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RESEARCH ARTICLE

Metabolic Syndrome, Thyroid Function and Autoimmunity - The PORMETS Study

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Abstract: ***Background:*** The prevalence of thyroid dysfunction and autoimmunity in the Portuguese population has not yet been estimated. However, the national prevalence of the metabolic syndrome remains high. The association of thyroid pathology with cardiovascular risk has been addressed but is still unclear. Our study aimed to evaluate the prevalence of thyroid dysfunction and autoimmunity and to assess the associations of thyroid-stimulating hormone and thyroid hormones and antibodies with metabolic syndrome, its components, and other possible determinants in a national sample.

Material and Methods: The present study included a subsample of 486 randomly selected participants from a nationwide cross-sectional study sample of 4095 adults. A structured questionnaire was administered on past medical history and socio-demographic and behavioural characteristics. Blood pressure and anthropometric measurements were collected, and the serum lipid profile, glucose, insulin, hs-CRP, TSH, FT4, FT3 and thyroid antibodies were measured.

Results: In our sample, the prevalence of hypothyroidism, hyperthyroidism and undiagnosed dysfunction was 4.9%, 2.5% and 72.2%, respectively. Overall, the prevalence of positivity for the thyroid peroxidase and thyroglobulin antibodies was 11.9% and 15.0%, respectively. A positive association was found between free triiodothyronine and metabolic syndrome (OR: 2.019; 95% CI: 1.196, 3.410). Additionally, thyroid peroxidase antibodies had a negative association with metabolic syndrome (OR: 0.465; 95% CI: 0.236, 0.917) and its triglyceride component (OR: 0.321; 95% CI: 0.124, 0.836).

Conclusion: The prevalence of undiagnosed thyroid dysfunction and autoimmunity was high. Thyroid peroxidase antibodies were negatively associated with metabolic syndrome and its triglyceride component, whereas the free triiodothyronine level was positively associated with metabolic syndrome.

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1. INTRODUCTION

Thyroid dysfunction is a common endocrine disorder that includes hypothyroidism and hyperthyroidism, and it may present as both overt and subclinical forms [1]. According to a recent meta-analysis on thyroid dysfunction in Europe [1], the mean prevalence of thyroid dysfunction was 3.82%, with 85.2% of cases displaying subclinical forms. Furthermore, according to the same study, the mean total prevalence of hypothyroidism and hyperthyroidism was 3.05% and 0.75%, respectively. The prevalence of undiagnosed hypothyroidism and hyperthyroidism was 4.94% and 1.72%, respectively.

Worldwide, the most common cause of thyroid disorder is iodine deficiency, which leads to goitre formation and a hypothyroidism state [2]. By contrast, Hashimoto thyroiditis, also known as chronic autoimmune or chronic lymphocytic thyroiditis, is the most prevalent form of autoimmune thyroid disease and is the leading cause of hypothyroidism in iodine-sufficient areas [2]. High levels of Thyroglobulin Antibodies (TgAb) and/or Thyroid Peroxidase Antibodies (TPOAb) are usually present in most patients.

Thyroid hormones have important effects on the cardiovascular system [3] and Cardiovascular Disease (CVD) risk,

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and mortality may be increased in hypothyroidism [4, 5]. In addition, thyroid autoimmunity may act as an independent CVD risk factor by promoting chronic inflammation [6, 7].

Metabolic Syndrome (MetS), a cluster of interrelated risk factors for CVD, is highly prevalent in Portugal [8]. According to the literature, thyroid hormones may have a major impact on all the components of MetS, and although the mechanisms remain unclear, the contribution of insulin resistance has been consistently reported [9]. In addition, thyroid hormones have a variety of effects on energy homeostasis, lipid and glucose metabolism and Blood Pressure (BP) [10]. By contrast, the role of thyroid autoimmunity in insulin resistance and in MetS risk is not yet well defined.

The aims of our study were to evaluate the prevalence of thyroid dysfunction and antibody positivity and to assess the associations of Thyroid-Stimulating Hormone (TSH), thyroid hormones and thyroid antibodies with metabolic syndrome, its components, and other possible determinants in a sample of the Portuguese population.

2. MATERIAL AND METHODS

PORMETS (Portuguese METabolic Syndrome), a population-based cross-sectional study, was designed to estimate the prevalence of MetS in mainland Portuguese population. This study, conducted from February 2007 to July 2009, included a sample of 4095 adults who were aged 18 years or older and registered in primary health care centres, and its study protocol has been previously explained [8]. According to Portuguese legislation, all citizens are enrolled in a primary health care centre of the National Health System. Briefly, 120 participants were randomly selected from the general practitioners' patient lists in each primary health care centre. Two primary health care centres were included for each of the 18 mainland administrative regions (districts), one located in the district's capital and the other in a non-urban area. All selected participants were specifically invited by the primary health care centres to be evaluated within the scope of the study and regardless of their state of health. Pregnant women were excluded [8].

A subsample, including five hundred participants, was randomly selected from the PORMETS study, as previously described [11]. After excluding 14 participants with missing values for TSH, 486 participants (281 women and 205 men) remained. Participants with previously diagnosed hypothyroidism (n=7) and those under treatment with L-thyroxine were included in the evaluation of the prevalence of thyroid dysfunction but were excluded from the remaining analyses to avoid the influence of medication on the results.

The sample size for this study was calculated, considering a margin of error of 5%, a confidence level of 95% and a response distribution of 50% for the proportion of participants with thyroid dysfunction or positivity of thyroid antibodies. The selected and non-included participants did not show significant differences in the analysed variables, except for systolic BP (p=0.047).

The methodological approach used in the study was previously described [8, 11]. A structured questionnaire was administered, in which information was collected on past medical history and socio-demographic and behavioural characteristics, including education level, smoking and drinking habits and physical exercise. In addition, BP and anthropometric measurements, including weight, height and Waist Circumference (WC), were collected. WC measurements were taken midway between the lower limit of the rib cage and the iliac crest. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in metres squared. Weight status was classified through the BMI according to the World Health Organization recommendations [12]: underweight (< 18.50 kg/m^2); normal range (18.50-24.99 kg/m^2); pre-obese (25.00-29.99 kg/m^2); obese (≥ 30 kg/m^2). Venous blood samples were drawn by trained nurses, after an overnight fast, and frozen and stored at -80°C. Insulin and high-sensitivity C-Reactive Protein (hs-CRP) were measured by an electrochemiluminescent immunoassay using a Cobas e411 automated analyser (Roche, Amadora, Lisboa, Portugal) and by a particle-enhanced immunonephelometric assay on a BN®II laser nephelometer (Siemens Healthcare, Amadora, Lisboa, Portugal), respectively. Conventional methods, with an Olympus AU5400® automated clinical chemistry analyser (Beckman-Coulter®, Oeiras, Lisboa, Portugal), were used for all other laboratory measurements [glucose, total cholesterol, triglycerides, HDL (high-density lipoprotein) cholesterol, TSH, Free Triiodothyronine (FT3), Free Thyroxine (FT4), TPOAb and TgAb]. Low-Density Lipoprotein (LDL) cholesterol was calculated by subtracting the value of HDL cholesterol and 20% of the value of triglycerides from the value of total cholesterol when its value was less than 400 mg/dL [13].

Insulin resistance was estimated according to the Homeostatic Model Assessment of insulin resistance (HOMA-IR) [14]. MetS was defined according to the Joint Interim Statement [15]. The *European* cut-off points were used to evaluate the WC component of the MetS: WC ≥ 88 cm in women and ≥ 102 cm in men. Euthyroidism was defined by normal TSH (0.4 to 3.99 mIU/L), FT4 (0.70 to 1.48 ng/dL) and FT3 (1.71 to 3.71 pg/mL) serum levels. Overt primary hypothyroidism was defined by serum TSH ≥ 4 mIU/L and serum FT4 below the lower range. Subclinical Hypothyroidism (SCH) was defined as a state of increased serum TSH, with circulating thyroid hormone within the reference range. SCH was divided into two categories according to TSH level: mildly increased TSH (4.0-10.0 mIU/L) and severely increased TSH (>10 mIU/L) [16]. Overt primary hyperthyroidism was defined as serum TSH <0.4 mIU/L and serum FT4 and/or FT3 above the normal range. Subclinical Hyperthyroidism (SHyper) was defined biochemically as serum TSH below the reference range, with normal thyroid hormone. According to its severity, SHyper was divided into two categories [17]: grade 1, which has low but detectable serum TSH (0.1-0.39 mIU/L), and grade 2, which has undetectable serum TSH (<0.1 mIU/L).

The presence of thyroid autoimmune disease was defined by the positivity of either of the measured thyroid antibodies. Positivity for TPOAb and TgAb was set to values greater than or equal to 5.61 and 4.11 IU/mL, respectively.

2.1. Statistical Analysis

Data are described as the mean values and Standard Deviations (SD). The chi-square test or *Fisher's* exact test was

used to compare proportions. Student's t-test was used to compare the means of continuous variables.

Multiple linear and unconditional logistic regression models were computed, with thyroid antibody positivity and TSH, FT4 and FT3 levels as independent variables. The respective regression coefficients and odds ratios (ORs), as well as their 95% confidence intervals (95% CIs), were estimated for several dependent variables after adjusting for sex and age. Dependent variables tested included age, sex, level of education, drinking and smoking habits, physical exercise, WC, BMI, systolic and diastolic BP, glucose, triglycerides, HDL cholesterol, total cholesterol, LDL cholesterol, insulin, HOMA-IR, hs-CRP, TSH, FT4, FT3, TPOAb, and TgAb. MetS and its five components were also tested in these models.

A two-tailed p-value of <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

3. RESULTS

Overall, 486 participants (281 women and 205 men), with a mean age (SD) of 53.5 (16.2) years 52.4 (16.3) years in women and 54.9 (16.0) years in men, were included in the present analysis. MetS was present in 37.8% of the participants; the prevalence was 40.7% in women and 33.8% in men (p=0.123). The mean (SD) TSH, FT4 and FT3 serum levels were 1.70 (2.13) mIU/L, 0.94 (0.19) ng/dL and 2.88 (0.43) pg/mL, respectively. Men had higher FT3 than women did (p=0.019).

The prevalence of previously diagnosed and undiagnosed thyroid dysfunction was 2.1% and 5.3%, respectively (Table **1**). The prevalence of hypothyroidism and hyperthyroidism, including subclinical forms, was 4.9% and 2.5%, respectively. According to our results, thyroid dysfunction was not diagnosed in 72.2% of the cases. Undiagnosed thyroid dysfunction was mainly subclinical (88.5%). Thyroid dysfunction was significantly more frequent in women (p=0.012). In addition, the prevalence of hypothyroidism was higher in participants over 50 years of age (p=0.027).

Table 1. Prevalence of thyroid dysfunction and of positive thyroid antibodies according to the type of dysfunction.

Thyroid Dysfunction	Prevalence n (%)	Men/Women n / n	Age Mean (SD)	TPOAb + n (%)	TgAb + n (%)	Any TAb n (%)	Both TAb n (%)
Any Hypo	24 (4.9) [a]	6/18	59.0 (14.8)	10 (41.7)	9 (37.5)	11 (45.8)	8 (33.3)
PD Hypo	7 (1.4)	0/7	59.6 (9.2)	4 (57.1)	3 (42.9)	4 (57.1)	3 (42.9)
UD Hypo	17 (3.5)	6/11	58.8 (16.8)	6 (35.3)	6 (35.3)	7 (41.2)	5 (29.4)
Overt Hypo	1 (0.2)	1/0	76.0 (-)	0	1 (100.0)	1 (100.0)	0
SCH - severe	3 (0.6)	0/3	52.0 (6.2)	3 (100.0)	2 (66.7)	3 (100.0)	2 (66.7)
SCH - mild	13 (2.7)	5/8	59.0 (18.2)	3 (23.1)	3 (23.1)	3 (23.1)	3 (23.1)
Euthyroidism	450 (92.6)	197/253	53.1 (16.2)	47 (10.4)	63 (14.0)	80 (17.8)	30 (6.7)
Any Hyper	12 (2.5) [b]	2/10	56.0 (15.8)	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)
PD Hyper	3 (0.6)	0/3	56.7 (26.1)	0	0	0	0
UD Hyper	9 (1.9)	2/7	55.8 (13.1)	1 (11.1)	1 (11.1)	1 (11.1)	1(11.1)
Overt Hyper	2 (0.4)	1/1	55.0 (12.7)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
SHyper grade 2	3 (0.6)	0/3	54.7 (18.8)	0	0	0	0
SHyper grade 1	4 (0.8)	1/3	57.0 (12.9)	0	0	0	0
Any TD	36 (7.4) [c]	8/28 [d]	58.0 (15.0)	11 (30.6)	10 (27.8)	12 (33.3)	9 (25.0)
PD TD	10 (2.1)	0/10	58.7 (14.5)	4 (40.0)	3 (30.0)	4 (40.0)	3 (30.0)
UD TD	26 (5.3)	8/18	57.7 (15.4)	7 (26.9)	7 (26.9)	8 (30.8)	6 (23.1)
Overt TD	3 (0.6)	2/1	62.0 (15.1)	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)
Subclinical TD	23 (4.7)	6/17	57.2 (15.7)	6 (26.1)	5 (21.7)	6 (26.1)	5 (21.7)
Total	486 (100)	205/281	53.5 (16.2)	58 (11.9) [e]	73 (15.0) [f]	92 (18.9) [g]	39 (8.0)

Two of the 486 participants included in the analysis had no TgAb assay (one with a prior diagnosis of hypothyroidism and one with normal thyroid function).
SD: standard deviation; TPOAb: thyroid peroxidase antibodies; TgAb: thyroglobulin antibodies; TAb: thyroid antibodies; Hypo: hypothyroidism; Hyper: hyperthyroidism; SCH: subclinical hypothyroidism; SHyper: subclinical hyperthyroidism; TD: thyroid dysfunction; PD: previously diagnosed; UD: undiagnosed.
[a] Prevalence of 2.4% and 6.8% (p=0.027) respectively below and above 50 years of age; [b] prevalence of 2.4% and 2.5% (p=0.948), respectively, below and above 50 years of age; [c] prevalence of 4.8% and 9.3% (p=0.062), respectively, below and above 50 years of age; [d] thyroid dysfunction was significantly more frequent in women: p=0.012; [e] 16.7% in women and 5.4% in men: p<0.001; [f] 21.5% in women and 6.8% in men: p<0.001; [g] 28.5% in women and 10.2% in men: p<0.001.

The diagnosis of autoimmune thyroid disease was made in 18.9% of the participants. The overall prevalence of positivity for TPOAb or TgAb was 11.9% and 15.0%, respectively. In addition, both antibodies were positive in 8.0% of the study sample. Positivity for TPOAb or TgAb was approximately 3 times higher in women ($p<0.001$). Furthermore, the participants with thyroid dysfunction presented a higher positivity for TPOAb ($p<0.001$) and TgAb ($p=0.021$) than did the euthyroid subjects. The prevalence of TPOAb and TgAb positivity by type of thyroid dysfunction is presented in Table **1**.

After adjusting for sex and age, the TSH level was not associated with MetS, its components, HOMA-IR, serum insulin, or serum hs-CRP (Table **2**). However, the TSH level was positively associated with physical exercise (OR: 1.183; 95% CI: 1.020, 1.371), TgAb positivity (OR: 1.295; 95% CI: 1.085, 1.546) and TPOAb positivity (OR: 1.161; 95% CI: 1.015, 1.327). By contrast, the TSH level was negatively associated with FT4 level (β: -009; 95% CI: -0.017, -0.002).

The serum FT4 level (Table **2**) showed no association with MetS, its components, HOMA-IR, serum insulin, or serum hs-CRP. However, FT4 level was positively associated with FT3 (β: 0.034; 95% CI: 0.005, 0.064) and negatively associated with TSH (β: -0.009; 95% CI: -0.017, -0.002).

A positive association was found between FT3 level (Table **2**) and MetS (OR: 2.019; 95% CI: 1.196, 3.410), but not with its individual components. Serum FT3 level was also positively associated with the male gender (OR: 1.859; 95% CI: 1.176, 2.940), insulin (β: 2.042; 95% CI: 0.630, 3453), triglycerides (β: 19.895; 95% CI: 6.951, 32.839) and FT4 (β: 0.934; 95% CI: 0.005, 0.064) and was negatively associated with age (β: -9.147; 95% CI: -12.418, -5.877).

TPOAb positivity (Table **3**) showed a negative association with MetS (OR: 0.465; 95% CI: 0.236, 0.917) and its triglyceride component (OR: 0.321; 95% CI: 0.124, 0.836). By contrast, TgAb was not associated with MetS or its components. The thyroid antibody levels presented a significant positive association with each other OR: 21.933 (95% CI: 10.968, 43.863) and OR: 22.128 (95% CI: 11.042, 44.343) for TPOAb and TgAb positivity, respectively and a negative association with male gender OR: 0.294 (95% CI: 0.147, 0.558) and OR: 0.282 (95% CI: 0.152, 0.524), for TPOAb and TgAb positivity, respectively. Other than the associations with serum TSH level, thyroid antibodies did not show further significant associations. Namely, we did not find any associations with HOMA-IR, serum insulin, or serum hs-CRP.

Table 2. Associations of TSH and thyroid hormones levels with metabolic syndrome, its components and other variables

-	-	TSH	FT4	FT3
Categorical variables	Prevalence (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metabolic syndrome	37.9	0.935 (0.833, 1.049)	0.503 (0.125, 2.032)	2.019 (1.196, 3.410)*
WC component	49.3	0.955 (0.864, 1.056)	0.731 (0.218, 2.450)	1.374 (0.855, 2.207)
BP component	64.4	0.955 (0.861, 1.060)	1.631 (0.398, 6.676)	1.203 (0.712, 2.031)
TG component	23.4	0.874 (0.712, 1.073)	0.689 (0.188, 2.533)	1.575 (0.928, 2.675)**
HDL-C component	55.1	0.989 (0.909, 1.077)	1.060 (0.396, 2.841)	1.099 (0.709, 1.705)
Glucose component	22.6	0.909 (0.764, 1.081)	0.699 (0.173, 2.814)	1.227 (0.697, 2.159)
Gender (men)	42.8	1.011 (0.929, 1.101)	1.040 (0.391, 2.765)	1.859 (1.176, 2.940)*
Physical exercise	28.5	1.183 (1.020, 1.371)*	0.900 (0.300, 2.705)	1.285 (0.790, 2.089)
Weight status Pre-obese	42.6	0.938 (0.845, 1.041)	0.500 (0.148, 1.691)	1.449 (0.866, 2.425)
Obese	24.3	0.926 (0.802, 1.069)	0.205 (0.033, 1.279)	1.435 (0.798, 2.579)
TPOAb positivity	11.3	1.161 (1.015, 1.327)*	2.800 (0.887, 8.840)	0.889 (0.458, 1.722)
TgAb positivity	14.6	1.295 (1.085, 1.546)*	1.846 (0.553, 6.164)	1.040 (0.575, 1.879)
Continuous variables	Median (P25, P75)	β (95% CI)	β (95% CI)	β (95% CI)
Age (years)	53 (41, 67)	0.516 (-0.164, 1.196)	4.840 (-3.034, 12.713)	-9.147 (-12.418, -5.877)*
WC (cm)	94.0 (85.5, 102.0	-0.157 (-0.628, 0.314)	-1.721 (-7.175, 3.732)	0.969 (-1.430, 3.368)
BMI (kg/m^2)	27.1 (24.1, 29.8)	-0.088 (-0.279, 0.102)	-1.796 (-3.998, 0.406)	0.433 (-0.539, 1.405)
Systolic BP (mmHg)	131 (119, 147)	0.508 (-0.274, 1.290)	1.483 (-7.585, 10.550)	1.029 (-2.959, 5.017)
Diastolic BP (mmHg)	79 (70, 87)	0.142 (-0.332, 0.616)	-3.124 (-8.591, 2.342)	0.306 (-2.109, 2.721)
TG (mg/dL)	103.0 (75.0, 143.0)	-1.788 (-4.349, 0.772)	-8.104 (-37.830, 21.622)	19.895 (6.951, 32.839)*
HDL-C (mg/dL)	47.0 (39.0, 55.0)	0.210 (-0.288, 0.708)	-2.763 (-8.526, 2.999)	0.778 (-1.758, 3.314)
LDL-C (mg/dL)	133.0 (109.8, 152.7)	-1.243 (-2.790, 0.304)	-3.555 (-21.506, 14.395)	0.269 (-7.587, 8.126)
Glucose (mg/dL)	85.5 (77.0, 97.0)	-0.937 (-2.112, 0.238)	0.177 (-13.550, 13.905)	0.080 (-5.939, 6.100)

Table (2) contd….

-	-	TSH	FT4	FT3
HOMA	1.725 (1.070, 2.850)	-0.065 (-0.160, 0.030)	-0.004 (-1.111, 1-103)	0.425 (-0.059, 0.908)***
Insulin (µlU/mL)	8.0 (5.3, 12.2)	-0.163 (-0.442, 0.117)	0.165 (-3.078, 3.408)	2.042 (0.630, 3.453)*
hs-CRP (mg/L)	0.160 (0.070, 0.370)	0.001 (-0.022, 0.023)	0.155 (-0.102, 0.411)	0.058 (-0.055, 0.171)
TSH (mlU/mL)	1.390 (0.930, 1996)		-1.252 (-2.289, -0.214)*	-0.060 (-0.519, 0.399)
FT4 (ng/dL)	0.920 (0.860, 0.990)	-0.009 (-0.017, -0.002)*		0.034 (0.005, 0.064)*
FT3 (pg/mL)	2.900 (2.657, 3.130)	-0.002 (-0.020, 0.015)	0.320 (0.045, 0.595)*	

Logistic and linear regression models adjusted for age and sex. This analysis included 479 subjects. Participants with previously diagnosed hypothyroidism or under treatment with L-thyroxine were excluded (n=7). The reference class for weight status was "normal range".
BMI: body mass index; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; WC: waist circumference; BP: blood pressure; TG: triglycerides; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; hs-CRP: high-sensitivity C-reactive protein; TPOAb: thyroid peroxidase antibodies; TgAb: thyroglobulin antibodies.
* $p < 0.05$; ** $p = 0.092$; *** $p = 0.085$.

Table 3. Associations of thyroid antibody positivity with metabolic syndrome, its components and other variables.

-		TPOAb (+)	TgAb (+)
Categorical variables		OR (95% CI)	OR (95% CI)
Metabolic syndrome		0.465 (0.236, 0.917)*	0.841 (0.474, 1.493)
WC component		0.984 (0.528, 1.836)	0.893 (0.513, 1.552)
BP component		0.788 (0.394, 1.575)	1.019 (0.546, 1.904)
TG component		0.321 (0.124, 0.836)*	0.710 (0.361, 1.394)
HDL-C component		0.792 (0.440, 1.425)	1.309 (0.764, 2.243)
Glucose component		0.637 (0.288, 1.410)	0.764 (0.377, 1.547)
Gender (men)		0.294 (0.147, 0.558)*	0.282 (0.152, 0.524)*
Weight status	Pre-obese	0.900 (0.442, 1.822)	0.969 (0.516, 1.823)
	Obese	1.400 (0.667, 2.936)	1.370 (0.698, 2.687)
TPOAb positivity		-	22.128 (11.042, 44.343)*
TgAb positivity		21.933 (10.968, 43.863)*	-
Continuous variables		β (95% CI)	β (95% CI)
Age (years)		3.202 (-1.458, 7.862)	0.876 (-3.324, 5.076)
WC (cm)		0.546 (-2.682, 3.773)	0.554 (-2.345, 3.452)
BMI (kg/m^2)		0.190 (-0.433, 2.176)	0.170 (-0.352, 1.994)
Systolic BP (mmHg)		-3.113 (-8.471, 2.245)	0.227 (-4.623, 5.076)
Diastolic BP (mmHg)		-1.459 (-4.707, 1.708)	0.195 (-2.742, 3.132)
TG (mg/dL)		-0.055 (-0.231, 0.120)	-0.039 (-0.197, 0.119)
LDL-C (mg/dL)		0.969 (-9.653, 11.590)	-4.384 (-13.925, 5.158)
HDL-C (mg/dL)		0.009 (-0.025, 0.043)	-0.007 (-0.037, 0.024)
Glucose (mg/dL)		0.003 (-0.077, 0.084)	0.015 (-0.058, 0.088)
HOMA		-0.036 (-0.686, 0.615)	0.267 (-0.321, 0.855)
Insulin (µlU/mL)		0.369 (-1.547, 2.285)	0.751 (-0.971, 2.473)
hs-CRP (mg/L)		-0.047 (-0.199, 0.105)	0.037 (-0.099, 0.174)

Logistic and linear regression models adjusted for age and sex. This analysis included 479 subjects. Participants with previously diagnosed hypothyroidism and under treatment with L-thyroxine were excluded (n=7). The reference class for weight status was "normal range".
BMI: body mass index; WC: waist circumference; BP: blood pressure; TG: triglycerides; HDL-C: HDL cholesterol; LDL cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; hs-CRP: high-sensitivity C-reactive protein; TPOAb: thyroid peroxidase antibodies; TgAb: thyroglobulin antibodies.
* $p < 0.05$.

4. DISCUSSION

4.1. Thyroid Dysfunction Prevalence

Compared to other European studies [1], we found a high prevalence of thyroid dysfunction. We also found a higher prevalence than found in a United States study [18] that showed a prevalence of hypothyroidism and hyperthyroidism of 4.6% (0.3% overt and 4.3% subclinical) and 1.3% (0.5% overt and 0.7% subclinical), respectively. The prevalence of thyroid dysfunction may vary according to the dietary iodine intake. The data from Portugal point to a borderline iodine intake, particularly in pregnant women and school populations [19]. Borderline iodine deficiency has been related to a higher prevalence of hyperthyroidism [20] and may help explain the high prevalence of hyperthyroidism observed in our study.

According to our data, undiagnosed thyroid dysfunction was present in 5.3% of the participants (3.5% in hypothyroidism and 1.9% in hyperthyroidism). Approximately 72.2% of individuals with thyroid dysfunction were not diagnosed. The prevalence of undiagnosed hypothyroidism and hyperthyroidism was, respectively, lower and higher compared to European findings [1]. According to a United States study [18], the prevalence of undiagnosed hypothyroidism and hyperthyroidism was 4.1% and 0.4%, respectively.

Although the structured questionnaire administered included questions about drug treatment, the data were incomplete in many participants. Thus, with the exception of L-thyroxine treatment, the interference of drugs with action on thyroid function cannot be excluded.

The associations of TSH with FT4 and with thyroid antibodies were expected. In addition, the associations between FT4 and FT3 are in agreement with thyroid physiology. The effect of physical exercise on TSH level has previously been described but remains controversial [21]. We also found an association of FT3 with age and gender. The finding of decreasing values of FT3 with age is supported by the literature [22]. In addition, higher FT3 has been reported in men [23].

4.2. Thyroid Antibody Prevalence

The prevalence of autoimmune thyroid disease, given by the positivity for TPOAb or TgAb, was high in our sample, even among participants with normal thyroid function. Epidemiological studies on thyroid antibody prevalence in Europe [24] are difficult to compare due to the different epidemiological and analytical approaches used. According to a recent review [25], the prevalence of positive TPOAb in European studies varied from 13.9% to 16.9% in women and between 2.9% and 7.3% in men. In addition, the NHANES III study showed a prevalence of positivity for TPOAb and TgAb of 13.0% (17% in women and 8.7% in men) and 11.5% (15.2% in women and 7.6% in men), respectively [18].

As expected, positive thyroid antibodies showed a significant positive association with each other and a negative association with the male gender. The high prevalence of thyroid antibody positivity is well documented in women [26]. Genetic abnormalities related to the X chromosome, parity, steroid hormones, miRNA expression differences and inflammation through leptin and other adipokines have been identified as possible causes. Thyroid antibodies also showed a positive association with TSH level, supporting the association of autoimmunity with hypothyroidism.

4.3. Associations of Thyroid Function and Autoimmunity with Metabolic Syndrome, its Components, and Other Possible Determinants

To the best of our knowledge, this is the first national study approaching thyroid function and autoimmunity and its associations with MetS in a sample of the mainland Portuguese population. We did not identify any association between TSH level and MetS or its components. Observational studies concerning the association between SCH and MetS have shown contradictory results. In addition, two recent meta-analyses also failed to clarify this problem; one of them found a positive association [27], whereas no association was found in the other study [28]. CVD risk and mortality are increased in SCH [4, 5], particularly among subjects younger than 65 years and in those with a TSH concentration greater than or equal to 10 mIU/L. However, a normal TSH level is not associated with an increase in CVD risk or mortality [29].

Similar to TSH, FT4 showed no association with MetS or its components. The contribution of low normal FT4 to the development of CVD and MetS remains controversial [3, 30]. A large study conducted in South Korea that included 41.196 participants found no association between serum FT4 and MetS [30]. Another large study in the Netherlands that included 26,719 participants found an association only in men [31]. However, the association of MetS with low normal FT4 has been documented in some epidemiological surveys [32]. In addition, several studies have found associations of the FT4 level with some of the components of MetS [30, 31, 32], but with some disagreement in the results. Furthermore, no association was observed between the FT4 level and the HOMA-IR or insulin levels. According to the literature, low normal FT4 levels have been associated with insulin resistance in some studies [32], while in other studies, no such association was found [33].

Higher FT3 was associated with an increased prevalence of MetS. This positive association has been increasingly reported in the literature [34, 35]. Despite this association, we did not find any association between the individual components of MetS. However, the positive association with the triglyceride component almost reached statistical significance ($p=0.092$). In addition, serum FT3 was positively associated with triglycerides ($p=0.003$). One possible explanation for the lack of associations may be that the sample size was insufficient to achieve statistical significance. In fact, there is a growing body of evidence for the association of FT3 blood levels and the triglyceride component in euthyroid subjects [34, 35].

Furthermore, the FT3 serum levels presented a positive association with insulin ($p=0.005$). Although a significant association with HOMA was not found, its p-value was close to statistical significance ($p=0.085$). Previous studies have shown a significant positive association of FT3 blood level with insulin resistance in clinical [36] and subclinical thyro-

toxicosis [37] and in euthyroid subjects [38]. The blood level of FT3 may be influenced by thyroid secretion and its peripheral conversion from Thyroxine (T4), especially through type 2 deiodinase. Although the mechanisms of elevation of FT3 in individuals in euthyroidism are not clear, the contribution of insulin resistance and/or hyperinsulinism, particularly through an increase in type 2 deiodinase activity, cannot be ruled out [38]. Obesity, particularly abdominal obesity, has also been implicated in increased type 2 deiodinase activity. In addition, an increase in FT3 could correspond to an adaptive mechanism of increasing resting energy expenditure to limit fat deposits [39]. On the other hand, a primary contribution of triiodothyronine (T3) to insulin resistance has been suggested [39]. Several adipocytokines may mediate thyroid hormone actions on insulin sensitivity through complex interactions [40]. However, in view of the physiological actions of thyroid hormones [41], T3 resistance cannot be ruled out in euthyroid subjects with high normal levels of the hormone. The presence of insulin or T3 resistance may explain the hypertriglyceridemia found in euthyroid individuals with high normal T3.

In addition, no association of hs-CRP with serum levels of TSH, FT4 or FT3 was found. These results are in agreement with the literature [42] and suggest that there is no direct action of the thyroid function indicators on this inflammatory marker.

According to our results, and considering both thyroid antibodies, only TPOAb positivity showed a negative significant association with MetS and its triglyceride component. No association of TPOAb with the markers of insulin resistance was found, suggesting a different mechanism for the associations. However, no association was found between hs-CRP and thyroid antibodies, which is in agreement with the limited evidence available [43] and does not support a role for inflammation. Evidence on the link between thyroid autoimmunity and MetS (or its components) is also lacking. Positivity for thyroid antibodies has not been associated with insulin resistance [44] or with MetS and its components, specifically in obesity [45] and in postmenopausal women [46].

Although some studies have suggested an increased risk of coronary heart disease [47, 48] and stroke [49] in autoimmune thyroiditis, the presence of TPOAb does not appear to correlate with CVD risk in patients with SCH [50]. The analysis of individual participant data from several studies [51] and a 20-year follow-up of the original Whickham survey [52] showed that the risk of coronary heart disease is likely mediated by thyroid dysfunction, without an independent contribution from thyroid autoimmunity. The negative association of TPOAb positivity with the triglyceride component is partially supported by a previous report of low fasting serum triglycerides in autoimmune thyroiditis and other autoimmune diseases [53]. Ghrelin, a hormone with important actions in the regulation of appetite, energy balance, adiposity and autoimmunity [54], may have a negative association with blood levels of thyroid antibodies [55, 56]. Inhibition of ghrelin's action may be accompanied by lower circulating triglycerides [57]. The different behaviour of the two thyroid antibodies may eventually be explained on the basis of their immunological differences [58].

In the present study, no information was collected on menopause status, a risk factor for MetS [59]. The sample size may have conditioned the statistical significance of some of our results. Future studies with larger sample sizes may clarify some of the doubts raised. Finally, due to the cross-sectional design of our study, a cause-effect relationship cannot be established for the associations described.

CONCLUSION

Our study showed a high prevalence of thyroid dysfunction, namely, subclinical and undiagnosed, supporting previous data. Thyroid antibody positivity was high in our sample, even among participants with normal thyroid function, thus reinforcing the role of autoimmunity in thyroid dysfunction. In addition, no association was observed between TSH or FT4 and MetS or its individual components. By contrast, the FT3 level presented a positive association with MetS and the insulin and triglyceride levels, thus strengthening its plausible role in CVD risk. Finally, according to our data, a negative association was found between thyroid autoimmunity, as represented by TPOAb, and MetS and its triglyceride component. These associations need further investigation.

LIST OF ABBREVIATIONS

95% CI	=	95% Confidence Interval
BMI	=	Body Mass Index
BP	=	Blood Pressure
CVD	=	Cardiovascular Disease
FT3	=	Free Triiodothyronine
FT4	=	Free Thyroxine
HDL	=	High-Density Lipoprotein
HOMA-IR	=	Homeostatic Model Assessment-Insulin Resistance
hs-CRP	=	High-Sensitivity C-Reactive Protein
Hyper	=	Hyperthyroidism
Hypo	=	Hypothyroidism
LDL	=	Low-Density Lipoprotein
MetS	=	Metabolic Syndrome
OR	=	Odds Ratio
PD	=	Previously Diagnosed
SCH	=	Subclinical Hypothyroidism
SD	=	Standard Deviation
SHyper	=	Subclinical Hyperthyroidism
T3	=	Triiodothyronine
T4	=	Thyroxine
TD	=	Thyroid Dysfunction
TgAb	=	Thyroglobulin Antibodies
TPOAb	=	Thyroid Peroxidase Antibodies
TSH	=	Thyroid-Stimulating Hormone
UD	=	Undiagnosed
WC	=	Waist Circumference

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The PORMETS study was approved by all the five continental Portuguese Regional Health Administrations, the Ethics Committee of the São João Hospital E.P.E., Porto, Portugal, in the 27th February 2007 and the Portuguese Data Pro-

tection Authority (CNDP:1053/2007). The Clinical Director of each health care center also provided authorization .

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The research was performed in human in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

All participants gave their written informed consent.

CONFLICT OF INTEREST

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