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ORIGINAL

Associations between subclinical thyroid disease and metabolic syndrome

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Abstract. Thyrotropin levels are outside normal reference range in subclinical thyroid disease. Metabolic syndrome (MetS) involves clustered cardiovascular risk factors, including abnormal lipids, insulin resistance, and hypertension. This study aimed to investigate associations between subclinical thyroid disease, thyrotropin levels, and metabolic syndrome in healthy subjects and identify associated biochemical markers. This cross-sectional study evaluated 9,055 healthy subjects examined at the Health Management Center, National Taiwan University Hospital from January 1, 2009 to December 31, 2009. Data collected included age, sex, height, weight, body mass index, waist circumference, pulse rate, and systolic/diastolic blood pressure. History of pregnancy, smoking/drinking status, family/personal thyroid disease, diabetes, dyslipidemia, and hypertension was obtained. Laboratory data included thyroid function tests, fasting glucose level, lipid profile, and C-reactive protein level. Participants were classified into subclinical hypothyroidism, subclinical hyperthyroidism, and euthyroid groups according to thyrotropin levels. In euglycemic subjects, thyroid-stimulating hormone (TSH) levels correlated positively with waist circumference, triglycerides (TG), non-high density lipoprotein (HDL) cholesterol, diastolic blood pressure. In subclinical hyperthyroid subjects, TSH levels correlated positively with low density lipoprotein cholesterol (LDL-C), non-HDL cholesterol. No significant correlations were found between TSH levels and variables in the subclinical hypothyroid group. In the entire study population, TSH levels correlated positively with TG, non-HDL cholesterol, and systolic blood pressure (SBP)/diastolic blood pressure (DBP), but no correlation was shown with HDL-C. No significant associations were seen between MetS prevalence and thyrotropin levels. No clinically relevant biochemical markers, differences in thyrotropin levels, or statistical correlations are shown between subclinical thyroid disease and metabolic syndrome in healthy individuals.

Keywords: Biochemical markers, Metabolic syndrome, Subclinical thyroid disease, Thyrotropin

SUBCLINICAL THYROID DISEASE is common among otherwise healthy middle-aged and older adults with abnormal levels of serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), or triiodothyronine (T3) [1]. Subclinical hypothyroidism and subclinical hyperthyroidism are diagnosed more frequently since widespread use of TSH screening with high-sensitivity assays [2]. However, studies defining which patients may require treatment are few and those published often disagree about population-based screening and treatment strategies.

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Subclinical hypothyroidism is defined as an elevated TSH (i.e., above high limit of reference range) with normal FT4 and T3 concentrations, and subclinical hyperthyroidism as a subnormal TSH (i.e., below lower limit of reference range) with normal FT4 and T3 levels [2]. Patients with subclinical hypothyroidism are usually asymptomatic, but may have cardiac dysfunction, elevated low-density lipoprotein, and neuropsychiatric symptoms [2]. Treatment may reduce progression to overt hypothyroidism, reduce symptoms, improve cardiac contractility, correct abnormal serum lipids, decrease goiter size, and reduce risk of adverse fetal effects in postpartum hypothyroidism.

Patients with subclinical hyperthyroidism are also usually asymptomatic or have only mild and nonspecific symptoms [2]. When subclinical hyperthyroidism is diagnosed, thyroid hormone levels are

repeated within three months or less if atrial fibrillation, cardiovascular disease, or osteoporosis are present, since these conditions are strongly associated with overt hyperthyroid disease [1]. Therapy is based upon TSH levels, risk of progression to overt hyperthyroidism, symptoms, and concurrent cardiac or skeletal diseases [1].

The metabolic syndrome (MetS) is a cluster of modifiable risk factors associated with increased risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus [3]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel Ⅲ (ATPⅢ) Guidelines (2001) defines MetS as having three of five modifiable risk factors: abnormal waist circumference (WC), high triglyceride levels, low levels of high-density lipoprotein cholesterol (HDL-C), high blood pressure, and high fasting plasma glucose concentration [4]. The updated NCEP ATPⅢ definition includes the American Diabetes Association (ADA) standard for normal fasting blood glucose value as less than 100mg/dL [5]. WC also may be defined using different ethnicity-specific values since Asian populations typically have a lower WC and/or BMI and a higher incidence of insulin resistance and diabetes mellitus [6].

MetS has been linked to subclinical thyroid disease in older adults due to the pathophysiology of thyroid function on lipid and glucose metabolism, blood pressure, and cardiovascular dysfunction [7]. However, studies examining whether subclinical thyroid disease and MetS share common biochemical markers or risk factors are still lacking. Also, few studies have analyzed associations between thyroid function and other biochemical data in patients with subclinical thyroid disease, primarily because sufficient data are not usually available for epidemiologic studies. The Health Investigation of the Health Management Center, National Taiwan University Hospital, collected ample data for determining whether early diagnostic evidence for subclinical thyroid disease and MetS is present in a large population of healthy individuals.

Thus, the purpose of this study was to investigate associations between subclinical thyroid disease, thyrotropin levels and MetS in healthy subjects and to identify possible specific associated biochemical markers. Identification of predictive biochemical markers may foster early detection of subclinical thyroid disease and help prevent progression to overt thyroid disease.

Methods

Design and subjects

This is a cross-sectional study reviewing medical records of 9095 consecutive healthy subjects who completed the routine Health Investigation at the Health Management Center, National Taiwan University Hospital, from January 1, 2009 to December 31, 2009. Participants in the Health Investigation in this study comprised healthy subjects without known systemic disease, not taking any medication that may affect thyroid function and not pregnant or within the first year of the postpartum period. Subjects with a history of thyroid dysfunction (hyperthyroidism or hypothyroidism) were excluded from this study after detailed review. The study protocol was reviewed and approved by the institutional review board of National Taiwan University Hospital. As this retrospective study was carried out with anonymous data without any link to personal information, the informed consent for the study was waived.

Subjects' demographic and clinical data

Basic demographic information (age, sex) and physical data were collected, including body height, body weight, BMI, WC, pulse rate, and systolic and diastolic blood pressure. Histories of pregnancy, smoking and drinking status, family and personal history of thyroid diseases, diabetes, dyslipidemia and hypertension were also obtained.

Laboratory data were derived from fasting blood samples obtained from each participant. Laboratory tests performed included thyroid function tests (TSH, T3, T4), fasting glucose level, lipid profile (triglyceride, low density lipoprotein cholesterol (LDL-C), HDL-C, non-HDL cholesterol), and high sensitivity C-reactive protein (hs-CRP).

Definition of subclinical thyroid diseases

For the purpose of this study, subclinical thyroid diseases are defined as abnormal TSH levels with normal free thyroxine (T4) and triiodothyronine (T3) concentration. Patients were classified into three TSH groups representing subclinical hypothyroidism, subclinical hyperthyroidism or euthyroid status. Classification into the three groups was based on serum levels of thyroid stimulating hormone (TSH) as previously defined for each group: subclinical hypothyroidism 4-10 mU/L, subclinical hyperthyroidism <0.4 mU/L, and euthyroid 0.4-4.0 mU/L) [1, 2].

Definitions of metabolic syndrome

For the purpose of this study, MetS is diagnosed based on the published NCEP ATP III criteria [4], along with updated threshold values for abdominal obesity and fasting glucose in the Asian population [5]. Diagnosis requires having any three of five risk factors: abnormal WC, high triglyceride levels, low HDL-C, high blood pressure, and high fasting blood glucose concentration.

Statistical analysis

Subjects' demographic data and laboratory examination data are presented as mean±SD by TSH groups, except for gender, for which data are shown as n (%). Data among three groups were compared using Pearson chi-square test for sex; Kruskal-Wallis test for other continuous variables due to data that were not normally distributed. Mann-Whitney U test was performed for the pair-wise *post-hoc* comparison between two groups. Partial correlation analysis was performed to identify the correlation of TSH levels and variables related to cardiovascular disease, MetS, liver function, and renal function after adjusting for age and sex for each group. Binary logistic regression analysis was applied to compare the prevalence of MetS and its components among TSH groups after adjusting for age and sex. All statistical assessments were two-tailed and $P<0.05$ was considered significant. An adjusted $P=0.0167$ (0.05/3) was considered for *post-hoc* multiple comparisons. Data were analyzed using SAS 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 9,095 consecutive healthy subjects (5,214 men and 3,881 women) were examined in the Health Investigation of the Health Management Center. Subjects with a history of thyroid dysfunction (hyperthyroidism or hypothyroidism) were excluded from this study after detailed disease review. A final total of 9,055 subjects were retained for evaluation. All subjects were classified into three groups according to TSH levels, including 239 subjects in the subclinical hyperthyroid group (TSH<0.40 mU/L), 8404 in the euthyroid group (TSH: 0.4-4.0 mU/L), and 412 in the subclinical hypothyroid group (TSH: 4.00-10 mU/L).

Table 1 shows subjects' demographic and physical/clinical data by group. The distribution in sex and age were significantly different between the groups. Subjects in both the subclinical hypo- and hyper-thyroid groups had lower body height and weight than the euthyroid group. However, BMI results were consistent between the three groups. Pulse rates were significantly different between the three groups.

Table 2 shows the comparison of laboratory examination results by TSH group. Values obtained for triglycerides, HDL-C, LDL-C, non-HDL cholesterol, free T4, and hs-TSH were significantly different between the three groups.

Table 3 represents the correlation of TSH levels with the variables related to cardiovascular disease, MetS by

Table 1 Subjects' demographic and physical/clinical data by TSH groups

Varaibles	Euthyroid 0.4-4.0 mU/L (n=8,404)	Subclinical hypothyroid 4.00-10 mU/L (n=412)	Subclinical hyperthyroid <0.40 mU/L (n=239)	*P*-value
Sex, n(%)				<0.001*
Males	4909 (58.4)	175 (42.5) †	110 (46.0) †	
Females	3495 (41.6)	237 (57.5)	129 (54.0)	
Age, years	51.62 ± 11.67	53.01 ± 11.55†	53.02 ± 13.27	0.014*
Body height, cm	164.34 ± 9.22	162.29 ± 8.25†	163.05 ± 7.94†	<0.001*
Body weight, Kg	65.27 ± 12.08	62.79 ± 10.89†	63.39 ± 12.19†	<0.001*
Body mass index, Kg/m^2	23.99 ± 3.45	23.71 ± 3.37	23.76 ± 3.57	0.170
Waist circumference, cm	85.64 ± 8.92	85.21 ± 8.15	85.37 ± 10.09	0.576
Pulse rate, beats/min.	72.9 ± 10.79	71.89 ± 11.45†	75.46 ± 12.29†‡	<0.001*
Systolic pressure, mmHg	119.3 ± 15.56	119.85 ± 16.36	119.45 ± 15.57	0.774
Diastolic pressure, mmHg	71.02 ± 10.43	70.91 ± 10.43	70.17 ± 9.38	0.457

Data were presented as mean±SD except for n(%) for sex. Data between three groups were compared using Pearson chi-square test for sex; Kruskal-Wallis test for other continuous variables due to lack of normal distribution of data. Mann-Whitney U test was performed for the pair-wise *post-hoc* comparison between two groups. *$P<0.05$, significantly different between three groups; †$P<0.0167$, significantly different compared with euthyroid group; ‡$P<0.0167$, significantly different compared with subclinical hypothyroid group

Table 2 Comparison of laboratory examination values by TSH levels

Variables	Euthyroid 0.4-4.0 mU/L (n=8,404)	Subclinical hypothyroid 4.00-10 mU/L (n=412)	Subclinical hyperthyroid <0.40 mU/L (n=239)	*P*-value
hs-CRP	0.17 ± 0.4	0.17 ± 0.36	0.22 ± 0.7	0.988
Fasting glucose, mg/dL	95.57 ± 18.07	94.07 ± 15.58	94.79 ± 17.32	0.211
Total cholesterol, mg/dL	203.44 ± 34.57	203.28 ± 36.02	198.12 ± 39.35	0.087
Triglycerides, mg/dL	118.72 ± 75.07	117.6 ± 71.37	104.8 ± 66.14†‡	0.001*
HDL-C, mg/dL	50.58 ± 12.93	51.75 ± 12.41†	52.59 ± 13.59	0.004*
LDL-C, mg/dL	116.23 ± 31.23	114.66 ± 30.19	109.97 ± 34.19†	0.005*
Non-HDL cholesterol, mg/dL	152.86 ± 34.35	151.54 ± 34.04	145.53 ± 38.35†‡	0.003*
Free T4 (CIA)	1.22 ± 0.18	1.13 ± 0.17†	1.48 ± 0.56†‡	<0.001*
hs-TSH (CIA)	1.63 ± 0.77	5.26 ± 1.27†	0.19 ± 0.14†‡	<0.001*

Data were presented as mean±SD. Data among three groups were compared using Kruskal-Wallis test for other continuous variables due to lack of normal distribution of data. Mann-Whitney U test was performed for the pair-wise post-hoc comparison between two groups. $^{*}P<0.05$, significantly different between three groups; $^{\dagger}P<0.0167$, significantly different compared with euthyroid group; $^{\ddagger}P<0.0167$, significantly different as compared with subclinical hypothyroid group

Table 3 Correlation of TSH levels and variables related to cardiovascular disease, metabolic syndrome, by TSH groups and all subjects after adjusting for age and sex

Variables	All (n=9,055)		Euthyroid 0.4-4.0 mU/L (n=8,404)		Subclinical hypothyroid 4.00-10 mU/L (n=412)		Subclinical hyperthyroid <0.40 mU/L (n=239)	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Waist circumference, cm			0.024	0.031*	0.006	0.900	0.075	0.251
Fasting glucose, mg/dL	0.011	0.314	<0.001	0.998	-0.028	0.572	-0.012	0.855
Triglycerides, mg/dL	0.053	<0.001*	0.054	<0.001*	0.089	0.073	0.087	0.186
HDL-C, mg/dL	-0.023	0.028*	-0.018	0.110	-0.044	0.376	0.052	0.430
LDL-C, mg/dL	0.017	0.101	0.020	0.069	0.010	0.837	0.173	0.008*
Non-HDL cholesterol, mg/dL	0.029	0.005*	0.035	0.002*	0.041	0.411	0.181	0.005*
Systolic pressure (RA), mmHg	0.025	0.020*	0.021	0.051	-0.018	0.713	0.020	0.756
Diastolic pressure (RA), mmHg	0.025	0.020*	0.022	0.044*	-0.012	0.808	0.060	0.358
hs-CRP	0.011	0.314	0.018	0.097	-0.005	0.916	-0.019	0.777

Results were presented as the coefficient (r) of partial correlation analysis after adjusting for age and sex for each group (euthyroid, subclinical hypothyroid, and subclinical hyperthyroid groups). $^{*}P<0.05$, indicated significant correlation with TSH levels

TSH levels in the three groups and in the entire investigated population after adjusting for age and sex. In the euthyroid group, TSH levels were positively correlated with WC, triglycerides, non-HDL cholesterol, and DBP. In the subclinical hyperthyroid group, TSH levels were positively correlated with LDL-C and non-HDL cholesterol. No significant correlation was found between TSH levels and variables observed in the subclinical hypothyroid group. In the entire population of 9055 subjects, the TSH level correlated positively with triglyceride, non-HDL cholesterol, and systolic blood pressure (SBP)/diastolic blood pressure (DBP), but no correlation was shown with HDL-C.

Table 4 shows the results of comparison of the prevalence of MetS and its components by TSH levels after adjusting for age and sex. The prevalence of MetS and its components are not associated with TSH levels (all *P*-values > 0.05).

Discussion

In this cross-sectional study of a large healthy population receiving routine health examination, no statistical correlation was found between subclinical thyroid diseases and MetS. The prevalence of MetS did not differ between the three levels of TSH that defined the three groups of healthy individuals. However, although the two disease entities had some common biochem-

Table 4 Comparison of the prevalence of metabolic syndrome and its components by TSH groups after adjusting for age and sex

Variables	Euthyroid 0.4-4.0 mU/L (n=8,404)	Subclinical hypothyroid 4.00-10 mU/L (n=412)	Subclinical hyperthyroid <0.40 mU/L (n=239)	*P*-value
Having metabolic syndrome				0.994
Yes	861 (10.25%)	44 (10.68%)	27 (11.30%)	
No	7543 (89.75%)	368 (89.32%)	212 (88.70%)	
Abnormal waist circumference				0.581
Yes	3646 (43.38%)	213 (51.70%)	110 (46.03%)	
No	4758 (56.62%)	199 (48.30%)	129 (53.97%)	
Abnormal TG level				0.683
Yes	1973 (23.48%)	94 (22.82%)	45 (18.83%)	
No	64.31 (76.52%)	318 (77.18%)	194 (81.17%)	
Abnormal HDL-C				0.975
Yes	2495 (29.69%)	122 (29.61%)	74 (30.96%)	
No	5909 (70.31%)	290 (70.39%)	165 (69.04%)	
Abnormal blood pressure				0.702
Yes	2144 (25.51%)	111 (26.94%)	59 (24.69%)	
No	6260 (74.49%)	301 (73.06%)	180 (75.31%)	
Abnormal fasting glucose				0.939
Yes	1994 (23.73%)	99 (24.03%)	51 (21.34%)	
No	6410 (70.79%)	313 (75.97%)	188 (78.66%)	

Abnormal waist circumference (males: waist circumference ≥ 90 cm, females: waist circumference ≥ 80 cm); abnormal TG (males or females: triglyceride levels ≥ 150 mg/dL); Abnormal HDL-C (males: < 40 mg/dL, females: < 50 mg/dL); Abnormal blood pressure (males or females: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg); Abnormal fasting glucose (males or females: ≥ 100 mg/dL) Results were summarized as n (%) for a given TSH level; Prevalence was compared using binary logistic regression analysis after adjusting for age and sex in each group.

istry markers, there were no significant relationships. These study results do not suggest meaningful associations between MetS and subclinical thyroid disease or that the two disease entities have specific significant biochemical markers in common.

Associations between subclinical thyroid disease and MetS have been suggested in previous studies. A recent study in Taiwan explored the relationship between serum TSH levels and components of MetS, concluding that even slight increases in TSH, as in subclinical hypothyroidism, may be a MetS risk factor; in that study, TSH levels were significantly higher in the MetS group than in the non-MetS group [8]. In a study of MetS prevalence, subclinical thyroid dysfunction was present in about 8% of elderly subjects, of whom only one-third had MetS, including 32.8% with subclinical hypothyroidism and 28.1% with subclinical hyperthyroidism [7]. The main findings in that study indicated that lipid profiles were more adversely affected by subclinical hypothyroidism and therefore would more often result in MetS than subclinical hyperthyroidism. In another large-scale study [9], MetS prevalence was similar in euthyroid individuals and those with subclinical thyroid disease. However, although TSH concentrations showed a positive correlation with total cholesterol, triglycerides and WC, FT4 correlated positively with HDL-C and inversely correlated with WC, insulin and HOMA-IR levels, suggesting that subclinical thyroid disease was not associated with increased risk for MetS [9]. In that study, low thyroid function, even in euthyroid subjects, predisposed subjects to higher glucose, insulin, and HOMA-IR levels. Subclinical hypothyroidism, even with small differences in thyroid function and normal TSH, was suggested to be related to MetS and its components, especially BMI and obesity [10]. Our initial hypothesis of a relationship between subclinical thyroid disease and MetS was formed based on the studies above, but may be unfounded. We agreed with other investigators that a large-scale study of healthy patients receiving complete analysis of an extensive range of clinical laboratory data would reveal possible relationships between subclinical thyroid disease and MetS, and might suggest specific associated biochemical markers.

The fact that our large scale study demonstrated no significant associations between subclinical thyroid diseases and MetS may reflect that subclinical hypothyroidism in most aging populations follows a physi-

ological course, as in hypertension, instead of assuming a typical pathological state. Therefore, although subclinical hypothyroidism has been linked to MetS in small-scale aged population-based studies, patients with subclinical hypothyroidism in our large-scale study may not be at risk for developing MetS. Since subclinical hyperthyroidism is related to a subclinically hypermetabolic state, dysmetabolic states such as hyperglycemia and hyperlipidemia are less likely to present. Thus, no associations between MetS and subclinical hypothyroid, subclinical hyperthyroid, and euthyroid groups will likely be shown in a very large population analysis, although hypermetabolic changes may still be noted with mild biochemical fluctuations.

Subclinical hypo- and hyperthyroidism were common among healthy participants evaluated in this study. This is true in other studies of large populations, and incidence generally increases with age, which suggested to some researchers that abnormal TSH levels are more a factor of aging than predictors of thyroid diseases. Clinical suspicion of hypothyroidism in older adults may be delayed because common complaints such as fatigue and constipation are attributed to aging rather than signs of thyroid dysfunction [1]. We, too, suggest that subclinical thyroid states are part of the physiological and aging process rather than a disease state. For example, impaired diastolic refilling has been suggested to be a result of subclinical thyroid disease [11], while large, longitudinal studies show it to be a result of aging [12, 13].

The present study still provides important findings for subclinical thyroid disease. For subclinical hyperthyroidism (TSH<0.40 mU/L), LDL-C, and non-HDL cholesterol, correlated significantly with TSH levels. They appear to be highly predictive, indicating that thyroid hormones influence all aspects of lipid metabolism, including synthesis, mobilization and degradation. Hypermetabolic states are unlikely to be strongly related to dysmetabolic states, but may still be related to mild biochemical fluctuation. More prospective observation is needed to further elucidate this observation. For subclinical hypothyroidism (TSH 4-10 mU/L), no positive correlations were found between laboratory values and TSH levels due to decreased activity of specific analytes (e.g., lipoproteins, liver fatty acids) corresponding to low TSH levels. Correlations were also not seen between the inflammatory marker C-reactive protein and thyrotropin levels in the three groups. Hypothyroidism typically is associated with elevated C-reactive protein and total homocysteine, which are risk factors for coronary heart disease, even though only C-reactive protein, and not homocysteine, is elevated in subclinical hypothyroidism [14]. This raises the question of whether C-reactive protein is a risk factor for heart disease in individuals with hypothyroidism. Although a large-scale study suggested that treating subclinical hypothyroidism improves several risk factors for coronary heart disease, including WC, LDL-C, total cholesterol, and endothelial function, C-reactive protein level was not reduced [15].

This study is limited in that it is cross-sectional and cause/effect relationships were not shown. The study also was not longitudinal. Although the incidence of subclinical thyroid disease in the large study population of healthy individuals is similar to that of the normal population, it lacks follow-up of subjects, and therefore is not a cohort study, which would be preferable. Future study is needed with a large cohort and a sufficient follow-up period to help determine the significance of early detection of subclinical thyroid disease and longer-term associations with metabolic syndrome.

In conclusion, no clinically relevant biochemical markers, differences in thyrotropin levels, or statistical correlations are shown between subclinical thyroid disease and metabolic syndrome in healthy individuals. LDL-C and non-HDL cholesterol, significantly correlate with subclinical hyperthyroidism and may be predictive risk factors, but future prospective studies are required for further investigation. Results of this study add to global knowledge and will be especially applicable to Asian populations. Future cohort studies in subclinical thyroid diseases should include more biomarkers for longitudinal observations.

References

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228-238.
2. J Jones DD, May KE, Geraci SA (2010) Subclinical thyroid diseases. *Am J Med* 123: 502-504.

3. Serafidis PA, Nilsson PM (2006) The metabolic syndrome: a glance at its history. *J Hypertens* 24: 621-626.
4. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) (2001) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486-2497.
5. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation* 112: 2735-2752.
6. Tan CE, Ma S, Wai D, Chew SK, Tai ES (2004) Can we apply the National Cholesterol education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 27: 1182-1186.
7. Lai CC, Tang SH, Pei D, Wang CY, Chen YL, Wu CZ, Hsiao FC, Chen HS, Wang JY (2011) The prevalence of subclinical thyroid dysfunction and its association with metabolic syndrorme in Taiwanese elderly. *Int J Gerontol* 5: 25-29.
8. Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, Liu H, Li C, Xue H, Li N, Yu J, Shi L, Bai X, Hou X, Zhu L, Lu L, Wang S, Xing Q, Teng X, Teng W, Shan Z (2011) The relationship between serum thyrotropin and components of metabolic syndrome. *Endocr J* 58(1): 23-30.
9. Garduño-Garcia Jde J, Alvirde-Garcia U, López-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas CA (2010) TSH and free thyroxine concentrations are associated with differeing metabolic markers in euthyroid subjects. *Eur J Endocrinol* 163(2): 273-278.
10. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, Jørgensen T (2005) Small difference in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab* 90(7): 4019-4024.
11. Biondi B, Cooper DS (2008) The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29(1): 76-131.
12. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB (1994) Low serum thyrotropin as a risk factor for atrial fibrillation in older patients. *N Engl J Med* 331(1): 1249-1252.
13. Parle JV, Maisonneuve P, sheppard MC, Boyle P, Franklyn JA (2001) Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet* 358: 861-865.
14. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Müller B (2003) Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? *Atherosclerosis* 166(2): 379-386.
15. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU (2007) The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 92: 1715-1723.