The Korean Journal of Internal Medicine : 23:53-57, 2008

Free T4 is negatively correlated with body mass index in euthyroid women

Ho Sang Shon, M.D.[1], Eui Dal Jung, M.D.[1],
Sung Hee Kim, M.D.[2] and Ji Hyun Lee, M.D.[1]

Departments of Internal Medicine[1] and Family Medicine[2],
Catholic University of Daegu School of Medicine, Daegu, Korea

Background/Aims : Overt thyroid dysfunction is well known to affect weight. However, the influence of normal-range changes in thyroid status on body mass index (BMI) is unclear. We sought to evaluate thyroid function (free T4, TSH) and its possible relationship with BMI and lipid profiles in euthyroid subjects.

Methods : A total of 1572 euthyroid women (mean age 46.2 years) who visited Daegu Catholic University Medical Centre for primary health screening participated in this cross-sectional study. Women who were not euthyroid and women who took thyroid medication were excluded. TSH, free T4, and lipid profile [total-cholesterol, triglyceride (TG), HDL-C, LDL-C] were evaluated.

Results : Obese euthyroid women had lower free T4 levels than did lean euthyroid women. After adjustment for age and smoking, free T4, but not TSH, was significantly negatively correlated with BMI. After adjustment for age, smoking, and BMI, free T4 was negatively correlated with TG to a significant degree.

Conclusions : We demonstrated a negative correlation between free T4 within the normal range and BMI in euthyroid subjects. These findings suggest that low free T4 is associated with obesity in euthyroid subjects.

Key Words : Free T4; TSH; Body mass index

INTRODUCTION

Overt thyroid dysfunction clearly influences body mass index (BMI). Overt hypothyroidism is associated with weight gain, while hyperthyroidism is associated with weight loss[1, 2]. In 2003, the American Association of Clinical Endocrinologists (AACE) issued a statement encouraging doctors to consider treatment for patients who test out of the boundaries of a narrower margin based on a target TSH level of 0.3-3.0 mIU/liter[3]. Therefore, thyroid activity considered within the normal range by the current assay may actually be categorized as dysfunctional according to the 2003 AACE recommendation.

The association between normal-range thyroid function and BMI and dyslipidemia has been the subject of much debate. The DanThyr Study showed a positive correlation between BMI and serum TSH, a negative correlation between BMI and serum free T4, and no association between BMI and serum free T3. Obesity (BMI〉 30 kg/m^2) and serum TSH levels were significantly associated in this cohort study[4]. Of 87 obese women without complications, severely obese (BMI〉 40 kg/m^2) women had a higher serum TSH than mildly or moderately obese women (BMI〈 40 kg/m^2), and TSH was positively correlated with BMI[5]. The fifth Troms study showed a positive correlation between normal-range serum TSH and BMI in nonsmokers and demonstrated no correlation between serum TSH and BMI in smokers[6]. Michalaki et al. reported that morbidly obese subjects had higher levels of T3, free T3, T4, and TSH than did control subjects[7]. However, investigation of another cohort of 401 euthyroid subjects showed no significant relationship between BMI and either serum TSH concentration or free T4

•Received : August 31, 2007
•Accepted : February 12, 2008
•Correspondence to : Eui Dal Jung, M.D., Daegu Catholic University Medical Centre, Namgu Daemyung 4 dong, 3056-6, Daegu 705-718, Korea
Tel : 82-53-650-4218, Fax : 82-53-651-4009, E-mail : jed15@cu.ac.kr

Table 1. Anthropometric and clinical characteristics of lean and obese euthyroid women

	BMI < 25 (n=1235)	BMI ≥ 25 (n=337)	*p*
Age (years)	44.5±10.6	52.4±11.2	< 0.01
Systolic BP (mmHg)	118±17	131±18	< 0.01
Diastolic BP (mmHg)	70±11	77±14	< 0.01
Total cholesterol (mol/L)	4.78±0.88	5.28±0.97	< 0.01
Triglycerides (nmol/L)	1.41±1.04	1.88±1.18	< 0.01
LDL-cholesterol (mmol/L)	2.97±0.87	3.47±0.97	< 0.01
HDL-cholesterol (mmol/L)	1.67±0.37	1.50±0.32	< 0.01
TSH (mU/L)	2.17±1.02	2.16±0.99	ns
Free T4 (pmol/L)	16.25±2.00	15.87±2.18	< 0.01
Fasting glucose (mmol/L)	5.15±1.17	5.62±1.63	< 0.01

BP, blood pressure; ns, not significant.
Data are expressed as mean±standard deviation.

concentration[8]. These findings suggest that thyroid function within the normal range may be associated with BMI, but a definitive relationship is not clear at this point.

In the present study we sought to evaluate thyroid function within the normal range and to determine its possible relationship to BMI in euthyroid subjects.

MATERIALS AND METHODS

Subjects

The study group consisted of 1572 euthyroid women who visited the health promotion centre of Daegu Catholic University Medical Centre for primary health screening in 2006. In general, the study subjects appeared to be healthy. All subjects were interviewed and examined by doctors working at the health promotion centre. Detailed age, medical history, and smoking data were obtained. Height and weight were recorded for each subject. Subjects with any history of previous thyroid disorder, or who took medication related to a thyroid disorder, were excluded. Any subject with an abnormal free T4 concentration (reference range: 9-24 pmol/L) or TSH concentration greater than 5 mU/L or less than 0.3 mU/L was excluded. Obesity was defined as BMI ≥ 25, based on criteria issued by the Korean Society for The Study of Obesity.

Methods

Serum free T4 and TSH concentrations were measured via electric chemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany). BMI was calculated by dividing weight in kilograms by height in meters squared. Fasting venous blood samples were collected, promptly centrifuged, and analyzed within hours.

Statistical analysis

The relationships between serum TSH or free T4 and BMI were evaluated as continuous variables and as categorical variables (i.e., as quartiles of similar size). Independent samples *t*-test was applied to evaluate the differences among all parameters. When more than two groups were compared, we applied ANOVA with Tukey *post hoc* analysis. Multiple linear regression models were performed for associations of thyroid function with BMI and serum lipid concentrations, with adjustment for age, smoking, and BMI. SPSS 12 (SPSS Inc, IL, USA) was used for data analysis, and $p<0.05$ was considered statistically significant.

RESULTS

Anthropometric and clinical characteristics of euthyroid women

The mean age of the euthyroid women in this study was 46.2±11.2 years. The mean BMI of these women was 22.8±2.9. The proportion of smokers was 3.4%. Free T4 was lower in euthyroid women than in euthyroid men, whereas TSH was higher in euthyroid women than in euthyroid men (data not shown).

Thyroid function and BMI

Anthropometric and clinical characteristics of euthyroid women are summarized in Table 1. Obese euthyroid women had lower serum free T4 than did lean euthyroid women, while TSH did not differ significantly between lean and obese euthyroid women or euthyroid men (data not shown). On continuous variable evaluation, free T4 was negatively correlated with BMI, and TSH was not found to be associated with BMI in euthyroid women (Table 2). Free T4 was negatively correlated with diastolic BP. When subjects were categorized according to free T4 (quartiles

Table 2. Correlation of free T4 and TSH in euthyroid women

	Free T4		TSH	
	β	p	β	p
BMI*	-0.069	0.004	0.011	ns
Total cholesterol (mol/L)†	-0.017	ns	0.019	ns
TG (nmol/L)†	-0.046	0.04	0.018	ns
LDL-cholesterol (mmol/L)†	-0.013	ns	0.026	ns
HDL-cholesterol (mmol/L)†	0.001	ns	-0.045	ns
Systolic BP (mmHg)†	0.041	ns	0.021	ns
Diastolic BP (mmHg)†	0.048	0.04	0.036	ns
Fasting glucose (mmol/L)†	0.04	ns	-0.003	ns

BMI, body mass index; BP, blood pressure.
Data are expressed as mean±standard deviation.
Values of β are standardized regression coefficients.
*After adjustment for age and smoking.
†After adjustment for age, smoking, and BMI.

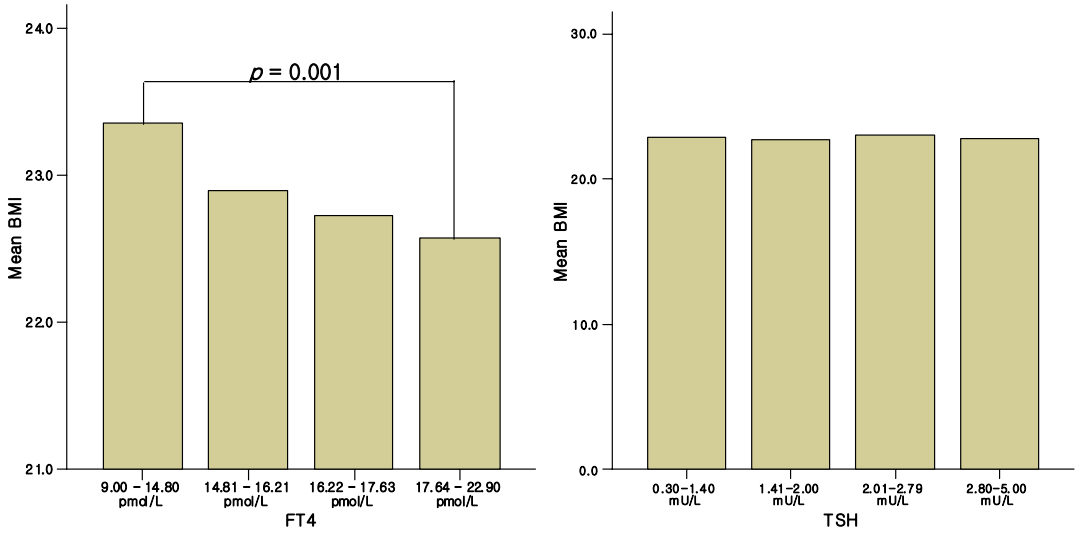

Figure 1. Association between free T4 and BMI. When subjects were divided according to category of free T4 (quartiles of similar sizes), higher levels of free T4 were associated with lower BMI (p=0.001), whereas there was no association between serum TSH and BMI.

of similar sizes), higher free T4 levels were associated with lower BMI, whereas serum TSH and BMI were not associated with each other (Figure 1).

Thyroid function and lipid profiles

After adjustment for age, smoking, and BMI, free T4 and triglyceride (TG) were found to be negatively correlated as continuous variables in euthyroid women (Table 2). TSH was not associated with total cholesterol, TG, HDL-cholesterol, or LDL-cholesterol in these same women. Free T4 was not found to be associated with total cholesterol, HDL-cholesterol, or LDL-cholesterol. When subjects were categorized according to free T4 (quartiles of similar sizes), higher free T4 levels were found to be associated with lower TG in euthyroid women. Conversely, free T4 was not found to be associated with total cholesterol, LDL-cholesterol, or HDL-cholesterol (Figure 2).

DISCUSSION

In the present study, free T4, but not TSH, was found to be negatively correlated with BMI in euthyroid women. Free T4 was

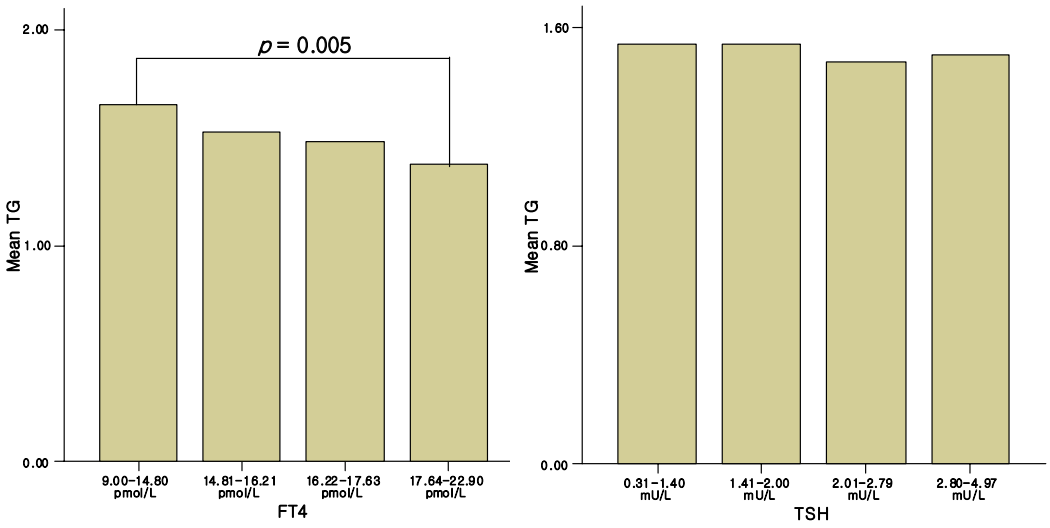

Figure 2. Association between free T4 and TG. When subjects were divided according to category of free T4 (quartiles of similar sizes), higher levels of free T4 were associated with lower TG (p=0.005), whereas no association was found between serum TSH and TG.

negatively correlated with BMI when considered as a continuous variable and when subjects were categorized according to serum TSH or free T4. Free T4 was lower in obese euthyroid women than in lean euthyroid women in the present study. Free T4 was negatively correlated with BMI after adjusting for age and smoking in euthyroid women, but the statistical significance of the relationship between the two variables was very low (β = -0.069). Other major factors correlating with BMI may exist.

Serum TSH did not differ between lean and obese euthyroid women. The relationship between thyroid status and BMI in euthyroid subjects has been investigated in previous studies. Our findings in this study are not in agreement with previous findings. Previous studies reported a positive association between TSH and BMI in euthyroid subjects[4-6], while we found that TSH was not associated with BMI in euthyroid women. This lack of correlation was sustained when analysis was repeated in men (data not shown). Knudsen et al.[4] reported that lower values of serum free T4 were associated with higher BMI, but found no association between serum free T3 and BMI. Roos et al.[9] reported that free T4 was significantly associated with four of the five components of the metabolic syndrome (abdominal obesity, TG, HDL-cholesterol, and blood pressure) independent of insulin resistance, but TSH was significantly associated with only TG. Free T4, but not TSH, was negatively correlated with tertile of HOMA-IR, and tertile of HOMA-IR was positively correlated with BMI in that study. This finding suggests that free T4 is negatively correlated with BMI.

Thyroid hormones may have discrepant effects on peripheral tissues, resulting in differential effects on central feedback inhibition of TSH release. Such a discrepancy might be due to differences between central and peripheral tissues in expression of type 1 and type 2 iodothyronine deiodinasewhich have different catalytic propertiesand to differences in expression of thyroid hormone receptor isoforms[10-12]. Polymorphism in the TSH receptor influences TSH effects and may also cause discrepant responses between central and peripheral tissues[13].

We found that free T4 was negatively correlated with diastolic blood pressure, but not with systolic blood pressure. Gumieniak et al.[14] reported that free T4 was lower, and TSH was higher, in hypertensive euthyroid subjects, compared with normotensive euthyroid subjects.

Roos et al.[9] reported that free T4 was lower in euthyroid women than in euthyroid men, whereas TSH was higher in euthyroid women than in euthyroid men. In the present study, we also found that free T4 was lower in euthyroid women than in euthyroid men, whereas TSH was higher in euthyroid women than in euthyroid men. This finding was sustained after adjusting for height, weight, body fat, and smoking. Therefore, other factors, such as sex hormones and genetic differences, may have an influence on the above T4 and TSH findings.

We found that free T4 was negatively associated with TG, whereas free T4 was not associated with total cholesterol, LDL-cholesterol, or HDL-cholesterol. TSH was not associated with any lipid parameters (total cholesterol, TG, LDL-cholesterol, or HDL-cholesterol), which is inconsistent with the well-known association of subclinical hypothyroidism and elevated levels of total cholesterol and LDL-cholesterol[15]. In euthyroid subjects, Roos et al.[9] reported that free T4 was negatively associated with

total cholesterol, LDL-cholesterol, and TG, whereas free T4 was positively associated with HDL-cholesterol, and TSH was positively associated with only TG. Therefore, the relationship between thyroid hormone and lipid profiles in euthyroid subjects must be further assessed.

Recently, Dullaart et al.[16] reported that carotid intima media thickness was associated with free T4, after controlling for clinical factors, lipid levels, and thyroid auto-antibodies in euthyroid subjects.

In conclusion, these findings suggest that, even within the euthyroid range, low normal thyroid function is associated with obesity.

REFERENCES

1) Baron DN. *Hypothyroidism: its aetiology and relation to hypometabolism, hypercholesterolaemia, and increase in body-weight. Lancet 271: 277-281, 1956*
2) Hoogwerf BJ, Nuttall FQ. *Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. Am J Med 76:963-970, 1984*
3) Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. *Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Endocr Pract 10:497-501, 2004*
4) Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jorgensen T. *Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90:4019-4024, 2005*
5) Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. *Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. Clin Endocrinol 62:487-491, 2005*
6) Nyrnes A, Jorde R, Sundsfjord J. *Serum TSH is positively associated with BMI. Int J Obes 30:100-105, 2006*
7) Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, Psyrogiannis AI, Kalfarentzos FE, Kyriazopoulou VE. *Thyroid function in humans with morbid obesity. Thyroid 16:73-78, 2006*
8) Manji N, Boelaert K, Sheppard MC, Holder RL, Gough SC, Franklyn JA. *Lack of association between serum TSH or free T4 and body mass index in euthyroid subjects. Clin Endocrinol 64:125-128, 2006*
9) Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. T*hyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 92:491-496, 2007*
10) Croteau W, Davey JC, Galton VA, St Germain DL. *Cloning of the mammalian type II iodothyronine deiodinase: a selenoprotein differentially expressed and regulated in human and rat brain and other tissues. J Clin Invest 98:405-417, 1996*
11) Zhang J, Lazar MA. *The mechanism of action of thyroid hormones. Annu Rev Physiol 62:439-466, 2000*
12) Flamant F, Samarut J. *Thyroid hormone receptors: lessons from knockout and knock-in mutant mice. Trends Endocrinol Metab 14:85-90, 2003*
13) Peeters RP, van Toor H, Klootwijk W, de Rijke YB, Kuiper GG, Uitterlinden AG, Visser TJ. *Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. J Clin Endocrinol Metab 88:2880-2888, 2003*
14) Gumieniak O, Perlstein TS, Hopkins PN, Brown NJ, Murphey LJ, Jeunemaitre X, Hollenberg NK, Williams GH. *Thyroid function and blood pressure homeostasis in euthyroid subjects. J Clin Endocrinol Metab 89:3455-3461, 2004*
15) Duntas LH. *Thyroid disease and lipids. Thyroid 12:287-293, 2002*
16) Dullaart RP, de Vries R, Roozendaal C, Kobold AC, Sluiter WJ. C*arotid artery intima media thickness is inversely related to serum free thyroxine in euthyroid subjects. Clin Endocrinol 67:668-673, 2007*