Original Article

Subclinical hypothyroidism and metabolic risk factors association: A health examination-based study in northern Taiwan

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is defined as elevation in serum thyroid-stimulating hormone (TSH) levels despite normal serum levels of free thyroxine. It remains controversial whether people with SCH have higher total cholesterol and low-density lipoprotein cholesterol levels compared to normal-thyroid subjects. The aim of this study was to assess the metabolic risk factors for SCH.

Methods: Subjects were recruited from the health examination center of Chang Gung Memorial Hospital, Linkou, from January 1, 2010 to December 31, 2011. This was a cross-sectional review of medical records. The subjects were ethnic Taiwanese residents without known thyroid disease at baseline.

Results: A total of 22,324 subjects received annual health examination at Chang Gung Memorial Hospital from 2010 to 2011. Among them, 15,943 subjects were included as the normal thyroid group (NG), and 203 subjects (101 men and 102 women) met the criteria for SCH. The prevalence of metabolic syndrome (MetS) in the NG was 26.2% in men and 18.7% in women, whereas that in the SCH group was 39.6% in men and 29.4% in women. Women in the SCH group showed significantly higher cholesterol, triglyceride, non-high density lipoprotein (HDL) and cholesterol/HDL levels than those in the NG ($p < 0.05$).

Conclusion: Because SCH is more prevalent in women and the risk increases with age, greater attention to the risk of MetS development is warranted. As for men, regardless of thyroid function, the risk of MetS development with age still warrants attention. Thus, our data suggest that national guidelines for screening for thyroid disease using serum TSH levels in the elderly are mandatory.

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At a glance commentary

Scientific background on the subject

It still remains controversial whether people with sub-clinical hypothyroidism had higher lipid abnormality or higher risk for cardiovascular disease development. The aim of this study was to assess the association of metabolic risk factors for subclinical hypothyroidism among people with health examination-based group.

What this study adds to the field

Subclinical hypothyroidism is more prevalent in women and the risk increases with age, greater attention to the risk of metabolic syndrome development is warranted. Our data suggest that national guidelines for screening for thyroid disease using serum TSH levels in the elderly are mandatory.

Subclinical hypothyroidism (SCH) is defined as elevation of serum thyroid-stimulating hormone (TSH) levels beyond the normal range despite normal serum levels of free thyroxine [1]. SCH or mild thyroid failure is a common problem, with a prevalence of 3%−8% in the population without known thyroid disease [2,3]. There were not many data about the prevalence of SCH in Taiwan. In aged people, there was a calculated 2.5% with abnormal high in TSH level [4], where in recent published data of aged 20 years or older with the prevalence around 1.5% [5]. The prevalence increases with age and is higher in women [2,5]. SCH may be associated with increased risks for cardiovascular disease (CVD), especially in patients with TSH levels above 10 mU/L.

According to the reports of Nutrition and Health Survey in Taiwan between 2006 and 2009, the prevalence of adult metabolic syndrome (MetS) was increased from 19.5% to 25.7% in males and 13.8%−20.4% in females. Recently, abnormalities in several parameters considered risk factors for CVD have been identified in patients with SCH. These risk factors include serum homocystein and C-reactive protein (CRP), endothelial dysfunction, and arterial stiffness [6]. With progressive thyroid failure over time, SCH gradually evolves into overt hypothyroidism, thereby rendering patients liable to an increased CVD risk with the atherogenic process having been initiated long before the clinical diagnosis of hypothyroidism is established [7].

Therefore, the purpose of this health examination-based study was to determine the prevalence of MetS in the SCH population. We used detectable markers such as weight, blood pressure, lipid profiles and blood glucose to establish early diagnostic markers for the risk of future CVD development among SCH subjects.

Methods

Subjects

Subjects were recruited from the health examination center of Chang Gung Memorial Hospital, Linkou, from January 1, 2010 to December 31, 2011. This was a cross-sectional review of medical records. The subjects were ethnic Taiwanese residents who had prior systemic diseases, but the majority was disease free when admitted to this center for their annually examination. Those healthy subjects without known prior systemic disease and who were not taking any medication at the time were included as the normal thyroid group (NG). All subjects were asked if they ever had hyperthyroidism, hypothyroidism, or thyroid surgery; individuals that had been treated with anti-thyroid drugs, radioiodine therapy, or thyroxine hormone supplement, or had undergone thyroid surgery were excluded. Those with a history of thyroid cancer or head and neck malignancies were also excluded.

From our health examination system, there were lacking free thyroxine data to confirm whether it is true hypothyroid or subclinical hypothyroidism. Therefore, we cut the point of TSH below 10 as subclinical hypothyroid, and we also ask every subject any symptoms and signs about the hypothyroidism when TSH above the normal range. When overt hypothyroid favored, then refer that subject to metabolic clinic and exclude from our enrollment.

Protocols

Standardized protocols were employed by all examiners, and data were collected by trained staff. Subjects were instructed to fast for 10−12 h prior to blood test; compliance was confirmed via an interview prior to examination. Information on health and lifestyle factors was also collected, as well as history of hypertension, diabetes mellitus, and hyperlipidemia, and information on daily use of medication. Among other data, clinical measurements included height, weight, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Blood from each subject was assayed for TSH, fasting glucose and postprandial glucose, uric acid (UA), cholesterol (Chol), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high-sensitivity (hs)-CRP. The study protocol was approved by the Ethic Committee on Research of Chang Gung Memorial Hospital; all subjects gave their informed written consent.

Biochemical measurements

Serum TSH levels were measured with a chemiluminescent immunometric assay using an automated immunoassay analyzer (Siemens Medical Solution Diagnostics, UK). The normal range of this index was 0.35−5.50 mU/L. Serum Chol,

HDL-C, LDL-C, TG, glucose, and UA levels were measured using standard techniques with a Hitachi-7600 chemistry analyzer (Tokyo, Japan), and according to the manufacturer's protocols.

Definitions of MetS

MetS was diagnosed based on the published NCEP ATP III criteria [8], along with updated threshold values for abdominal obesity and fasting glucose levels in the Asian population [9]. Diagnosis by these criteria requires having any three of five risk factors: abnormal WC (men $\geq$ 90 cm, women $\geq$ 80 cm), high TG levels ($\geq$150 mg/dL), low HDL-C (men < 40 mg/dL, women < 50 mg/dL), high BP ($\geq$130/85 mmHg), and high fasting glucose concentration ($\geq$100 mg/dL).

Statistical analyses

The comparison of clinical and laboratory data between the SCH group and NG was made by independent-sample t-test. The association between SCH and each MetS component was tested using both univariate and multivariate logistic regression with the adjustment of BMI and age because they were important confounders to MetS. Furthermore, the linear trend of the prevalence of MetS across age groups was assessed by Cochran-Armitage chi-square analysis, which was also used to test the linear trend of the prevalence of SCH across different numbers of MetS components. All statistical analyses were conducted separately in men and women. All of the data analyses were performed using Statistics Package for the Social Sciences 15.0 (SPSS Inc., Chicago, IL).

Results

A total of 22,324 subjects received their annual health examination at Chang Gung Memorial Hospital, Linkou, from January 1, 2010 to December 31, 2011. Among them, 15,943 subjects (9620 men and 6323 women) were included as the NG; that is no prior history or previous management of hypertension, diabetes, hyperlipidemia, or thyroid abnormality. There were 203 normal subjects (101 men and 102 women) that met the criteria for SCH, as judged by elevated serum TSH levels (5.5−10 mU/L; normal range 0.35−5.5 mU/L). In our data base were all exclude the possibility of overt hypothyroid. Table 1 showed the demographic and biochemical data of study groups (SCH, NG) by gender difference.

The mean age of the SCH group was 53.8 ± 14.4 years for men and that of the NG was much younger (48.1 ± 12.1 years, p < 0.001). There was no statistical difference in the mean age of women between the SCH group and NG. The distribution of WC was significantly different between the SCH group and NG in men (p = 0.019). There was no difference in BMI between the groups in both genders. The SBP was significantly different in both men and women between the SCH group and NG (p < 0.05). The DBP was much higher in the SCH group than in the NG in men (p < 0.05), but not in women. However, significantly higher Chol, TG, Non-HDL, and Chol/HDL levels were found in the SCH (women) group than in the NG (p < 0.05). There was no statistical significance in hs-CRP levels in both the SCH group and NG between men and women (Table 1).

Table 2 shows the association between the two groups and each component of MetS stratified by gender. No significant association between SCH and abdominal girth, HDL, blood

Table 1 The demographic and clinical data of study groups (NG, SCH) by gender difference.

Variable	Men			Women		
	NG	SCH	p	NG	SCH	p
	(n = 9620)	(n = 101)		(n = 6323)	(n = 102)	
Age (year)	48.1 ± 12.1	53.8 ± 14.4	<0.001	48.5 ± 12.3	50.9 ± 11.0	0.053
Height (cm)	169.4 ± 6.2	168.8 ± 6.4	0.338	156.9 ± 5.8	156.6 ± 4.4	0.637
Weight (kg)	71.2 ± 11.1	71.7 ± 11.7	0.671	56.4 ± 8.8	57.4 ± 9.3	0.245
WC (cm)	86.8 ± 8.8	88.9 ± 8.0	0.019	79.9 ± 9.4	81.4 ± 9.3	0.101
BMI (kg/m2)	24.8 ± 3.3	25.1 ± 3.5	0.339	22.9 ± 3.5	23.4 ± 3.6	0.178
SBP (mm Hg)	132.4 ± 16.6	137.9 ± 21.6	0.001	124.7 ± 19.0	128.8 ± 20.8	0.034
DBP (mm Hg)	82.5 ± 11.1	85.1 ± 13.1	0.021	75.8 ± 10.8	76.9 ± 11.1	0.280
Laboratory data						
AC (mg/dL)	95.2 ± 22.6	92.7 ± 12.2	0.272	91.0 ± 17.1	93.8 ± 21.3	0.094
PC (mg/dL)	101.7 ± 43.2	101.1 ± 36.1	0.897	97.6 ± 31.6	101.6 ± 38.8	0.218
UA (mg/dL)	6.5 ± 1.3	6.8 ± 1.2	0.136	4.9 ± 1.1	4.9 ± 1.0	0.646
Chol (mg/dL)	194.2 ± 35.2	200.1 ± 34.1	0.150	193.2 ± 35.0	204.1 ± 40.4	0.006
TG (mg/dL)	151.7 ± 122.6	167.6 ± 101.6	0.196	106.3 ± 62.7	135.8 ± 77.3	<0.001
HDL (mg/dL)	48.3 ± 11.7	47.0 ± 10.3	0.283	59.9 ± 14.2	59.4 ± 16.8	0.751
LDL (mg/dL)	117.1 ± 31.0	121.1 ± 34.5	0.206	112.8 ± 31.1	117.8 ± 34.1	0.112
Non-HDL (mg/dL)	146.0 ± 35.6	153.2 ± 35.3	0.080	133.5 ± 34.6	143.1 ± 38.8	0.013
Chol/HDL	4.2 ± 1.3	4.5 ± 1.2	0.080	3.4 ± 1.0	3.7 ± 1.1	0.007
LDL/HDL	2.6 ± 0.9	2.7 ± 0.9	0.087	2.0 ± 0.8	2.1 ± 0.8	0.100
hs-CRP (mg/dL)	2.3 ± 5.9	2.5 ± 5.0	0.781	1.7 ± 3.9	1.7 ± 2.1	0.936

Abbreviation: NG: normal thyroid group; SCH: subclinical hypothyroidism; WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AC: fasting blood glucose; PC: postprandial blood glucose; UA: uric acid; Chol: cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; hs-CRP: high sensitivity C-reactive protein.

Table 2 The association of subclinical hypothyroidism *v.s.* normal thyroid group with each component of metabolic syndrome stratified by gender.

	Normal thyroid group		Subclinical hypothyroidism		Crude OR (95% CI)[a]	p[a]	Adjusted OR (95% CI)[b]	p[b]
	Total No	No. of case (%)	Total No	No. of case (%)				
WC								
Male (≥90 cm)	9620	3398 (35.3)	101	47 (46.5)	1.59 (1.08–2.36)	0.020	1.53 (0.85–2.73)	0.155
Female (≥80 cm)	6323	3077 (48.7)	102	58 (56.9)	1.39 (0.94–2.06)	0.102	1.24 (0.74–2.09)	0.410
TG ≥ 150 mg/dL								
Male	9620	3487 (36.2)	101	49 (48.5)	1.66 (1.12–2.45)	0.012	1.66 (1.10–2.50)	0.015
Female	6323	1013 (16.0)	102	33 (32.4)	2.51 (1.65–3.82)	<0.001	2.40 (1.53–3.75)	<0.001
HDL<40 or 50 mg/dL								
Male	9620	2201 (22.9)	101	24 (23.8)	1.05 (0.66–1.67)	0.834	0.99 (0.61–1.59)	0.966
Female	6323	1561 (24.7)	102	33 (32.4)	1.46 (0.96–2.22)	0.077	1.37 (0.88–2.12)	0.166
SBP≥130 or DBP≥85 mm Hg								
Male	9620	5425 (56.4)	101	65 (64.4)	1.40 (0.93–2.10)	0.110	1.24 (0.82–1.89)	0.314
Female	6323	2257 (35.7)	102	45 (44.1)	1.42 (0.96–2.11)	0.080	1.23 (0.80–1.87)	0.347
AC ≥100 mg/dL								
Male	9620	1754 (18.2)	101	19 (18.8)	1.04 (0.63–1.72)	0.881	0.72 (0.43–1.23)	0.229
Female	6323	763 (12.1)	102	13 (12.7)	1.06 (0.59–1.91)	0.835	0.91 (0.49–1.69)	0.775

[a] Crude odds ratio (not adjusted).
[b] Adjusted for BMI and age.

pressure, or raised fasting glucose was observed in both men and women after adjusting for BMI and age. The prominent positive finding was that the TG level (above 150 mg/dL) was higher in the SCH group than in the NG, in both men and women (odds ratio (OR) = 1.66, p = 0.015; OR = 2.40, p < 0.001, respectively).

For the purpose of this study, Table 3 shows the association between the two groups and MetS. The prevalence of MetS in the NG subjects was 26.2% in men and 18.7% in women. The prevalence of MetS was much higher in the SCH group (39.6% in men and 29.4% in women) than in the NG group. The multivariate analysis revealed that the SCH group was significantly associated with a higher risk of MetS when compared to the NG after adjustment for age and BMI, in both men and women (OR = 1.70, p = 0.025; OR = 1.68, p = 0.043, respectively) (Table 3).

The prevalence of MetS stratified by age was categorized into five groups per 10 years (Fig. 1). The prevalence of MetS significantly increased with age in both the SCH group and NG in women (*p*-values for linear trends for NG and SCH are < 0.001 and 0.006 respectively). The prevalence of MetS in NG males was positively correlated with increasing age (*p*-value for the linear trend is < 0.001) whereas that of SCH males was not significant (*p*-value for linear trend is 0.338).

As for the prevalence of MetS in the SCH group, we further evaluated the numbers of MetS components. As seen in Fig. 2, when increasing the numbers of MetS components, there was a positive correlation with the prevalence rate of SCH, in both men and women (*p*-value for the linear trend is 0.018 in men and 0.011 in women).

Discussion

In this cross-sectional study of a large population receiving health examination, we attempted to determine the metabolic risk factors for SCH. We found no difference in BMI between the SCH group and NG in both genders. Higher TSH levels correlated with increasing BMI [10], whereas others have reported a negative correlation [11,12]. The SBP was significantly different in both men and women between the SCH group and NG and the DBP was much higher in the SCH group than in the NG in men, but not in women. The association between hypertension and SCH was not so conclusive; indeed, some studies have reported that a higher SBP or DBP or prevalence of hypertension correlated with SCH [13,14], whereas others found no such correlation [15,16].

Table 3 The association of subclinical hypothyroidism *v.s.* normal thyroid group with metabolic syndrome (number of risk factors ≥ 3) stratified by gender.

	Normal thyroid group		Subjects with subclinical hypothyroidism		Crude OR (95% CI)[a]	p[a]	Adjusted OR (95% CI)[b]	p[b]
	Total No	No. of case (%)	Total No	No. of case (%)				
Gender								
Male	9620	2521 (26.2)	101	40 (39.6)	1.85 (1.24–2.76)	0.003	1.70 (1.07–2.69)	0.025
Female	6323	1185 (18.7)	102	30 (29.4)	1.81 (1.17–2.78)	0.007	1.68 (1.02–2.78)	0.043

[a] Crude odds ratio (not adjusted).
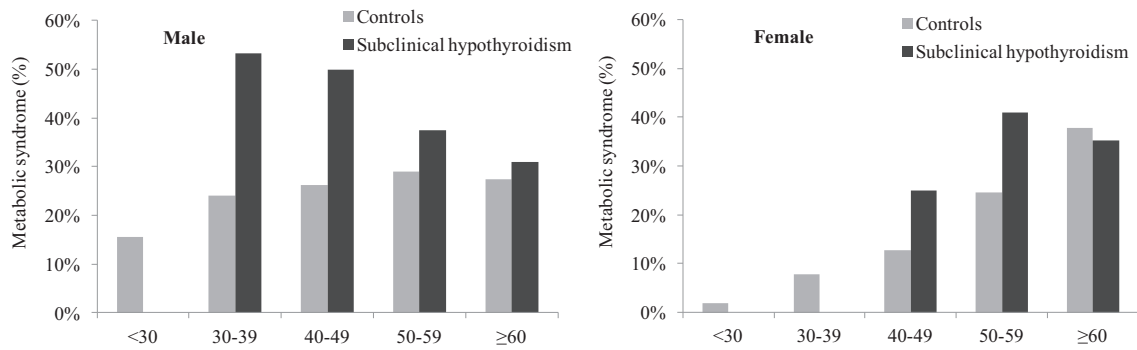[b] Adjusted for BMI and age.

Fig. 1 The prevalence of metabolic syndrome stratified by age group for subjects with and without subclinical hypothyroidism (Controls mean normal thyroid group). *p* for linear trend for normal group was <0.001 and that of subclinical hypothyroidism was 0.338 in male group. *p* for linear trend for normal group was <0.001 and that of subclinical hypothyroidism was 0.006 in female group.
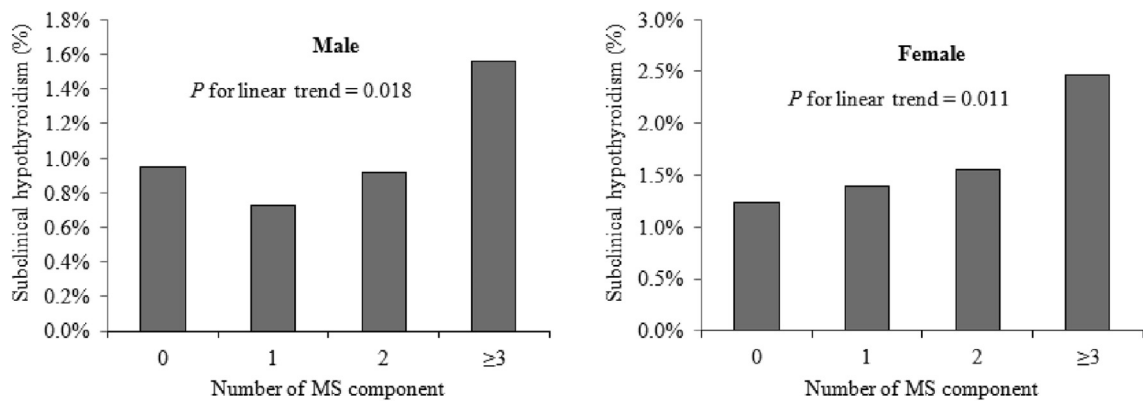

Fig. 2 The prevalence of subclinical hypothyroidism stratified by number of metabolic syndrome components.

SCH may cause hyperlipidemia, and some studies reported that the levels of Chol and LDL-C were positively correlated with TSH [17,18]. However, our biochemical results show that Chol, TG, Non-HDL, and Chol/HDL levels were significantly higher in females with SCH than those in females in the NG were.

The prevalence of SCH increases with age and is higher in women [2,5]. Our data show that the prevalence of SCH was around 1.3% (1.0% in men and 1.6% in women), which is consistent with a report by Tseng et al. from Taiwan, although not exactly same TSH cut of point [5]. Owing to limitations in the numbers of factors analyzed in the health examination, our study lacks thyroid auto-antibodies data. The presence of anti-thyroperoxidase and anti-thyroglobulin antibodies might suggest of the underlying Hashimoto's disease possibility to the prevalence of TSH elevations in SCH. Thyroid auto-antibodies can be detected in 80% of patients with SCH, and 80% of patients with SCH have a serum TSH concentration of less than 10 mU/L [19]. Consequently, Hashimoto's disease is considered to be the most likely cause of SCH and the accompanying increased cardiovascular risk. This hypothesis is indirectly supported by the observation that patients with Hashimoto's thyroiditis over 50 years of age exhibit a threefold increase in CVD hospital admissions, indicating increased

morbidity compared to controls [20]. Regardless of the chosen upper limit of normal, a convincing argument can be made for closer follow-up of patients with a TSH level of 3–5 mU/L, particular if thyroid auto-antibodies are detected [19]. As our study lacks data of free thyroxine levels in our population, we set our threshold TSH level to 5.5–10 mU/L.

The prevalence of MetS in our SCH group (39.6% in men and 29.4% in women) was higher than in the NG. The multivariate analysis also revealed that the SCH group was significantly associated with a higher risk of MetS development. MetS has been linked to subclinical thyroid disease due to the pathophysiology of thyroid function in energy metabolism, that overt hypothyroidism or SCH were more prevalent in MetS parameters abnormality [21,22]; increase in metabolic CVD risk factors among elderly people with SCH [12,21]. The relationship between serum TSH and MetS components revealed that a mild elevation in TSH may be a risk factor of MetS [23]. Fig. 1 shows that the prevalence of MetS significantly increased with age in women in both the SCH group and NG. Fig. 2 shows that with increasing number of MetS components there was a positive correlation with the prevalence of SCH in both men and women. Thus, because SCH is more prevalent in women and the risk increases with age, greater attention to the risk of MetS development is warranted. As for men, regardless of

thyroid function, the increased risk for MetS with age warrants attention. National guidelines for screening for thyroid disease by using serum TSH levels have not been established. However, because of the high prevalence of SCH and associated metabolic risk factors such as hyperlipidemia, the American Thyroid Association recommends screening by measuring serum TSH beginning at age 35 and every 5 years thereafter [24].

Most studies agree that SCH is correlated with increased prevalence of coronary heart disease or ischemic heart disease [5–7,25,26]. Nevertheless, other studies could not demonstrate substantial associations between SCH and CVD [27,28]. Factors associated with the prevalence of these diseases include iodine intake, distribution of autoimmune thyroid disease, cutoff values of TSH for SCH, definition of CVD, and the thyroxine replacement regimen, all of which may confound the results of these association studies [25].

A potential limitation of this study is that it is cross sectional and does not reflect the longitudinal effects of SCH on metabolic risk factors. Further study is needed with a larger cohort and with a sufficient follow-up period in order to determine the significance of early detection of SCH and long-term associations with metabolic risk factors.

Conclusions

Our analysis of 15,943 healthy Taiwanese revealed a 1.3% prevalence of SCH in this population. Among them, the prevalence of MetS was higher (39.6% in men and 29.4% in women) than in the normal population. Because SCH is more prevalent in women and the risk increases with age, greater attention to the risk of MetS development is warranted. As for men, regardless of thyroid function, the risk of MetS development with age still warrants attention. Thus, our data suggest that national guidelines for screening for thyroid disease using serum TSH levels in the elderly are mandatory.

Conflicts of interest

The authors have no relevant conflict of interest to disclose.

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