High prevalence of subclinical thyroid dysfunction and the relationship between thyrotropin levels and cardiovascular risk factors in residents of the coastal area of China

Jinqian Wang MD[1], Xiuyun Ma MB[2], Shuying Qu MB[3], Yingzheng Li MB[2], Lihui Han MD[2], Xun Sun MD[2], Peimei Li MD[2], Xue Liu MB[2], Jinhua Xu MB[4]

J Wang, X Ma, S Qu, et al. High prevalence of subclinical thyroid dysfunction and the relationship between thyrotropin levels and cardiovascular risk factors in residents of the coastal area of China. Exp Clin Cardiol 2013;18(1):e16-e20.

OBJECTIVES: To investigate the prevalence of subclinical thyroid dysfunction and the relationship between thyrotropin levels and cardiovascular risk factors in residents of the coastal area of China.
METHODS: A total of 4256 individuals (mean [± SD] age 50.51±14.24 years; 2079 males, 2177 females,) were enrolled in the present study. Sex, blood pressure, body mass index, waist-to-hip ratio, serum levels of fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid and smoking status were measured. The relationship between thyrotropin levels and cardiovascular risk factors was analyzed.
RESULTS: The overall prevalence of thyroid dysfunction was 11.07%. The prevalence of subclinical hypothyroidism (6.32%) was higher than that of hyperthyroidism (1.53%). The prevalence of thyroid dysfunction among female subjects was higher than that among male subjects (16.54% versus 5.34%, respectively; P<0.001). Significant differences were detected with respect to body mass index (P=0.026), waist-to-hip ratio (P<0.001), fasting glucose levels (P=0.001), total cholesterol levels (P=0.013), triglyceride levels (P=0.003) and smoking status according to different thyrotropin levels.
CONCLUSION: The prevalence of thyroid dysfunction was high in residents of China's coastal area. Significant differences were detected with regard to body mass index, waist-to-hip ratio, fasting glucose levels, total cholesterol levels, triglyceride levels and smoking status according to different thyrotropin levels.

Key Words: *Cardiovascular risk factors; Coronary heart disease; Thyroid dysfunction*

Subclinical thyroid disease has been defined biochemically: subclinical hyperthyroidism occurs when serum thyroid-stimulating hormone (TSH) concentrations are low or undetectable but free thyroxine (FT4) and tri-iodothyronine (FT3) concentrations are normal; and subclinical hypothyroidism occurs when serum TSH concentrations are raised and serum thyroid hormone concentrations are normal. Large population studies (1,2) have shown that subclinical thyroid dysfunction is common and highlight the usefulness of screening to allow early detection and, therefore, prevent associated adverse health outcomes.

The population prevalence of subclinical thyroid dysfunction is dependent on age, sex and iodine intake. Subclinical hypothyroidism occurs in 4% to 20% of the adult population, and the prevalence of subclinical hyperthyroidism varies from 0.6% to 9.8% (3). Subclinical hypothyroidism is more common in iodine-sufficient countries, and iodine supplementation may increase the incidence (4). By contrast, the prevalence of subclinical hyperthyroidism appears to be far higher in iodine-deficient populations (5). Therefore, determining the prevalence of subclinical thyroid dysfunction in specific populations is necessary.

Cardiovascular risk factors include central obesity, glucose intolerance or type 2 diabetes, dyslipidemia, low high-density lipoprotein cholesterol (HDL-C) levels and hypertension (6). Because cardiovascular disease is the leading cause of death, prevention and early recognition of these factors is an important public health issue that deserves more attention.

The pathophysiology of thyroid function with regard to lipid levels, glucose metabolism and blood pressure in subjects with thyroid disorders is well known (7-10). However, there are data both against (11) and in favour of (12,13) the role of subclinical thyroid dysfunction as a risk factor for cardiovascular disease, and the debate regarding the issue remains unresolved. On the other hand, controversy has grown following the recent publication of several reports demonstrating a positive correlation between TSH levels and several cardiovascular risk factors, even in healthy euthyroid populations (14,15).

The aim of the present study was to investigate the prevalence of subclinical thyroid dysfunction among the population of China's coastal area, and to assess its association with cardiovascular risk factors in this group of individuals.

METHODS

Subjects

Subjects who had resided mainly in China's coastal area for at least 10 years were recruited during their routine health checkup at the Health Screening Center of Weihai Hospital, affiliated with Qingdao University (Weihai, China). All participants were examined by physicians. Information regarding medication and history of medical or surgical diseases in each subject was obtained. Blood pressure was recorded as the mean of two measurements in the sitting position according to a standardized protocol. Subjects were excluded from the study if they were taking medications for glucose control, blood pressure, dyslipidemia or thyroid function. A total of 4256 individuals (mean [± SD] age 50.51±14.24 years; 2079 men, 2177 women) were enrolled in the study.

All of the subjects were anonymous, and informed consent was obtained from each participant. The Ethics Committee of Weihai Hospital approved the retrospective review of patients' medical records, and records were reviewed for research purposes in accordance with medical statutes.

[1]*Department of Cardiology;* [2]*Department of Endocrinology, Weihai Hospital, Medical School of Qingdao University;* [3]*Weihai Wendeng Center Hospital, Wendeng;* [4]*Institute of Epidemiology and Statistics, Binzhou Medical College, Yantai, China*
Correspondence: Dr Jinqian Wang, No 51 Guangming Road, Weihai, Shandong Province, China 264200. Telephone 86-631-5271262, fax 86-631-5216911, e-mail doctorx_0@163.com

TABLE 1
Characteristics of the subjects

Characteristic	Men	Women	P
Age, years	52.36±15.16	48.74±13.68	<0.001
Body mass index, kg/m^2	24.79±3.65	22.58±3.41	<0.001
Waist-to-hip ratio	0.95±0.31	0.81±0.27	<0.001
Systolic blood pressure, mmHg	137.47±17.01	122.15±14.33	<0.001
Diastolic blood pressure, mmHg	85.33±10.77	76.15±9.33	<0.001
Free plasma glucose, mmol/L	5.73±1.57	5.31±1.32	<0.001
Total cholesterol, mmol/L	5.33±1.18	5.34±1.03	0.769
Triglycerides, mmol/L	1.93±1.64	1.55±1.32	<0.001
Low-density lipoprotein cholesterol, mmol/L	3.06±0.85	3.02±0.66	0.087
High-density lipoprotein cholesterol, mmol/L	1.15±0.29	1.48±0.35	<0.001
Uric acid, μmol/L	397.96±167.94	287.49±104.56	<0.001

Data presented as mean ± SD unless otherwise indicated. The groups were compared using a one-way ANOVA or Z-test of variance. P<0.05 was considered to be statistically significant. The following reference ranges were based on the authors' laboratory standards: Plasma glucose (3.9 mmol/L to 6.1 mmol/L), total cholesterol (3.6 mmol/L to 6.2 mmol/L), triglycerides (<1.71 mmol/L), low-density lipoprotein cholesterol (0 mmol/L to 3.36 mmol/L), high-density lipoprotein cholesterol (>1.15 mmol/L) and uric acid (142 μmol/L to 339 μmol/L).

TABLE 2
Prevalence and distribution of thyroid dysfunction according to sex

			Thyroid dysfunction			
	Cases, n	Euthyroid	Hyperthyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	Hypothyroidism
Total	4256	3785 (88.93)	58 (1.36)	65 (1.53)	269 (6.32)	79 (1.86)
Male	2079	1968 (94.66)	17 (0.82)	25 (1.20)	58 (2.79)	11 (0.53)
Female	2177	1817 (83.46)	41 (1.88)	40 (1.84)	211 (9.69)	68 (3.12)
P		<0.001	0.003	0.091	<0.001	<0.001

Data presented as n (%) unless otherwise indicated. The groups were compared using a χ^2 test. P<0.05 was considered to be statistically significant

Laboratory analysis

All measurements were performed at the clinical laboratory of Weihai Hospital. Blood samples were collected from all subjects between 08:00 and 10:00 after at least 10 h of fasting. A procedure involving chemiluminescence (Cobas E610, Roche, Switzerland) was used to determinate thyroid function (TSH, free T3 and T4). The laboratory reference ranges were 0.27 mIU/L to 4.2 mIU/L for TSH, 3.1 pmol/L to 6.8 pmol/L for free T3 and 12 pmol/L to 22 pmol/L for free T4.

Levels of plasma glucose (3.9 mmol/L to 6.1 mmol/L), total cholesterol (3.6 mmol/L to 6.2 mmol/L), triglycerides (<1.71 mmol/L), low-density lipoprotein cholesterol (LDL-C) (0 mmol/L to 3.36 mmol/L), HDL-C (>1.15 mmol/L) and uric acid (142 μmol/L to 339 μmol/L) were determined using an Auto Biochemical Analyzer (MODULAR-000GS, Roche, Switzerland).

Definitions

Based on the laboratory standards of Weihai Hospital, normal thyroid function was defined as a TSH value between 0.27 mU/L and 4.2 mU/L. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Diagnosis of diabetes was established according to the criteria of the WHO published in 1999 (16), and the revised criteria of the National Cholesterol Education Program-Adult Treatment Panel III were used for the definition of the metabolic syndrome (17).

Statistical analyses

Before statistical analysis, the normality of the distribution and the homogeneity of the variances were evaluated using Levene's test, and variables were subjected to a log transformation if necessary. Data are presented as mean ± SD, or medians with interquartile ranges in the case of a skewed distribution. For continuous variables, ANOVA followed by multiple-comparison tests were used. Categorical variables were compared using the χ^2 test. The log transformation of lipid parameters was performed to correct the skewed distribution.

All calculated P values were two-sided; P<0.05 was considered to be statistically significant. Statistical tests were performed using SPSS version 17.0 (IBM Corporation, USA) for Windows (Microsoft Corporation, USA).

RESULTS

General characteristics of the subjects

The composition and general characteristics of the sample are summarized in Table 1. A total of 4256 subjects were included in the present study (2079 men and 2177 women; male:female ratio = 1:1.05). Median urinary iodine excretion, measured in 200 individuals, was 357.67±92.15 μg/L, reflecting an adequate to excessive iodine intake in this population (18).

Prevalence and distribution of thyroid dysfunction

The prevalence of thyroid dysfunction among participants was 11.07% (Table 2 and Table 3). Overt and subclinical hyperthyroidism were found in 58 (1.36%) and 65 (1.53%) subjects, respectively. In addition, 79 (1.86%) and 269 (6.32%) subjects exhibited overt and subclinical hypothyroidism, respectively.

After separating the subjects according to sex, 111 (5.34%) men and 360 (16.54%) women exhibited thyroid dysfunction (Table 2). The prevalence of thyroid dysfunction was significantly higher among women compared with men (16.54% versus 5.34%, respectively; P<0.001). The prevalence of overt and subclinical hyperthyroidism was 0.82% and 1.88% in men and 1.20% and 1.84% in women, respectively. In contrast, the number of subjects with overt and subclinical hypothyroidism were 11 (0.53%) and 58 (2.79%) men and 68 (3.12%) and 211 (9.69%) women, respectively. It is clear that the prevalence of hyperthyroidism, hypothyroidism and subclinical hypothyroidism was significantly higher among women.

The prevalence of overt and subclinical hyperthyroidism tended to decrease with age (Table 3). However, the prevalence of overt and subclinical hypothyroidism increased with age and markedly increased in individuals 50 to 69 years of age. The prevalence of subclinical hypothyroidism was 12.11% in individuals 50 to 59 years of age and 13.28% in individuals 60 to 69 years of age.

TABLE 3
The prevalence and distribution of thyroid dysfunction according to age

Age, years	Total n	Thyroid dysfunction			
		Hyperthyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	Hypothyroidism
<30	165	4 (2.42)	3 (1.82)	11 (6.67)	3 (1.82)
30–39	2005	32 (1.6)	33 (1.65)	102 (5.09)	22 (1.10)
40–49	1314	15 (1.14)	17 (1.29)	62 (4.72)	16 (1.22)
50–59	479	4 (0.84)	6 (1.25)	58 (12.11)	24 (5.01)
60–69	256	2 (0.78)	4 (1.56)	34 (13.28)	11 (4.30)
≥70	37	1 (2.70)	2 (5.41)	2 (5.41)	3 (8.11)
Total	4256	58 (1.36)	65 (1.53)	269 (6.32)	79 (1.86)

Data presented as n (%) unless otherwise indicated

TABLE 4
Age and sex-adjusted measures of cardiovascular risk factors according to categories of serum TSH concentration

	Serum TSH concentration, mIU/L					
	<0.27	0.27–1.57	1.58–2.88	2.89–4.19	≥4.2	P
Body mass index, kg/m^2	22.85±3.71	22.89±3.67	22.01±3.56	25.13±3.11	25.28±3.72	0.026
Waist-to-hip ratio	0.82±0.53	0.84±0.36	0.86±0.22	0.93±0.49	0.98±0.38	<0.001
Systolic blood pressure, mmHg	137.21±16.08	127.27±21.32	130.33±19.27	131.69±20.97	137.45±21.03	0.367
Diastolic blood pressure, mmHg	80.33±8.79	79.91±12.56	79.12±12.06	78.84±11.38	80.17±10.45	0.174
Fasting plasma glucose, mmol/L	5.12±1.36	5.17±1.17	5.34±1.28	5.79±1.58	6.12±1.81	0.001
Total cholesterol, mmol/L	4. 63±1.33	4.87±1.13	4.96±1.25	4.99±1.23	5.35±1.64	0.013
Triglycerides, mmol/L	1.32±0.67	1.39±0.84	1.76±1.63	1.71±1.85	1.96±1.76	0.003
LDL cholesterol, mmol/L	3.03±0.85	2.97±0.71	2.88±0.84	2.91±0.73	3.18±0.91	0.124
HDL cholesterol, mmol/L	1.15±0.31	1.31±0.33	1.39±0.38	1.22±0.33	1.39±0.28	0.145
Uric acid, μmol/L	297.97±107.94	313.97±90.85	321.15±101.73	341. 62±70.90	371.63±109.47	0.174
Smoking status, n						
Nonsmokers	17	121	159	72	60	<0.001
1–339 cigarettes/year	8	53	26	39	21	0.0008
440–1099 cigarettes/year	2	37	21	26	16	0.0009
>1100 cigarettes/year	1	4	7	3	2	0.2222

Data presented as mean ± SD unless otherwise indicated. Groups were compared using a one-way ANOVA or χ^2 test. P<0.05 was considered to be statistically significant. HDL High-density lipoprotein; LDL Low-density lipoprotein; TSH Thyroid stimulating hormone

Relationship between thyrotropin levels and cardiovascular risk factors

The normal TSH levels were stratified into three groups (0.27 mIU/L to 1.57 mIU/L, 1.58 mIU/L to 2.88 mIU/L and 2.89 mIU/L to 4.19 mIU/L) and the subjects were divided into five groups according to serum TSH concentrations. Table 3 shows cardiovascular risk factors among subjects with different TSH serum concentrations. Significant differences were detected among the five groups with respect to body mass index (BMI) (P=0.026), waist-to-hip ratio (P<0.001), fasting plasma glucose (FPG) levels (P=0.001), total cholesterol levels (P=0.013), triglyceride levels (P=0.003) and smoking status. No significant differences were observed among the five groups with regard to age, systolic blood pressure, diastolic blood pressure, and levels of LDL-C, HDL-C and uric acid.

Participants with higher TSH levels exhibited higher measures of BMI, waist-to-hip ratio, FPG levels, total cholesterol levels and triglyceride levels than subjects with normal or lower TSH levels. In addition, their rate of smoking was lower than the rate observed among individuals with normal values of TSH. Subjects with TSH concentrations ≥4.2 mU/L exhibited the highest adjusted values of BMI, waist-to-hip ratio, FPG levels, total cholesterol levels and triglyceride levels.

DISCUSSION

The present study reported the prevalence of subclinical thyroid dysfuntion and the relationship between TSH levels and cardiovascular risk factors in residents of the coastal area of China. Thyroid function has an important role in the risk stratification of patients with suspected CHD and should be routinely tested in patients at risk of CHD. Maintaining serum TSH levels within an appropriate range will achieve homeostasis of lipid levels and slow the progression of atherosclerosis in CHD patients.

There is a relative lack of epidemiological data regarding thyroid dysfunction in China's coastal area. The present study found that the prevalence of thyroid dysfunction was 11.07% among all participants, which was somewhat higher than reported in other studies that were conducted in regions with a sufficiency of iodine (19-21). Because the prevalence of these disorders may be affected by the type of study population, ethnicity and dietary iodine intake, the difference between the present study and previous reports may result from the specific population analyzed, the method of enrollment and the strict inclusion criteria used.

The prevalence of thyroid dysfunction among female subjects was higher than that among male subjects in the present study (16.54% versus 5.34%, respectively; P<0.001), which is consistent with previous reports (2,21-23). In the Whickham survey (23), the prevalence of subclinical hypothyroidism was three times higher in women than in men. One possible reason for this difference is that the majority of cases of thyroid dysfunction are due to autoimmune disease, which is more common in women. Therefore, it is necessary to routinely evaluate thyroid function among women during health examinations.

The prevalence of subclinical hypothyroidism (6.32%) was higher than that of hyperthyroidism (1.53%) in the present study. This is likely due to a more than adequate iodine intake in our population. Universal salt iodization was initially introduced in China in 1996. National monitoring data show that Chinese inhabitants experienced excessive iodine intake during the period from 1997 to 2001, and more than adequate iodine intake after 2001 (24,25). On the other hand, high seafood and

seaweed consumption in China's coastal area may also lead to high iodine intake. The acute Wolff-Chaikoff effect (26,27) suggested that iodine-induced hypothyroidism, especially in patients on amiodarone therapy, is caused by a chronic acute inhibition of the thyroid gland (28,29). However, the exact mechanism by which chronic high iodine intake induces hypothyroidism remains unclear.

It has been reported that overt hypothyroidism may cause cardiovascular disease and atherosclerosis by leading to an adverse lipid profile or, potentially, affecting cardiovascular function (30). The relationship between subclinical thyroid dysfunction and cardiovascular disease may be mediated by the higher levels of serum lipids found in subclinical hypothyroidism. Some cross-sectional studies have demonstrated that the serum levels of total cholesterol and LDL-C are significantly higher in patients with subclinical hypothyroidism than in euthyroid patients (31,32). However, other studies have shown nonstatistically significant differences between the two groups (33) or even lower total cholesterol levels in subclinical hypothyroid patients (34), compared with those with normal thyroid function.

Recently, the associations between TSH levels and cardiovascular risk factors, especially serum lipid status, have become a popular area of research. Several studies have already found positive correlations between TSH and lipid profiles. The Nord-Trøndelag Health Study (HUNT), which was performed in Norway, showed linear and significant increases in serum total cholesterol, LDL-C and triglyceride levels with a TSH level that increased within the reference range (35). Similar results were also obtained in euthyroidic populations of Korean (36), Latin American (37) and Spanish (38) individuals. However, the relationship between subclinical hypothyroidism, dyslipidemia and cardiovascular disease remains a topic of debate (39).

Most recently, a study reported the relationship between TSH levels and lipid status after adjustments for the thyroid hormones and/or other potentially confounding factors in patients with CHD (40). They found that even after adjusting for the thyroid hormones, the significant positive correlation between TSH level and the log of the total cholesterol level persisted (r=0.095; P=0.036). In the present study, significant differences were detected with respect to BMI (P=0.026), waist-to-hip ratio (P<0.001), FPG levels (P=0.001), total cholesterol levels (P=0.013), triglyceride levels (P=0.003) and smoking status according to different TSH levels.

The importance of thyroid function should not be overlooked, and thyroid function should always be assessed in patients at risk of CHD to exclude not only thyroid dysfunction but also secondary dyslipidemia. The serum TSH levels of these patients with suspected CHD can serve as important biomarkers that can be used to perform risk stratification. Furthermore, an increasing number of studies have shown that relatively low serum TSH levels within the reference range are beneficial for CHD patients (14). Particularly, compared with the measurement of other biomarkers, such as C-reactive protein and homocysteine, measurement of TSH is simple and can be performed in most hospitals.

One of the limitations of the present study is that it used a cross-sectional design. The causality between TSH levels and cardiovascular risk factors cannot be fully established (ie, we can only suggest an association). A well-designed prospective research study will be necessary to address the relationship between TSH and cardiovascular risk factors.

CONCLUSIONS

The prevalence of thyroid dysfunction was high in residents of China's coastal area. Significant differences were detected with respect to BMI, waist-to-hip ratio, FPG, total cholesterol and triglyceride levels and smoking status according to different TSH levels. It is necessary to routinely test thyroid function in patients at risk of CHD. Maintaining serum TSH levels in an appropriate range will achieve homeostasis of lipid levels and slow the progression of atherosclerosis.

ACKNOWLEDGEMENTS: This work was supported, in part, by grants from the National Natural Science Foundation of China (81000039), Medicine & Health Technology Development Project (2011QW031) of Shandong Province of China, and the Science and Technology Development Plan of Jinan (201101108).

REFERENCES

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
2. Hollowell J, Staehling N, Flanders D, et al. Serum TSH, T4 and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.
3. David S Cooper, Bernadette Biondi. Subclinical thyroid disease. Lancet 2012;379:1142-54.
4. Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006;354:2783-93.
5. Laurberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E, Knudsen PR. Iodine intake and the pattern of thyroid disorders: A comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. J Clin Endocrinol Metab 1998;83:765-69.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
7. Danese MD, Ladenson PW, Meinert CL, et al. Clinical review 115: Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: A quantitative review of the literature. J Clin Endocrinol Metab 2000;85:2993-3001.
8. Kutty KM, Bryant DG, Farid NR. Serum lipids in hypothyroidism – a re-evaluation. J Clin Endocrinol Metab 1978;46:55-6.
9. Torrance CJ, Devente JE, Jones JP, et al. Effects of thyroid hormone on GLUT4 glucose transporter gene expression and NIDDM in rats. Endocrinology 1997;38:1204-14.
10. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeo-stasis: Evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab 2002;87:1996-2000.
11. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk and mortality in older adults. JAMA 2006;295:1033-41.
12. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 2005;165:2460-6.
13. Walsh JP, Bremmer AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk for cardiovascular disease. Arch Intern Med 2005;165:2467-72.
14. Waterhouse DF, McLaughlin AM, Walsh CD, Sheehan F, O'Shea D. An examination of the relationship between normal range thyrotropin and cardiovascular risk parameters: A study in healthy women. Thyroid 2007;17:243-8.
15. Roos A, Bakker S, Links T, Gans R, Wolffenbuttel B. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 2007;92:491-6
16. World Health Organization Department of Non Communicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Geneva, World Health Organization; 1999 (WHO/NCD/NCS/99.2).
17. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.
18. Assessment of the iodine deficiency disorders and monitoring their elimination. Geneva: World Health Organization, 2001.
19. Wilson S, Parle JV, Roberts LM, et al. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: A community-based cross-sectional survey. J Clin Endocrinol Metab 2006;91:4809-16.
20. Hoogendoorn EH, Hermus AR, de Vegt F, et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: Influences of age and sex. Clin Chem 2006;52:104-11.

21. Lai C-C, Tang S-H, Pei D, et al. The prevalence of subclinical thyroid dysfunction and its association with metabolic syndrome in Taiwanese elderly. Int J Gerontol 2011;5:25-9.
22. Karmisholt J, Andersen S, Laurberg P. Variation in thyroid function tests in patients with stable untreated subclinical hypothyroidism. Thyroid 2008;18:303-8.
23. Tunbridge WM, Evered DC, et al. The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrinol. 1977;7:481-93.
24. Chen Z, Yan Y, Shu Y. Analysis of iodine intake levels and safe range of iodine intake after universal salt iodization in China. Chinese J Control Endemic Dis 2001;16:185-8.
25. Chen Z. Should we insist on monitoring iodine deficient disorders? Chinese J Endemiol 2006;25:237-8.
26. Wolff J, Chaikoff IL, Goldberg RC, Meier JR. The temporary nature of the inhibitory action of excess iodide on organic iodine synthesis in the normal thyroid. Endocrinology 1949;45:504-13.
27. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem 1948;74:555-64.
28. Pitsiavas V, Smerdely P, Boyages SC. Amiodarone compared with iodine exhibits a potent and persistent inhibitory effect on TSH-stimulated cAMP production in vitro: A possible mechanism to explain amiodarone-induced hypothyroidism. Eur J Endocrinol 1999;140:241-9.
29. Theodoropoulos T, Braverman LE & Vagenakis AG. Iodide-induced hypothyroidism: A potential hazard during perinatal life. Science 1979;205:502-3.
30. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
31. Efstathiadou Z, Bitsis S, Milionis HJ, et al. Lipid profile in subclinical hypothyroidism: Is L-thyroxine substitution beneficial? Eur J Endocrinol 2001;145:705-10.
32. Kong WM, Sheikh MH, Lumb PJ, et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med 2002;112:348-54.
33. Vanderpump MP, Tunbridge WM, French JM, et al. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. Thyroid 1996;6:155-60.
34. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. Ann Intern Med 2000;132:270-8.
35. Iqbal A, Jorde R, Figenschau Y. Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: The Tromsø Study. J Intern Med 2006;260:53-61
36. Jung CH, Sung KC, Shin HS, et al. Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP, and waist hip ratio in Korea. Korean J Intern Med 2003;18;146-53.
37. Diehl LA, Garcia V, Bonnema SJ, Hegedüs L, Albino CC, Graf H; Latin American Throid Society. Management of the nontoxic multinodular goiter in Latin America: Comparison with North America and Europe, an electronic survey. J Clin Endocrinol Metab 2005;90:117-123.
38. Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R, Ricart W. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. J Clin Endocrinol Metab 2006;91:3337-43.
39. Neves C, Alves M, Medina JL, Delgado JL. Thyroid diseases, dyslipidemia and cardiovascular pathology. Rev Port Cardiol 2008;27;1211-36.
40. Xu C, Yang X, Liu W, Yuan H, Yu C, Gao L, Zhao J. Thyroid stimulating hormone, independent of thyroid hormone, can elevate the serum total cholesterol level in patients with coronary heart disease: A cross-sectional design. Nutr Metab (London) 2012;9:44-52