–29, 41]. In particular, Eliakim et al. concluded that there are no beneficial effects on body weight, body mass index, linear growth, and body lipids in treated subjects [29].

Thyroid antibody tests were carried out in 211 children with subclinical hypothyroidism, with just 13% testing positive [22, 23, 25, 29, 33, 34], which would appear to support the notion of isolated hyperthyrotropinaemia.

Dursun et al. compared the positivity for thyroid autoantibodies between prepubertal and pubertal age, finding a prevalence in pubertal age (81%) [31]. These data were recently confirmed by Calcaterra et al. [108]. These results support the idea that sexual hormonal changes during puberty could play a fundamental role in immune function [109–111]. In obese subjects, this seems to amplify the obesity-related, chronic, low-grade inflammation process, which could initiate the autoimmune cascade and consequently affect the autoimmunological response [112]. It is widely accepted that white adipose tissue is a significant source of cytokines, chemokines, and adipokines, such as interleukin 6 (IL-6), tumour necrosis factor-alpha (TNF-α) [113], and leptin, a hormone well-known for its role in inflammatory processes and autoimmunity [112]. Indeed, leptin, a 16-kDa polypeptide hormone, appears to exercise several functions in metabolism [114], but it is also implicated in innate and acquired immunity by stimulating the proliferation of monocytes and the production of pro-inflammatory cytokines, such as IL-6, IL-12, and TNF-α [115]. In addition, it promotes an increase in naive T cells, a decrease in T regulatory cells (Tregs), and the differentiation of memory T cells toward T helper 1 (Th1) suppressing T helper 2 (Th2), resulting in an increase of pro-inflammatory cytokines [115]. Therefore, leptin regulates immune response by promoting a pro-inflammatory profile and facilitating the onset of autoimmune disorders, such as AITDs, in the context of obesity [20].

By contrast, greater attention should be paid to obese children with AITDs, insofar as there is the non-negligible risk of progression from subclinical to overt hypothyroidism, indicating that levothyroxine replacement therapy should be started early [116–118].

In terms of obese adults, thyroid diseases are more frequently associated with women, as in the general population [4, 8]. Thyroid impairments occur five times more frequently in obese adults than in obese children. This could be due, firstly, to sexual hormones, which play an unquestionable role in autoimmune regulation. It is well known that male sex protects against the development of autoimmune disease, and it is likely that this is due to sexual hormones and the Y chromosome [119, 120]. On the other hand, women have a marked preponderance of many autoimmune diseases, and this is likely due, at least in part, to the stronger female system. Oestrogen has numerous effects on the regulation of autoimmune cascade, in particular enhancing Th1 responses [121]. Second, it is believed that longer exposure to obesity triggers thyroid diseases *di per se* [122–128]. In agreement, we showed that adults affected by thyroid diseases had a higher BMI, with one-third showing overt-hypothyroidism. We cannot, however, state that the obesity is caused by hypothyroidism; we are back to the chicken and the egg. Sami et al. give us a *Giano Bifronte* (two-sided) explanation: "on one side, lack of thyroid hormone leads to weight gain culminating in overt obesity, which in turn predisposes patients to develop autoimmune hypothyroidism. On the other side, raised TSH in obese patients does not show hypothyroidism but it is the result of weight gain rather than its cause" [56].

However, this review clearly showed a direct correlation between BMI and thyroid function (Fig. 4): AITD patients in spontaneous euthyroidism showed a BMI that was midway between hyperthyroid and hypothyroid, as widely expected. Indeed, as *Giano* teaches us, among a large series of patients, hypothyroidism was more frequent in obese than in non-obese subjects ($p < 0.005$), even though the prevalence of autoim-

munity was superimposable (p = 0.178). According to the data collected, we can assume that the main cause of the rise in TSH levels in adults is progressive thyroid impairment. This is not surprising. On one side, it is reported that pro-inflammatory cytokines can inhibit sodium/iodide symporter (NIS) mRNA expression and iodide uptake [116, 129, 130], leading to a reduction in thyroid function. On the other side, the long-standing inflammation can lead to organ damage. However, these data are in contrast with a recent review by Gajda et al. The Authors described a two-fold higher prevalence of hyperthyrotropinaemia among obese patients, even if the data were gathered from a small number of articles and patients [131].

Differently from that reported for obese children, in adult patients, treatment with levothyroxine should also always be considered for mild hypothyroidism, in line with current guidelines [132]. The Endocrine Work-up in Obesity recommended in any case that hyperthyrotropinaemia should not be treated with the aim of reducing body weight [133].

The major limitation of the present review is the lack of some data which are, unfortunately, often not provided by the authors when requested. However, the large set of patients, the careful selection procedure, and detailed analysis of data strengthen these results.

In conclusion, we summarized the available studies on the association between obesity and thyroid disorders in children and in adults. There is an undeniable relationship between obesity and thyroid impairments, mainly caused by the state of obesity. Isolated hyperthyrotropinaemia is frequently seen in obese children, often followed by spontaneous resolution. BMI appears to be correlated with TSH levels in obese adults. Hyperthyrotropinaemia should never be treated in children and in adults with the aim of reducing body weight.

Authors' contributions

F.B.: review of literature, writing — original manuscript; E.G.: review of literature, formal analysis, writing — original manuscript; R.D.: review of literature, writing — review and editing; F.D.: review of literature, formal analysis, writing — review and editing; G.P.: conceptualization and methodology, writing — review and editing; I.P.: formal analysis, supervision, validation, and visualization; F.B.: conceptualization and methodology, supervision, validation, and visualization; C.C.: project administration, conceptualization and methodology, writing — review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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