FAT DISTRIBUTION AND METABOLIC PROFILE IN SUBJECTS WITH HASHIMOTO'S THYROIDITIS

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Abstract

Context. Previous studies have associated overt/subclinical hypothyroidism and obesity but have failed to confirm a causative relationship between them. Confusion is even more for subjects with Hashimoto's Thyroiditis (HT).

Objective. In this study, we aimed to evaluate the fat distribution and metabolic profile of subjects with euthyroid HT as well as to establish an appropriate cut-off level of TSH for the development of metabolic syndrome (Mets) in both groups.

Patients and Methods. All subjects were euthyroid whether under levothyroxine replacement or not. We recruited 301 volunteers (99 with HT and 202 without thyroid autoimmunity). Together with some metabolic variables, we measured the waist circumference, hip circumference, neck circumference manually; the total body fat with a body composition analyzer; and the visceral fat/ trunk fat percentage via abdominal bioelectrical impedance analysis.

Results. A significant positive correlation was established between TSH levels and insulin, fasting plasma glucose, HOMA-IR and body mass index ($r=0.28$; $p<0.001$; $r=0.27$; $p<0.05$; $r=0.32$; $p<0.001$; $r=0.13$; $p<0.05$ respectively). The prevalence of Metabolic Syndrome (Mets) was comparable in HT and control groups (27.3% vs. 30.7%; $p>0.05$). The prevalence of Mets was similar when HT subjects using levothyroxine or HT subjects with accompanying thyroid nodules were taken into consideration. Similarly, anthropometric and metabolic parameters were similar in both the HT group and the control group.

We were unable to establish the TSH cut-off level by ROC analysis with desired sensitivity and specificity (AUC: 0.563 with 95% C.I. $p=0.35$; standard error 0.76).

Conclusions. Although weight gain is frequently encountered in subjects with HT, such subjects with thyroid function tests in the euthyroid range have a similar prevalence of Mets and similar metabolic and anthropometric measurements compared to subjects without autoimmunity.

Key words: Hashimoto's thyroiditis, metabolic syndrome, visceral fat.

INTRODUCTION

The Relationship of thyroid function with Obesity and Metabolic syndrome (Mets) is far from being fully understood, and researchers present new data each day.

Hypothyroid subjects are expected to have a lower basal metabolic rate, and this has been kept responsible for the development of obesity for years (1, 2). Both subclinical and overt hypothyroidism has been established to associate with higher body mass index (BMI) and obesity (3). Also, small changes in thyroid function tests, even in the normal reference range, contribute to weight gain and development of regional obesity (4). Accordingly, small changes in Thyroid Stimulating Hormone (TSH), resulting from small changes in the levothyroxine dosages (LT4), triggers significant changes in resting energy expenditure (5).

However, even after we establish euthyroidism via levothyroxine (LT4) replacement therapy, obesity seems to persist (6, 7). Interestingly, a recent study concluded that LT4 replacement is associated with adiposity independent from TSH levels (7).

Many studies performed on different populations have accused insulin resistance and increased fat percentage rather than hypothyroxinemia itself for the development of obesity in subjects with hypothyroidism (8-11). Pratz-Puig *et al.* demonstrated that a free thyroxine level (FT4) close to the lower limit is related to increased visceral fat and insulin resistance (8).

Another finding complicating the understanding of the relationship of hypothyroidism and obesity is the positive correlation between TSH and body weight. Many authors have attributed this relationship to the adipokine leptin. Leptin regulates thyrotropin-releasing hormone (TRH) gene expression in the paraventricular nucleus and TSH, in turn, increases leptin production

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from adipose tissue. Leptin also regulates the conversion of T4 to T3 (12, 13). A recent study performed including obese males, and obese postmenopausal females demonstrated that leptins' pro-immunologic effect might even contribute to the development of autoimmune thyroid dysfunction (14).

Individuals with elevated TSH levels have a tendency to gain weight. On the other hand, overweight and obese individuals have a higher TSH level than those being normal weight. This data may complicate the diagnosis of a possible mild thyroid dysfunction in overweight and obese patients (15-17). Interestingly, mild elevations in FT3 levels are reported in obese individuals (10).

Thus, it seems that a two-dimensional relationship exists between obesity and thyroid dysfunction. Debate exists whether thyroid dysfunction leads to insulin resistance or whether obesity itself alters thyroid function.

Hashimoto's Thyroiditis (HT) is the most frequent reason of hypothyroidism and subclinical hypothyroidism in developed countries (17). These patients frequently complain about having difficulties in losing weight. Researchers have not been able to enlighten whether euthyroid HT cases, under LT4 replacement therapy or not, have an altered metabolic state or fat distribution increasing their tendency for weight gain.

In this study, we aimed to evaluate the fat distribution and metabolic profile of subjects with euthyroid HT. All subjects were euthyroid either under levothyroxine replacement therapy or not.

SUBJECTS AND METHODS

This study is approved by the 'Baskent University Medical and Health Sciences research and ethical Committees' and supported by the Baskent University Research Fund. It was assigned a project code number KA 11/196.

Before the study, a statistical calculation revealed that at least 300 cases would be sufficient with 85.72% reliability.

Study design and patients

In this cross-sectional survey, we included participants without thyroid autoimmunity attending Baskent University Ankara Hospital and Umitkoy outpatient Endocrinology departments between March 2011 and March 2012.

All volunteers attending this study provided

written informed consent. All individuals in this study were euthyroid having TSH levels, FT3 and FT4 levels in the normal laboratory ranges (TSH: 0.35-5.0 mIU/L; FT3 1.71-3.71 pg/ml; FT4 0.7-1.48 ng/dl). Subjects who were positive for Thyroid Peroxidase antibodies (TPO-ab) or Thyroglobulin antibodies (Tg-ab) or both with thyroid parenchymal heterogeneity and reduced echogenicity detected via ultrasonography were diagnosed as HT (18). Cases with identified thyroid nodules were confirmed to be benign with a fine needle aspiration biopsy if indicated by the researcher.

Volunteers with HT or NG were patients who were under the routine follow-up of Baskent University Hospital Endocrinology Outpatient Clinic or who were newly diagnosed at the time of enrolment.

Exclusion criteria were overt hypothyroidism, pregnancy, renal failure, hepatic failure, cardiac insufficiency, previous diagnosis of diabetes, history of abdominal surgery, history of thyroidectomy, history of malignancy, usage of rosiglitazone, pioglitazone, metformin, antilipidemic therapy, antipsychotic therapy, anti depressant therapy, anti diabetic therapy or hormone replacement therapy, amiodarone therapy, lithium therapy, beta blockers, herbal products and any other drug that could interfere with thyroid function or TSH levels. Cases with TSH levels <0.35 mIU/L and > 5 mIU/L were not eligible for this study. The control group was also recruited in the same manner and consisted of subjects with no evidence of autoimmune thyroiditis (i.e. normal thyroid ultrasound, negative autoantibodies, and normal thyroid function tests).

We performed case-based matching in the two groups. We matched the study groups according to age (16-25 years, 26-35 years, 36-45 years, 46-55 years and 56-65 years), body mass index (<25 kg/m², 25-29.9 kg/m², >30 kg/m²), sex, smoking habits (active smoker, non-smoker, ex-smoker), coexistence of thyroid nodules and menopausal status in female participants (premenopausal *versus* postmenopausal). Permanent cessation of menses defines menopause.

Initially, we managed to recruit 108 participants with HT and 228 subjects as controls. After applying the matching process, we completed the study with 99 HT and 202 controls.

We aimed to establish the presence of Metabolic Syndrome (Mets) in both groups and correlate thyroid function tests with some metabolic and anthropometric variables. We also aimed to analyze some subgroups of subjects with HT (Nodular *vs.* non-nodular and LT4 on *vs.* LT4 off). Those using LT4 had been using the same dose for at least six months before being recruited.

Anthropometric measurements and body fat measurements

We measured the body weight to the nearest kilogram and height to the nearest centimeter. We calculated the body mass index by dividing the weight in kilograms by height in meters squared (kg/m^2). The waist circumference was measured when the participant was standing upright with a tape measure over the umbilicus (Manually measured waist circumference). We also measured the waist circumference via the AB-140 viscan device in the supine position (Tanita Corp, Tokyo, Japan) (Device measured waist circumference). We measured the hip circumference over the most pronounced area of the buttocks with a tape measure. We measured the neck circumference over the laryngeal prominence parallel to the ground again with a tape measure. We calculated the waist/hip ratio by dividing the manually measured waist circumference by the hip circumference. The same investigator took all anthropometric measurements to avoid inter-individual variations. We performed all measurements after the participants had at least 10 hours fasting period. Visceral fat levels (VFL) and Trunk fat percentages (TF %) were measured by directly by abdominal bioelectrical impedance (BIA) (AB-140 viscan, Tanita Corp, Tokyo, Japan) by placing a belt containing four conductors over the abdomen. Every measurement took approximately 30 seconds for each participant. Total body fat mass, fat percentage (Fat %) and total body water percentage (TBW%) was measured by a body composition analyzer (TBF-300, Tanita Corp, Tokyo, Japan) at the same visit with abdominal BIA measurements. Participants were informed not to intake alcohol 24 hours before the measurements and not to intake caffeine including beverages 4 hours before the measurements according to the manufacturer's instructions. All participants had light clothing, and we removed earrings, rings, bracelets and any metal which could influence the results before the measurement.

Blood sampling and laboratory assays

We evaluated Fasting plasma glucose (FPG; mg/dL), fasting insulin ($\mu\text{U/mL}$), triglycerides (TG; mg/dL), high-density lipoprotein cholesterol (HDL-C; mg/dL), free Triiodothyronine (FT3; pg/mL), free Thyroxine (FT4; ng/dL), Thyroid-stimulating hormone (TSH; mIU/L), Tg-ab (IU/mL), TPO-ab (IU/mL) via a venous puncture. We performed FT4, FT3, TSH and insulin measurements by Immunochemiluminescent assay (ICMA, Architect i2000, Abbott). We performed Tg-ab and TPO-ab measurements by ICMA (Immulite

2000, Siemens). The serum glucose level was measured 120 minutes after a 75-gram glucose load. Homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated by the formula $\text{FPG} \times \text{fasting insulin} / 405$. We measured the patient's blood pressure with a sphygmomanometer after 30 minutes resting period.

Thyroid ultrasonography

The same investigator performed thyroid ultrasonography (Logiq 5 Pro, GE medical systems, WI, USA) with a 10 MHz probe. We evaluated the presence of a thyroid nodule and parenchymal structure. Cases with thyroid nodules were offered fine needle aspiration cytology (FNAC) according to the American Thyroid Association (ATA) 2009 guidelines (19).

We used the National Cholesterol Education program (NCEP) Adult Treatment Panel III criteria for diagnosing the presence of Mets (Waist circumference $> 88\text{cm}$ for females and $> 102\text{ cm}$ for males, triglyceride $> 150\text{ mg/dL}$, HDL-C $< 50\text{ mg/dL}$ for females and $< 40\text{mg/dL}$ for males, blood pressure $\geq 130/85\text{ mmHg}$, impaired fasting glucose or impaired glucose tolerance or overt diabetes). Three positive criterion confirmed the diagnosis of Mets (20).

Statistical analysis

We used SPSS for Windows v16.0 (Statistical Package for Social Sciences, Chicago, IL) software program for statistical analysis. We used the Chi-square test to compare the ratios between groups. We used Pearson correlation analysis for correlating variables. We used the independent samples t-test to compare means between groups. We used the Mann-Whitney U test for comparing the means of non-parametric values. We used the Kolmogorov-Smirnov test of normality to confirm the normal variation of the data. A p level < 0.05 was defined as being statistically significant.

RESULTS

We confirmed that our data had a normal distribution by the Kolmogorov-Smirnov test of normality. We included 202 participants with no evidence of autoimmune thyroiditis (control group) and 99 participants with HT in the study. Two hundred and twenty-four were females (74.4%), and 77 were male (25.6%). The female/male ratio was 3:1. The average age was 40.42 ± 11.39 years (range 16-65) and the average BMI $28.2 \pm 13.4\text{ kg/m}^2$ (range 18-45 kg/m^2). The general properties of the study population matched for sex, age group, body mass index, smoking habits,

the presence of thyroid nodules and female menopausal status are seen in Table 1.

Correlations between TSH and anthropometric/ metabolic parameters

FT3 and FT4 levels were within the normal reference ranges for all participants in both groups. TSH levels correlated positively with fasting insulin levels, FPG, HOMA-IR and BMI ($r=0.28$; $p<0.001$; $r=0.27$; $p<0.05$; $r=0.32$; $p<0.001$; $r=0.13$; $p<0.05$ respectively). Although weak, we determined that the strongest correlation was between TSH and HOMA-IR. We could not establish any significant correlation between TSH and HDL-C, triglycerides, fat %, VFL, trunk Fat %, manual waist circumference, device measured waist circumference, hip circumference, neck circumference and waist/hip ratio.

When we took the HT group into consideration, we established similar correlations between TSH and insulin, FBG, HOMA-IR whereas no correlations between TSH and BMI.

FT3 levels correlated positively with visceral fat level ($r=0.341$; $p<0.05$), FPG ($r=0.281$; $p<0.05$),

FT4 ($r=0.44$; $p<0.001$) and triglycerides ($r=0.34$; $p<0.05$) and negatively with TSH ($r=-0.42$; $p<0.001$). FT4 levels correlated positively with FPG ($r=0.28$; $p<0.05$); FT3 ($r=0.44$; $p<0.001$) and negatively with TSH ($r=-0.42$; $p<0.001$).

Prevalence of Metabolic Syndrome in the study groups

The total prevalence of Mets was 29.6% in the study population. The prevalences were similar in both groups ($p>0.05$) (Table 2) (HT: 27.3 %; control 30.7%; $p>0.05$).

The prevalence of Mets was 18.4% in HT subjects not using levothyroxine and 34% in subjects under levothyroxine replacement therapy. The comparison was statistically similar ($p>0.05$). The prevalence of Mets of HT subjects with accompanying thyroid nodules was 30.6% whereas the prevalence was 19.6% in HT subjects without thyroid nodules, statistically similar ($p>0.05$). The prevalences of Mets was also similar when compared between nodular and non-nodular controls (30.2% vs. 28.6%; $p>0.05$).

Table 1. General properties of the study group according to sex, age group, BMI group, smoking habits, presence of thyroid nodules and menopausal status

	Control n (%)	HT n (%)	P value (χ^2)
Sex	F: 145 (71.8%)	F: 79 (79.7%)	NS
	Pre: 36/145	Pre: 20/79	
	Post: 109/145	Post: 59/79	
	M: 57 (28.2%)	M: 20 (20.3%)	
Age	16-25: 15 (7.4%)	16-25: 9 (9.1%)	NS
	26-35: 52 (25.7%)	26-35: 25 (25.2%)	
	36-45: 64 (31.7%)	36-45: 29 (29.2%)	
	46-55: 43 (21.3%)	46-55: 23 (23.2%)	
	56-65: 28 (13.9%)	56-65: 14 (13.3%)	
BMI	<24.9: 50 (24.8%)	<24.9: 28 (28.2%)	NS
	25-29.9: 76 (37.6%)	25-29.9: 45 (45.4%)	
	>30: 76 (37.6%)	>30: 26 (26.4%)	
Smoking	no: 129 (63.8%)	no: 70 (70.7%)	NS
	yes: 56 (27.7%)	yes: 24 (24.2%)	
	ex-smoker: 18 (8.5%)	ex-smoker: 5 (5.1%)	
Nodule	Yes: 75 (37.1%)	Yes: 34 (34.3%)	NS
	No: 127 (62.9%)	No: 65 (65.7%)	

Note: F: female; M: male; HT: Hashimoto's thyroiditis; BMI: Body mass index; χ^2 : Chi-square; pre: premenopausal; post: postmenopausal; NS: non-significant

Table 2. The prevalence of metabolic syndrome in the study groups

		Group		Total
MetS	Negative	Control	HT	
	Positive			
	Total			
		140 (69.3%)	72 (72.7%)	212 (70.4%)
		62 (30.7%)	27 (27.3%)	89 (29.6%)
		202 (100%)	99 (100%)	301 (100%)

METs: Metabolic syndrome. HT: Hashimoto's thyroiditis

Comparison of metabolic and anthropometric properties of HT and controls

In both groups TSH, BMI, Manual waist circumferences, device measured waist circumferences, neck circumferences, hip circumferences, waist/hip ratios, trunk fat %, VFL, Fat %, fasting insulin levels, HOMA-IR, FPG, triglycerides were similar ($p>0.05$ for all parameters) (Table 3). We also compared the same parameters between nodular and non-nodular controls and also between unimodular and multinodular controls. All parameters were statistically similar.

Subgroup analysis of HT cases**Levothyroxine on versus levothyroxine off**

Out of the 99 cases with HT enrolled in this study 45 were off, and 54 were on levothyroxine replacement therapy. All cases were euthyroid. Anthropometric and metabolic parameters were similar among both groups (Table 4).

Comparisons according to presence of thyroid nodules

Thirty-four cases of the HT group were accompanied by thyroid nodules whereas thyroid nodules accompanied 75 cases of the control group.

Table 3. Comparison of metabolic and anthropometric properties of the study groups

	Control (Mean $\pm$ sd)	HT (Mean $\pm$ sd)	P value
Age (years)	39.79 $\pm$ 10.42	41.56 $\pm$ 11.68	NS
BMI (kg/m ²)	28.8 $\pm$ 5.35	27.57 $\pm$ 5.20	NS
WC manual (cm)	98.32 $\pm$ 11.17	95.12 $\pm$ 13.47	NS
WCAB-140 (cm)	104.23 $\pm$ 13.26	102.29 $\pm$ 13.06	NS
HC (cm)	108.22 $\pm$ 9.30	106.66 $\pm$ 10.43	NS
Waist/hip	0.91 $\pm$ 0.07	0.89 $\pm$ 0.07	NS
NC (cm)	36.43 $\pm$ 5.14	35.55 $\pm$ 2.62	NS
Fat %	33.60 $\pm$ 6.72	33.25 $\pm$ 7.89	NS
TBW %	52.1 $\pm$ 4.5	54.3 $\pm$ 3.7	NS
VFL	12.91 $\pm$ 3.62	11.47 $\pm$ 3.72	NS
TF %	42.16 $\pm$ 7.19	40.06 $\pm$ 7.34	NS
Insulin (μ U/mL)	11.26 $\pm$ 4.41	9.22 $\pm$ 6.11	NS
HOMA-IR	2.63 $\pm$ 1.07	2.21 $\pm$ 1.64	NS
TSH (mIU/L)	1.73 $\pm$ 0.81	2.13 $\pm$ 1.38	NS
FPG (mg/dL)	92.88 $\pm$ 11.21	93.48 $\pm$ 9.67	NS
TG (mg/dL)	127.27 $\pm$ 72.17	121.11 $\pm$ 52.01	NS
HDL-C (mg/dL)	48.34 $\pm$ 12.47	51.01 $\pm$ 15.47	NS

Sd: standard deviations; BMI: Body mass index; WC: waist circumference; HC: hip circumference; NC: neck circumference; Fat %: fat percentage; VFL: Visceral fat level; TF %: Trunk fat percentage; HOMA IR: Homeostasis model for assessment of insulin resistance; FBG: Fasting blood glucose; TG: Triglyceride HDL-C: High density lipoprotein-cholesterol; TBW%: Total body water percentage; NS: non-significant.

Table 4. Comparison of metabolic and anthropometric parameters of HT subjects according to levothyroxine usage

	LT4 off (mean $\pm$ sd)	LT4 on (mean $\pm$ sd)	P value
Age (years)	40.00 $\pm$ 13.31	42.80 $\pm$ 10.18	NS
BMI (kg/m ²)	28.17 $\pm$ 5.58	27.10 $\pm$ 5.29	NS
WC manual (cm)	97.88 $\pm$ 14.26	92.95 $\pm$ 12.37	NS
WCAB-140 (cm)	103.54 $\pm$ 14.41	101.27 $\pm$ 12.12	NS
HC (cm)	107.92 $\pm$ 10.72	105.70 $\pm$ 10.26	NS
Waist/Hip	0.89 $\pm$ 0.06	0.87 $\pm$ 0.07	NS
NC (cm)	36.01 $\pm$ 2.76	35.20 $\pm$ 2.57	NS
Fat %	33.50 $\pm$ 8.04	33.00 $\pm$ 7.83	NS
TBW %	53.6 $\pm$ 4.2	54.7 $\pm$ 3.8	NS
VFL	12.34 $\pm$ 4.38	10.74 $\pm$ 3.16	NS
TF %	40.58 $\pm$ 8.28	39.61 $\pm$ 6.59	NS
Insulin (μ U/mL)	8.77 $\pm$ 5.74	9.56 $\pm$ 6.39	NS
HOMA-IR	1.98 $\pm$ 1.10	2.39 $\pm$ 1.92	NS
TSH (mIU/L)	2.29 $\pm$ 0.94	1.99 $\pm$ 1.62	NS
FPG (mg/dL)	90.92 $\pm$ 9.32	95.48 $\pm$ 9.54	NS
TG (mg/dL)	123.15 $\pm$ 34.30	120.42 $\pm$ 61.03	NS
HDL-C (mg/dL)	51.95 $\pm$ 18.77	50.27 $\pm$ 12.86	NS

Sd: standard deviation; BMI: Body mass index; WC: waist circumference; HC: hip circumference; NC: neck circumference; Fat %: fat percentage; VFL: Visceral fat level; TF %: Trunk fat percentage; HOMA IR: Homeostasis model for assessment of insulin resistance; FPG: Fasting blood glucose; TG: Triglyceride HDL-C: High density lipoprotein-cholesterol; TBW%: Total Body Water Percentage; NS: non-significant.

The prevalence of thyroid nodules was similar in both groups (34.3% vs. 37.1%; $p>0.05$). Metabolic and anthropometric parameters were similar in both nodular vs. nonnodular controls and nodular vs. non-nodular HT.

ROC analysis

We performed Receiver Operating Characteristic (ROC) analysis to estimate a cut-off level of TSH for the development of Mets, if any. We calculated the areas under each ROC curve (AUC) with 95% confidence interval (CI) for each curve. The AUC was 0.563 ($p=0.35$; standard error 0.76) for the HT group and 0.527 ($p=0.524$; Standard error 0.44) for the control group. We were unable to calculate a cut-off level of TSH for the development of MetS with desired sensitivity and specificity (Figs 1 and 2).

DISCUSSION

There are limited studies in the literature performing extensive anthropometric and metabolic measures in euthyroid subjects with HT. Studies involving direct measurement of visceral fat is even rarer. In this cross-sectional survey, we compared the prevalence's of Mets, waist circumferences, hip circumferences, neck circumferences, waist-hip ratios, visceral fat levels, trunk fat percentages, fat percentages, triglyceride levels, HDL-cholesterol levels, insulin levels in subjects with HT with a control group consisting of subjects without thyroid autoimmunity.

TSH correlated positively with insulin, FPG, HOMA-IR and BMI. All correlation coefficients were

weak, and the strongest correlation was established between TSH and BMI ($r=0.32$). These findings were compatible with some previous studies (1, 17, 21, 26, 27). In a study by Topaloglu *et al.* which correlated thyroid function with obesity in a cohort of polycystic ovary syndrome subjects, the correlation of TSH with BMI was significant but weaker than our findings ($r: 0.122$; $p: 0.02$) (26).

A review by Amanda de Moura Souza published in 2011 analyzed data from 29 studies. Some of these studies demonstrated a positive correlation between body mass index and TSH but approximately half of the studies showed no such correlation (16). The hypothesis for correlation was that TSH is involved in the differentiation of pre-adipocytes and induced adipogenesis. Another hypothesis is the leptin hypothesis. Some studies have demonstrated a positive correlation between leptin and TSH (13).

An interesting finding of our study was the significant positive correlation between FT3 and visceral fat level, FPG and triglycerides. However, FT4 correlated only with FPG. There are conflicting reports in the literature associating free thyroid hormone levels with metabolic and anthropometric variables. Moon MK *et al.* it was reported that FT3 levels were inversely associated with hepatic fat quantity and intramuscular fat area (22). Kim B *et al.* reported FT4 was positively associated with blood pressure, FPG, HDL and triglyceride levels and negatively associated with waist circumference in euthyroid subjects. However, there was no relationship of FT4 with the presence of Mets after adjustment for age (23). Garduno-Garcia *et al.* reported that subclinical hypothyroidism is not

Figure 1. Receiver Operating characteristics curve for TSH levels in predicting Metabolic syndrome in subjects with Hashimoto's Thyroiditis.

Figure 2. Receiver Operating characteristics curve for TSH levels in predicting Metabolic syndrome in the control group.

associated with an increased risk for MetS. They concluded that the combined use of TSH and FT4, compared with the assessment based on only FT4, is a more convenient approach to evaluating the association between thyroid function and metabolic variables (24). HT and control groups were matched for age, sex, menopausal status, BMI, smoking habits and prevalence of coexisting thyroid nodules. Because overweight and obese subjects have a higher TSH level, independent of thyroid function, compared to normal weight individuals, we performed a case based matching in groups according to BMI and other variables. In this way we aimed to overcome weight dependent possible changes in TSH. We tried to exclude all parameters other than thyroid autoimmunity in making the correct comparison.

The prevalence of Mets was similar in the HT and control groups. Supporting this finding, all anthropometric (waist circumference, hip circumference, neck circumference, waist/hip ratio, fat percentage, visceral fat level) and metabolic (FPG, insulin, HDL-C, triglycerides) were similar in both groups. Findings did not differ when taking HT subjects under LT4 and HT subjects with accompanying thyroid nodules into consideration. However, Ruhla S. *et al.* determined that levothyroxine therapy was associated with adiposity in their study (7).

In our study, we also aimed to establish a cut-off level of TSH for the development of Mets, if any. We were unable to calculate such a cut-off with 95% C.I. at desired sensitivity and specificity.

In a study by Waring *et al.*, 2119 participants were enrolled. Cases under LT4 replacement therapy were excluded. At the beginning of the study, there were 684 cases diagnosed as Mets. After six years follow-up 239 more cases were diagnosed as Mets. Every 1 unit increase in TSH increased prevalence of Mets by 3%. This relationship was even more pronounced in the euthyroid range where every 1 unit increase increased prevalence of Mets by 18% (25). We were unable to reach such results in our study. A possible reason for this is the relatively lower study population and that our study was not prospectively performed.

A study by Roos A *et al.* demonstrated that thyroid functions in euthyroid cases are related to components of the metabolic syndrome. In this study, all cases on LT4 replacement therapy were excluded and presence of thyroid autoimmunity was not verified. All euthyroid cases were eligible (11).

A superiority of our study to previous studies

is that an extensive metabolic and anthropometric evaluation was performed including visceral fat level and fat percentage.

We conclude that although weight gain is frequently encountered in subjects with HT, such subjects with thyroid function tests in the euthyroid range have a similar prevalence of Mets and similar metabolic and anthropometric measurements compared to subjects without autoimmunity.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This study was supported by the Baskent University Research Fund.

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