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Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population

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Abstract

Thyroid hormones play an important role in regulating energy homeostasis and lipid and glucose metabolism. This study assessed the relationship between free thyroxine and clinical features of metabolic syndrome (MS). A total of 4938 Taiwanese subjects (2891 men and 2047 women with a mean age of 50.1 ± 12.6 years) with normal serum free thyroxine levels were enrolled. A modified National Cholesterol Education Program definition of MS was adopted substituting body mass index (BMI) for waist circumference. Serum free thyroxine concentrations were determined by immunoassay. Overall, 14% of subjects had a high fasting glucose, 27% had high blood pressure, 14% had high serum total triglyceride, 8% had low high-density lipoprotein cholesterol, and 18% were obese. The serum free thyroxine concentrations showed a statistically significant correlation with triglyceride and body mass index, respectively ($P < .01$), but not with blood pressure, glucose level, or high-density lipoprotein cholesterol level. According to the presence of 0, 1, 2, and 3 or more features of MS, age and sex-adjusted means of serum free thyroxine were 17.8 ± 3.7, 17.6 ± 3.7, 17.5 ± 3.7, and 17.1 ± 3.3 pmol/L, respectively, with a modest, but statistically significant, decreasing trend ($P < .05$). When comparing subjects in the highest and lowest quartile of free thyroxine, the former group demonstrated a 2-fold decrease in the odds ratio for MS with 3 or more metabolic features. Low circulating free thyroxine levels, albeit normal, were associated with MS in a Chinese population. Further study is necessary to document the role of thyroid hormones in metabolic abnormalities of MS.

1. Introduction

Metabolic syndrome (MS) is a complex disease characterized by several abnormalities including central obesity, impaired glucose tolerance (or type 2 diabetes), hypertension, low high-density lipoprotein cholesterol (HDL-C) levels, and/or hypertriglyceridemia [1]. According to the Third National Health and Nutritional Survey, MS is present in more than 20% of the US adult population [2]. This high prevalence is of considerable concern because more and more evidence indicates that MS is associated with an increased risk in cardiovascular disease [3]. To obtain a better therapeutic and preventive strategy for this metabolic disorder, more understanding of its pathogenetic mechanisms seems necessary.

Thyroid hormones play an important role in regulating energy homeostasis [4,5]. They can stimulate expression of uncoupling proteins in the mitochondria of fat and skeletal muscle, modulate adrenergic receptor numbers by enhancing responsiveness of catecholamines, and thus regulate metabolic rate and body weight [6]. It has been reported that hypothalamic-pituitary thyroid axis is dysregulated in obese people and an inverse relationship between serum free thyroxine and body mass index (BMI) is observed [7]. In addition, thyroid hormones can regulate lipoprotein and glucose metabolism and blood pressure (BP) [8-10]. Because obesity, blood lipids, and glucose are all features of MS, we speculated a potential relationship between thyroid hormones and MS. Recently, the National Cholesterol Education Program proposed a simple definition for MS [11]. The present study investigated the association of

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Table 1
Age- and sex-specific prevalence of each feature of MS

	Men					Total	Women					Total
Age (y)	20-30	30-40	40-50	50-60	>60		20-30	30-40	40-50	50-60	>60	
n	111	401	898	708	773	2891	109	298	572	580	488	2047
MS features (%)												
HBP	23	29	26	30	28	29	26	26	26	28	27	26
Obesity	27	20	22	19	16	20	20	7	11	20	22	15
HFPG	4	6	12	20	24	16	2	2	7	15	24	12
HTG	8	21	20	17	13	17	1	4	7	12	16	10
LHDL	9	14	11	13	12	12	1	2	3	4	5	3

HBP indicates high blood pressure; HFPG, high fasting plasma glucose; HTG, high TG; LHDL, low HDL-C.

thyroid hormones with this MS definition in a large Chinese population.

2. Patients and methods

2.1. Subjects

A total of 7460 adult individuals who had attended health examination of their volition from January 2001 to December 2002 at Taichung Veterans General Hospital were initially enrolled in this study. Upon study entry, participants were interviewed by physicians, and medical history and smoking habits were documented. During the physical examination, body weight (kg) and height (m) of subjects were measured for computing BMI. Blood pressure was measured in the right arm using standard mercury sphygmomanometers at sitting position after 5 minutes of rest, and the mean systolic and diastolic BP values of 2 measurements were recorded. A fasting venous blood sample was also obtained.

2.2. Laboratory measurement

Serum total triglyceride (TG), cholesterol, and HDL-C levels were measured by enzymatic method using a chemistry analyzer (Hitachi 7600, Tokyo, Japan) at the central laboratory of the hospital. The serum glucose was determined by glucose oxidase procedure (Hitachi 7170, Tokyo, Japan). The serum free thyroxine levels were determined by radioimmunoassay (Diagnostic Products Corporation, Tianjin, China). The lowest detectable value is 0.1 pmol/L, and a normal reference range is 9.0 to 24.5 pmol/L at this hospital. The intra- and interassay coefficients of variation were 5% and 7% to 9%, respectively.

2.3. Definitions

The definition of various components of MS was as follows: (1) systolic BP $\geq$130 mm Hg or diastolic BP $\geq$85 mm Hg; (2) TG levels $\geq$150 mg/dL (1.69 mmol/L); (3) HDL-C level <40 mg/dL (1.03 mmol/L) for men and <50 mg/dL (1.29 mmol/L) for women; (4) fasting plasma glucose $\geq$110 mg/dL (6.1 mmol/L); (5) BMI $\geq$27 kg/m^2, a modification variable based on a recently proposed classification system in Taiwan Chinese [12]. According to the national health and nutrition examination survey between 1993 and 1996 at Taiwan, a BMI value of 27 kg/m^2 in Taiwanese had a similar adiposity percentage to whites with a BMI value of 30 kg/m^2. In addition, at this BMI level, Taiwanese have a mean abdominal circumference of 90 cm in males and 80 cm in females, respectively, which are comparable to the definition of central obesity in Asians by the International Obesity Task Force [13]. We adopted this modified variable to classify people with obesity. Because hyperthyroidism and hypothyroidism probably change eating behavior and physical activity, patients with abnormal serum free thyroxine levels were not enrolled for analysis [14,15]. In addition, subjects with apparent hepatic, renal, cardiovascular diseases, and severe hypertriglyceridemia (serum TG >400 mg/dL) were also excluded as these disorders themselves might potentially cause blood pressure, glucose or lipid abnormalities, or interfere the free thyroxine assay. Finally, a total of 4938 subjects (2891 men and 2047 women with a mean age of 50.1 $\pm$ 12.6 years) were included.

2.4. Statistical analysis

Continuous variables measured in this study were expressed as mean $\pm$ SD. The mean serum free thyroxine

Table 2
Age- and sex-specific prevalence of combinations of MS features

	Men					Total	Women					Total
Age (y)	20-30	30-40	40-50	50-60	>60		20-30	30-40	40-50	50-60	>60	
n	111	401	898	708	773	2891	109	298	572	580	488	2047
No. of features (%)												
0	47	42	38	36	37	38	64	58	54	41	36	47
1	37	30	35	35	41	36	34	37	35	38	36	36
2	13	20	18	19	12	17	2	4	9	15	20	12
$\geq$3	3	8	9	10	10	9	0	1	2	6	8	5

values were first compared across the 5 categorized MS features and all means were adjusted by sex, age, and the remaining MS components by means of a multiple general linear regression model. In addition, the partial Spearman correlations (adjusting for age and sex) for free thyroxine values with features of MS were also estimated. Second, all the subjects were divided into 4 groups according to the number of MS features as follows: group 1 without any of MS features, groups 2 with 1 MS feature, group 3 with 2 MS features, and cluster 4 with 3 to 5 MS features. Then, age- and sex-adjusted means of serum free thyroxine for each cluster were calculated by a general linear regression model and compared by the analysis of variance test. Finally, circulating free thyroxine concentrations were divided into quartiles arbitrarily, and logistic regression analysis was used to evaluate the relative risk of MS in all subjects without and with 3 or more MS features for each category of free thyroxine level and other potential risk factors (eg, age, sex). For each risk, a 95% confidence interval was established. All statistical analyses were performed with the SPSS statistical package for Windows, version 10.0 (SPSS Inc, Chicago, Ill), and a 2-tailed P value of less than .05 was considered statistically significant.

3. Results

Distribution of the MS components and prevalence of MS in both sexes by 10-year age groups are shown in Tables 1 and 2, respectively. In the total population studied, 7.2% of subjects had 3 or more metabolic features (9% in men and 5% in women). Fourteen percent of subjects had high fasting glucose, 27% had high BP, 14% had high serum total TGs, 8% had low HDL-C, and 18% were obese.

Adjusted mean serum free thyroxine concentrations for categorized features of MS in both sexes are listed in Table 3. Serum free thyroxine levels were significantly lower in subjects with obesity and hypertriglyceridemia. There was a modest but statistically significant correlation with TG (r = 0.05; P < .01) and BMI values (r = 0.05; P < 0.01), but not with BP, glucose levels, or HDL-C levels. In addition, serum free thyroxine levels in the presence of 0, 1, 2, and 3 or more features of the MS were 17.8 ± 3.7, 17.6 ± 3.7, 17.5 ± 3.7, and 17.1 ± 3.3 pmol/L, respectively (P < .01). Table 4 shows risks for MS calculated according to quartile distribution of serum free thyroxine levels. Subjects in the lowest quartile of free thyroxine values had a 1.5- to 2-fold increase in the odds ratio for MS with 3 or more metabolic features compared with subjects in the highest quartile of free thyroxine.

Table 3
Adjusted means of serum free thyroid hormone levels for categorized features of MS

Variables	Means of FT4 (pmol/L)	P
Obesity		
BMI (kg/m^2) ≥ 27	17.2 ± 3.3	<.01
BMI (kg/m^2) < 27	17.8 ± 3.4	
HBP		
SBP ≥130 mm Hg or DBP ≥85 mm Hg	17.7 ± 3.7	NS
SBP <130 mm Hg and DBP <85 mm Hg	17.7 ± 3.3	
HFPG		
FPG ≥110 mg/dL (6.1 mmol/L)	17.2 ± 3.7	NS
FPG <110 mg/dL (6.1 mmol/L)	17.2 ± 3.6	
HTG		
TG ≥150 mg/dL	17.0 ± 3.7	<.01
TG <150 mg/dL	17.8 ± 3.7	
LHDL		
HDL <40 mg/dL (men)/<50 mg/dL (women)	17.6 ± 3.7	NS
HDL ≥40 mg/dL (men)/≥50 mg/dL (women)	17.4 ± 3.5	

FT4 indicates free thyroxine 4.

Table 4
Prevalence and risk for 3 or more features of MS according to circulating free thyroxine (FT4) levels in all subjects with no and 3 or more MS features

Characteristics	Prevalence (%)	Odds ratio (95% confidence interval)
FT4 (pmol/L)		
9.0-15.3	8.6	1
15.4-17.4	6.7	0.70 (0.51-0.93)
17.5-19.7	6.7	0.65 (0.48-0.88)
19.8-24.5	6.5	0.63 (0.47-0.86)
Sex		
Female	9	1
Male	20	2.55 (2.01-3.22)
Age (y)		
20-39	8	1
40-59	14	1.91 (1.35-2.71)
≥60	25	2.65 (1.83-3.84)

4. Discussion

Thyroid hormones have pleitropic effects upon regulation of energy homeostasis, lipid and glucose metabolism [4,5,8-10]. Accordingly, we evaluated a potential relationship between serum free thyroxine levels and MS. Because hypothyroidism and hyperthyroidism are both likely to change behavior and physical activity, and thus may obviate the relationship between thyroid hormones and components of MS (eg, BMI and serum lipids) [14,15], only those people with normal serum free thyroxine levels were analyzed. It has been reported that more than 95% of subjects are actually in an euthyroid status if their free thyroxine values are within the normal reference range [16]. Thus, all these subjects were presumed to have normal thyroid function, although the possibility of subclinical thyroid disorders could not be excluded completely. In addition, considering the narrow reference range of normal serum thyroxine levels, a large number of subjects were enrolled to find a subtle relationship between serum thyroid hormone and MS. Indeed, this study demonstrated for the first time that serum free thyroxine values decreased with the number of the manifestations of MS in a Chinese population. The odds ratio for MS increased in a dose-dependent manner from the highest to the lowest

quartiles of serum free thyroxine; therefore, low serum free thyroxine levels, albeit normal, were associated with an increased risk of MS.

The exact reasons for this association were not clear, and there were several possible explanations. First, it was possible that thyroid hormones may play a role in the development of MS. Insulin resistance and/or hyperinsulinemia are generally considered the basis of MS, and there is a positive relationship between numbers of MS components and severity of insulin resistance [17]. Recently, some experimental studies demonstrated that thyroid hormones can stimulate expression and activation of uncoupling protein, β-2 adrenergic receptor, and perixisome proliferator–activated receptor γ, all of which are known as important candidates for regulating insulin sensitivity [18-20]. Accordingly, the regulation of these insulin sensitivity–related molecules by thyroid hormones could hypothetically be an explanation to our observation. Indeed, it has been shown in obese diabetic rodents that use of thyroid hormone at non- or subthyrotoxic levels enhanced insulin sensitivity and reduced both hyperinsulinemia and hyperglycemia [9]. By contrast, deprivation of thyroid hormone in animals or genetic mutation of deiodinase, an important regulator of thyroid hormone metabolism, in humans induce an obesity and insulin resistance state [21,22]. In addition, thyroid hormones can also cooperate with catecholamines to enhance lipolysis, decrease visceral fat mass, and improve insulin resistance [23]. Importantly, the stimulation of insulin sensitivity and lipolysis by thyroid hormones may only occur at physiologically circulating thyroxine concentrations. Therefore, this is not the case at abnormally high thyroxine levels; for example, insulin sensitivity or adipocyte lipolysis can be reduced by experimental thyrotoxicosis [6,9]. Our observation that free thyroxine levels between subjects with no and 3 or more MS features differed only by 0.7 pmol/L would support the sensitive effect of small thyroid concentration changes upon glucose and lipid metabolism.

Second, it could be possible that underlying pathogenetic factors in the MS led to low circulating free thyroxine levels. Recently, chronic inflammation was proposed to be an important etiologic factor in the origin of the MS and/or insulin resistance. Increased adipose tissue and circulating levels of inflammatory cytokines, including tumor necrosis factor α and interleukin 6, were found in obese and diabetic subjects [24]. In patients with nonthyroid illness, hypothalamic-pituitary thyroid function was suppressed at either hypothalamic-pituitary or thyroid gland levels by the activated cytokines, and a negative correlation between circulating thyroid hormones and cytokine concentrations was observed [25]. Accordingly, we speculated that chronic inflammatory status in MS might suppress the hypothalamic-pituitary-thyroid axis, thus resulting low circulating free thyroxine values.

Third, the association between thyroid hormones and MS could be indirect via some components of MS. When various features of the MS were analyzed separately, only BMI and hypertriglyceridemia were found to be associated with free thyroxine levels. Because obesity and hypertriglyceridemia are major determinants of the MS [26], an association of free thyroxine with these 2 components may result in a significant clustering of metabolic disorders. However, the interrelationship of free thyroxine with the other parameters of MS was inconsistent. For example, there was no difference of serum free thyroxine levels between subjects with and without high blood pressure. Although euthyroid subjects with low serum free thyroxine index and overt hypothyroid patients have been reported to be associated with hypertension [27,28]. It is thought there might be additional factors other than thyroid hormones involving in the regulation of blood pressure.

Finally, several epidemiologic studies have shown that MS poses a significant risk for atherosclerosis, even higher than diabetes mellitus [3]. Because thyroid hormones could increase cardiac oxygen consumption and whole blood volume, both of which might exacerbate the heart workload, lowered thyroid hormone levels would then become an adaptive response of human bodies to the preexisting cardiovascular disorders [29]. Indeed, lower serum free thyroxine concentrations have been reported in patients with ischemic heart disease with a more favorable prognosis [29].

If low serum thyroid hormone levels play role in the development of MS, then use of thyroid hormone might be potentially beneficial in patients with MS [30]. Alternatively, if low serum free thyroxine levels were coincidentally associated with MS, the circulating free thyroxine would be merely a marker of the MS, and treatment with thyroid hormone would be fruitless and even might cause some adverse effects, such cardiac arrhythmia or bone mass loss [31].

Clearly, this study had some limitations. First, it was cross-sectional in design, and a causal relationship between low free thyroxine and MS could not be identified. Second, the insulin resistance or systemic inflammation indexes, 2 probable cores of MS, were not measured. Thus, the more direct relationship between thyroid hormones and insulin sensitivity or inflammation could not be delineated. Third, the study did not make a complete evaluation of the pituitary-thyroid axis function, including the measurement of blood thyrotropin and triiodothyronine concentrations. It has been proposed that triiodothyronine, the active form of thyroid hormones in tissues [32], can cooperate with insulin to regulate glucose and lipid homeostasis [33,34]. Besides, subclinical thyroid disorders (eg, normal thyroid hormone levels, but with elevated or suppressed thyrotropin values) have also been reported to modify insulin sensitivity or lipid profiles in MS [35]. Therefore, this lack of thyrotropin and triiodothyronine measurement might potentially obviate the study results.

In summary, our study found that low serum free thyroxine levels, albeit normal, were associated with an increased risk of MS in a Chinese population. It is postulated that a maladaptive thyroid hormone response

may have led to MS. On the other hand, it is also plausible that MS may have given rise to this hormone pattern. Further studies are required to test these hypotheses.

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