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Brief Report

Relationship between high normal TSH levels and metabolic syndrome components in type 2 diabetic subjects with euthyroidism

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ABSTRACT

Objective: Thyroid hormones as modulators of adaptive thermogenesis can potentially contribute to development of obesity. The purpose of our study is to observe a relationship between TSH and BMI, blood lipids, BP and HbA1c in type 2 diabetic subjects with euthyroidism.
Methods: A total of 120 subjects with type 2 diabetes were recruited for this study from November 2012 to June 2014. Subjects were included in the study with TSH values between 0.4 and 4.5 mU/l, who did not take any thyroid medication and had a similar iodine diet. Subjects were weighed and anthropometric indices, lipid parameters, fasting plasma glucose, HbA1c, eGFR, blood pressure (BP) were documented. TSH was measured by an electrochemiluminescence immunoassay. Statistical analysis was performed by using SPSS 18(P value <0.05 was considered significant).
Results: The mean age of the participants was 60.6 ± 11.6 years with a BMI of 25.3 ± 3.1 kg/m^2. Serum TSH levels were significantly and positively associated with BMI, systolic and diastolic BP, serum triglyceride and HbA1c levels, whereas negatively with eGFR. Subjects with a TSH in a higher normal range (2.5–4.5 mU/I, $n = 58$) had a significantly higher BMI (26.7 ± 3 vs. 24.1 ± 2.7) and this relation remained significant adjusted for age and sex ($P < 0.001$). When TSH was in low normal range, the number of patients with glycemic goal (HbA1c > 7%) decreased from 27.5% to 12.5% ($P = 0.02$, adjusted for age and sex).
Conclusion: In type 2 diabetic subjects with biochemical euthyroidism we found significant association between high normal TSH levels and components of metabolic syndrome. High normal TSH levels were associated with more number of subjects with glycemic goal (HbA1c >7%).

Introduction

Sharply rising abdominal adiposity is probably the main cause of MetS. In obese subjects, in the setting of insulin resistance, insulin is unable to properly suppress accelerated free fatty acids (FFAs) mobilization (lipolysis) from stored adipose tissue triglyceride [1,2]. Increased FFAs [3] also appear to cause insulin resistance. Both, insulin resistance and increased fatty acids increase the sympathetic nervous system activity and themselves contribute to vasoconstriction [4,5] by triggering hypertension.

It is generally well accepted that hypothyroidism, with its accompanying dyslipidemia and hypertension, similar to the components of MetS is associated with CVD [6,7]. However, most cardiovascular events occur in subjects with normal thyroid function, and, little information is available about weight changes and insulin resistance when thyroid functions are in the normal range. Some investigators have suggested the existence of partially bio inactive TSH in obese subjects [8]. Others display that there may be certain thyroid hormone resistance. Ideally, early TH (thyroid hormone) therapy and lowing high-normal TSH levels should increase fat loss by stimulating thermogenesis and basal metabolic rate. Such therapy is also justified in diabetic patients as FT3 has an anti-apoptotic and protective effect on the pancreatic beta cells and higher T3 levels induce kinase activity of the TR beta1-associated PI3 kinase and stimulates insulin secretion [9].

The aim of the study was to establish TSH levels association with MetS components in insulin resistance subjects. It was further to compare MetS components association with low normal and high normal TSH levels in type 2 diabetic patients and to assess diabetes control in patients with high-normal TSH levels.

Table 1
Clinical characteristics in subjects with low and higher normal TSH levels

Variables	All subjects	Subjects with		T-test	P value (2-tailed)
		Low normal TSH levels (0.4–2.49 ml/ml)	Higher normal* TSH levels (2.5–4.5 ml/ml)		
No (M/F)	120 (62/58)	62 (35/27)	58 (27/31)	N/A	N/S
Age	60.6 ± 11.6	59.8 ± 11.6	61.2 ± 11.6	0.577	N/S (0.565)
BMI	25.3 ± 3.1	24.1 ± 2.7	26.7 ± 3	4.957	<0.001
SBP	124.8 ± 15.8	120.3 ± 13.9	129.4 ± 16.5	3.252	<0.01
DBP	75.7 ± 11	73 ± 10.2	78.6 ± 11.3	2.797	<0.01
TG	137.8 ± 84.4 n/p	117.6 ± 75.4	159.4 ± 88.5	2.788	<0.01
HDL-C	52.3 ± 16.3 n/p	54 ± 17.2	50.3 ± 15.3	−1.292	N/S (0.199)
LDL-C	97.6 ± 31.8	95.3 ± 32.1	99.4 ± 31.5	0.600	N/S (0.550)
FPG	137.7 ± 39.4 n/p	134.1 ± 39.8	141.6 ± 38.7	1.052	N/S (0.295)
HBA1C	7 ± 1.3 n/p	6.6 ± 1	7.5 ± 1.3	3.827	<0.001
eGFR	77.7 ± 20.8	82 ± 19.8	73 ± 21.2	−2.424	N/S (>0.05)

*P value <0.05.

Subjects and methods

In our study, subjects, who met the inclusion criteria, were 120 Caucasian patients with type 2 diabetes mellitus. Patients who met metabolic syndrome by WHO criteria [10], who were seeking care to improve their diabetes control from November 2012 to June 2014 were evaluated for inclusion into this study. The exclusion criteria were autoimmune conditions (Hashimoto thyroiditis, Grave's disease, type 1 diabetes or positive diabetes-related auto-antibodies), medications for thyroid disease and medications, such as steroids, dopamine, iodine, amiodarone. The inclusion criteria were nonsmokers with euthyroidism (TSH values between 0.4 and 4.5 mU/l) and negative for thyroid autoantibodies (thyroid peroxidase and thyroglobulin antibodies). Subjects recruited for this study had a similar iodine diet. All the participants were given questionnaires to assess dietary habits. In addition, they were from the same iodine deficiency zone. The study subjects were weighed and their anthropometric indices were taken. Total cholesterol (TC), TG, HDL-C, LDL-C, fasting plasma glucose (after 12 h fasting), HbA1c, eGFR, SBP, DBP were documented, and TSH, FT4, FT3 were measured by an electrochemiluminescence immunoassay. The laboratory reference ranges were 0.4–4.5 mU/l for TSH. In our study we used BMI (weight divided by the squared value of height) of 25.0 kg/m^2 as cut-off for overweight and normal weight individuals.

Statistical analysis

All correlation analyses were performed with partial correlation analyses using TSH as a continuous variable. Adjustments were made for age and gender. $P < 0.05$ was considered to indicate statistical significance. Statistical analysis was performed on a personal computer using a statistical software package SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The study was approved by the regional ethics committee. All subjects gave their written informed consent.

Results

Characteristics of study subjects

The mean age of the participants was 60.6 ± 11.6 years with a BMI of 25.3 ± 3.1 kg/m^2. TSH, FT4, and TT3 levels were not significantly different between male and female participants. Spearman rank correlation coefficient was used to determine associations of variables with serum levels of TSH, FT4 and TT3. We found no significant association between FT4, TT3 and MetS components. Thereby we focused on TSH for further analysis. Subjects with a TSH in a higher normal range (2.5–4.5 mU/l, $n = 58$) had a strong association with higher BMI (26.7 ± 3 vs. 24.1 ± 2.7) and HbA1c levels (HbA1c > 7) (Table 1). This association remained significant in linear regression analysis after adjustment for sex and age ($P < 0.001$). TSH was also associated with TG, SBP, DBP ($P < 0.01$), but neither with eGFR and FPG ($P > 0.05$).

HbA1c

In the group with high-normal TSH levels, subjects with overweight or obesity (BMI − 25kg/m^2 or higher) had about three times higher prevalence of HbA1c > 7 levels (Fig. 1). The research shows, that when TSH is in low normal range, the number of patients with glycemic goal (HbA1c > 7%) decreases from 27.5% to 12.5% ($P = 0.02$, adjusted for age and sex).

MetS prevalence

The prevalence of MetS was 26% in this study population. Subjects with high normal TSH levels (2.5–4.0 mIU/L) demonstrated a significantly higher prevalence of MetS than those with low normal TSH levels (0.4–2.5 mIU/L) at a rate of 37.93% vs. 14.51% ($P < 0.01$).

Lipids

Among lipids only triglycerides were significantly associated with TSH levels ($P < 0.05$). Triglycerides were significantly higher in subjects in the upper normal TSH range compared with those in the low normal TSH range (159.4 ± 88.5 vs. 117.6 ± 75.4, $P = 0.006$). Fig. 2 displays that mean of TG by categories of TSH is more obviously increased in subjects with normal weight than in overweight/obese subjects (adjusted for age, sex and time since last meal).
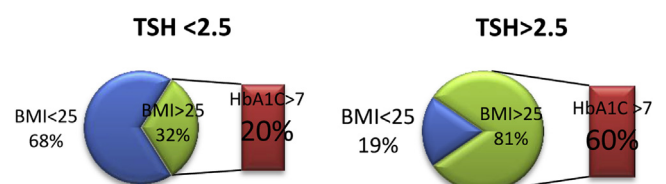

Fig. 1. Comparison of diabetes control in euthyroid MetS subjects with low normal and high normal TSH levels.

Mean of TG by categories of TSH
Adjusted for age, sex and time since last meal.

◆ Overweight (BMI 25.0 kg/m2 or higher)

■ Normal weight (BMI<25kg/m2)

152 ——————— 162
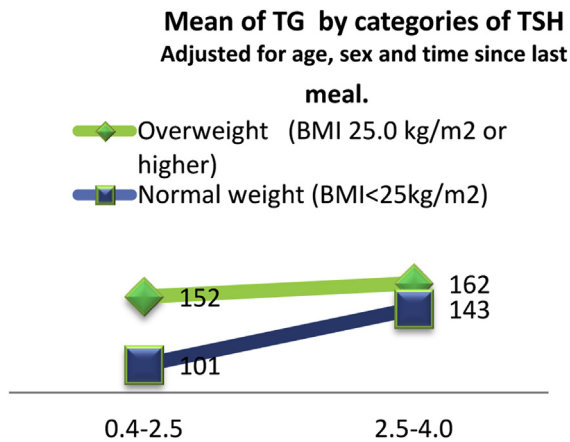   143
101

0.4-2.5   2.5-4.0

Fig. 2. Mean TG by categories of TSH.

Medication and TSH levels

There were no associations between TSH levels and medications used for the treatment of diabetes, dyslipidemia and hypertension (Table 2).

Discussion

Insulin sensitivity and TSH

There are many reports about the association between thyroid hormones and MetS in non-diabetic subjects. But reports about the relationship between thyroid hormones and MetS components in type 2 diabetic patients are very rare. In our study, we found not only a positive association between TSH levels and MetS components in diabetic subjects, but we also could show that diabetes control was somehow complicated when subjects had a high-normal range of TSH. Some studies described decreased insulin sensitivity in hypothyroidism [11,12], while others did not [13,14]. The study of Jackson et al. even reported increased insulin sensitivity [15]. Recently, an experimental study in an animal model has demonstrated that the mutation in the α-isoform of the thyroid hormone receptor caused insulin resistance and thyroid hormone resistance [16]. In addition, studies investigating thyroid hormone receptors in MetS subjects (mostly in obese individuals) demonstrated a decrease of thyroid hormone receptor density [17,18].

In our study we found no significant association between FT4 and total T3 levels with Mets components in diabetic subjects. This may be explained that T3 levels in the normal range do not have very strong physiological activity and do not reflect in peripheral tissue, which are known to actually exert the metabolic effects. There are also differences in expression of thyroid hormone receptors on central and peripheral tissues and can, therefore, also

play a role in inducing a discrepancy of thyroid hormones effects in central and peripheral tissues [19].

BMI and TSH

Our data revealed positive association between TSH and BMI. This association could be affected by a third factor. To control for the effect of age, age was included as an independent variable in the multiple regression analysis. Furthermore, the positive association between TSH and BMI was also significant in those above the age of 50. Age was therefore an unlikely explanation for the association between elevated TSH and BMI. Moreover, this association could be causal. Many reports have shown that after reducing body weight or after bariatric surgery [20,21], there was a significant decrease in TSH levels. The mechanism could be explained by the leptin levels secreted by adipose tissue, which is directly correlated to the amount of adipose tissue. In experimental stage, leptin has been reported to stimulate the biosynthesis of TSH [22]. On the other hand, we could not ignore the possible role of hyperglycemia on TSH-depend BMI levels.

Lipids and TSH

Among MetS components TSH was correlated with triglyceride levels. In 1980s: it was demonstrated that LDL receptor activity was regulated by thyroid hormone [23]. Increased level of triglycerides in high-normal TSH subjects could be caused by a reduced activity of lipoprotein lipase, or impaired clearance of lipoproteins dependent on LDL receptor function. LDL-C clearance is different between subjects with high normal and subjects with low normal TSH levels [24]. In our study this difference remained unnoticed, probably, because of insulin resistance. In the liver of insulin-resistant patients, triglyceride synthesis and storage are increased, and excess triglyceride is secreted as VLDL [25]. However, LDL-C concentrations remain essentially unchanged in insulin-resistant states because of a decrease in cholesterol content per LDL particle, resulting in higher concentrations of small dense LDL particles [10,26,27]. This positive association between TSH levels and TG could have long-term harmful effects on cardiovascular disease.

Study limitation

The main limitation of our study is the relatively small size and regional homogeneity of the population visiting the aforementioned Hospital. This data does not reflect that of the general population. Further larger randomized trials are necessary to evaluate increased risk of early stage of thyroid dysfunction and to display the potential benefit for the earlier stage management of thyroid dysfunction.

Conclusion

In summary, we found a significant association between high normal TSH levels and components of metabolic syndrome in type 2 diabetic subjects with biochemical euthyroidism. High normal TSH levels were associated with more diabetic subjects with glycemic goal (HbA1c > 7%).

Conflicts of interest/financial disclosure

None.

Acknowledgments

Table 2
Regression analyses

Medications	Number of subjects	*P* value
Diet only	23	N/S (−0.074)
OHAs	76	N/S (−0.188)
Insulin	11	N/S (−0.084)
Insulin + OHAs	10	N/S (0.192)
Anti-hypertensive drugs	(−) 94	N/S (0.241)
	(+) 26	
Lipid-lowering drugs	(−) 80	N/S (0.969)
	(+) 40	

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