CLINICAL STUDY

Associations between cardiovascular risk, insulin resistance, β -cell function and thyroid dysfunction: a cross-sectional study in She ethnic minority group of Fujian Province in China

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Abstract

Objective: To investigate the associations between cardiovascular risk, insulin resistance (IR), β -cell function and thyroid dysfunction in She ethnic minority group in China.

Methods: We enrolled 5080 participants of She ethnicity in this analysis eventually. We measured serum TSH and thyroid peroxidase antibody (TPOAb) concentrations, blood glucose and insulin levels in both fasting and 2-h postprandial states, serum lipid levels, blood pressure (BP), brachial-ankle pulse wave velocity (baPWV), electrophysiological parameters, including $T_{peak}-T_{end}$ interval (T_{p-e}), QT interval and height of the R wave in lead aVL (RaVL), and anthropometric parameters.

Results: The total prevalence of thyroid dysfunction in this population is 12.1%. Hyperthyroid subjects had shorter T_{p-e} interval and QT interval in electrocardiogram (ECG), while hypothyroid subjects had shorter T_{p-e} interval and longer QT interval in ECG than euthyroid subjects. Neither hyperthyroid nor hypothyroid subjects showed significant difference in BP, pulse pressure, and baPWV compared with euthyroid subjects. RaVL was slightly higher in hyperthyroid subjects, though the difference did not reach statistical significance ($P=0.08$). Subjects with $TSH < 0.3$ mIU/l had higher blood glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and β -cell function (HOMA- β), whereas subjects with $TSH > 10$ mIU/l had lower insulin, HOMA-IR, and HOMA- β than the reference group. There was a significant negative correlation, albeit weak, between TSH and HOMA-IR, HOMA- β after adjustment for confounding factors.

Conclusions: Hypothyroid subjects may carry higher cardiovascular risk than euthyroid subjects. Moreover, IR and β -cell function are inversely correlated with TSH, which may be explained by the decreasing insulin-antagonistic effects of thyroid hormones along with increasing TSH.

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Introduction

Thyroid dysfunction is common (1–4). Differences in prevalence rates may be due to variations in diagnostic criteria, diverse populations studied, iodine intake in different regions, and the discrepancy in the sensitivity of thyroid function measurements. The reference range for TSH according to the current recommendations from the AACE guidelines is 0.3–3.0 mIU/l (5). However, many laboratories are still using the old range, and epidemiological surveys based on a TSH reference range of 0.3–3.0 mIU/l are relatively rare. In this study, we report the prevalence of abnormal TSH according to the recent recommendations (0.3–3.0 mIU/l) and the prevalence of positive TPOAbs in the She ethnic minority group of Fujian province in China.

Thyroid dysfunction has important health implications, including increased risk of dyslipidemia, abnormal glucose

intolerance, cardiovascular disorders, and so on. As is well known, dyslipidemia in thyroid disease is common (6), and thyroid dysfunction is associated with an increased cardiovascular risk (7). The mechanism by which thyroid hormones contribute to the regulation of glucose and insulin homeostasis is a complex subject. So, despite several investigations, many aspects of insulin activity dependent on thyroid status are still not quite clear. That is, the association between thyroid function and insulin resistance (IR), β -cell function is not very clear.

We undertook this study to determine the prevalence of thyroid dysfunction and thyroid peroxidase antibodies (TPOAbs) in the She ethnic minority group of Fujian province in China and to investigate the associations with other diseases and metabolic abnormalities such as lipid metabolism, cardiovascular disorders, IR, and β -cell function.

Participants and methods

Study population

Ningde City is a middle-sized city in the northeast of Fujian province in China, with She population of 170 000, accounting for 25% of She population in China. Between April 2009 and September 2009, 5523 participants of She ethnicity aged 20–80 years, living in Ningde City, and age- and sex-stratified were randomly selected. Participants were required to complete a questionnaire, and blood samples were collected. Subjects who did not complete the questionnaire and those in whom thyroid function tests were not carried out were excluded from analyses of the other laboratory parameters. Finally, 5080 participants were enrolled in our study. All the participants signed informed consent authorized by the Diabetes Branch of the Chinese Medical Association, and the study has been approved by an ethical committee.

Data collection

After an 8- to 12-h overnight fast, blood samples were collected followed by a 75 g oral glucose tolerance test (OGTT), with additional blood samples being drawn at 2 h for the measurement of glucose and insulin. Blood samples were stored at -20°C until analysis. Serum TSH was assessed using a chemiluminescence immuno-metric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The working range for this method is 0.01–100 mIU/l. The reference range for TSH was 0.3–3.0 mIU/l according to the AACE guidelines (5). Serum TPOAb levels were measured by a highly sensitive, direct RIA system (Kronus, San Clemente, CA, USA). The normal range for TPOAb in humans is ≤ 35 IU/ml. Specific insulin was measured using the Elecsys 1010 immunoassay analyzer (Roche Diagnostics) and electrochemiluminescence immunoassay. Blood glucose levels were determined by the glucose oxidase method (Sclavo, Siena, Italy). Glucose tolerance status was categorized using 1999 World Health Organization criteria (8). Serum lipids (triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol) were determined by an automatic colorimetric method (Hitachi; Boehringer Mannheim). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald formula (9).

More sophisticated indices of glucose and insulin control included the calculation of the homeostasis model (HOMA) of IR index, the HOMA β -cell index as a measure of reserve pancreatic insulin production, and the Gutt insulin sensitivity index, which includes body weight measurement and OGTT that gives glucose and insulin information and is similar to a glucose disposition index (10, 11).

Height and weight were recorded, and body mass index (BMI) was calculated as $\text{weight}/(\text{height})^2$ and

expressed in kg/m^2 . Waist circumference (WC) was taken at the level of the umbilicus with the patient in the standing position. Brachial–ankle pulse wave velocity (baPWV) was measured using an automatic device (VP-2000, Colin Co., Komaki, Japan). baPWV, blood pressure (BP), and heart rate were recorded simultaneously. We used the mean value of bilateral baPWV in our analyses. Standard 12-lead electrocardiogram was recorded with a standard digital recorder. Electrophysiological parameters, including height of the R wave in lead aVL (RaVL), QT interval and T_{p-e} interval, were manually measured.

Statistical analyses

Data analyses were conducted with SPSS 13 statistical software package (SPSS, Chicago, IL, USA). Data are presented as proportions, mean $\pm$ s.d., or median (interquartile range) where appropriate. Statistical comparisons were performed by means of *t*-tests for data with a normal distribution, Mann–Whitney *U* tests for data with a skewed distribution, and χ^2 tests for percentages.

To study the influence of thyroid function on glucose control and insulin action, nondiabetic participants were divided into six groups, i.e. TSH <0.3 , 0.3–0.99, 1.0–1.99, 2.0–2.99, 3.0–10, and >10 mIU/l. By using covariance analysis, blood glucose, insulin, HOMA-IR, and HOMA- β were measured after adjusting for age, sex, serum lipids, BMI, and smoking status. Multivariate linear regression models were performed for associations of thyroid function with IR and with β -cell function. $P < 0.05$ was considered statistically significant.

Results

TSH and TPOAbs

The distribution of subjects with thyroid dysfunction by age and sex is shown in Table 1. Based on an abnormal TSH alone, the prevalence of thyroid dysfunction was 12.1%. Among the subjects with hypothyroidism, 8.7% had a level between 3 and 10 mIU/l; 1% had a value >10 mIU/l. Females had higher prevalence of hypothyroidism than males for all age groups, but the difference was not significant in the subjects with hypothyroidism aged 20–29 years or 70–80 years.

The prevalence of positive TPOAbs was 10.8% (7.4% of males and 13.5% of females). In all the age groups, TPOAbs were found more frequent in females than in males. The prevalence of positive TPOAbs did not change significantly with age in these subjects ($P > 0.05$).

Electrophysiological, biochemical, and metabolic characteristics

The levels of TG, TC, and LDL-C were lower, and the heart rate was significantly higher in hyperthyroid subjects than in euthyroid subjects as shown in Table 2.

Table 1 Prevalence of thyroid abnormalities in the study.

	Subjects	Abnormal TSH <i>n</i> (%)	Hyperthyroidism <i>n</i> (%)	Hypothyroidism <i>n</i> (%)	Positive TPOAb <i>n</i> (%)
Females					
20–29	218	42 (19.3%)	4 (1.8%)	38 (17.4%)	27 (12.4%)
30–39	652	92 (14.1%)	17 (2.6%)	75 (11.5%)	83 (12.8%)
40–49	883	108 (12.2%)	24 (2.7%)	84 (9.5%)	128 (14.5%)
50–59	770	109 (14.2%)	26 (3.4%)	83 (10.8%)	99 (12.9%)
60–69	294	45 (15.3%)	6 (2.0%)	39 (13.3%)	39 (13.3%)
70–80	76	13 (17.1%)	2 (2.6%)	11 (14.5%)	13 (17.1%)
All females	2893	409 (14.1%)	79 (2.7%)	330 (11.4%)	389 (13.5%)
Males					
20–29	218	23 (10.6%)	0 (0%)	23 (10.6%)	11 (5.1%)
30–39	417	41 (9.8%)	12 (2.9%)	29 (7.0%)	23 (5.6%)
40–49	542	38 (7.0%)	2 (0.4%)	36 (6.6%)	31 (5.7%)
50–59	568	46 (8.1%)	18 (3.2%)	28 (4.9%)	47 (8.3%)
60–69	321	42 (13.1%)	12 (3.7%)	30 (9.3%)	41 (12.9%)
70–80	121	16 (13.2%)	1 (0.8%)	15 (12.4%)	7 (5.8%)
All males	2187	206 (9.5%)	45 (2.1%)	161 (7.4%)	160 (7.4%)
All subjects	5080	615 (12.1%)	124 (2.4%)	491 (9.7%)	549 (10.8%)

Hypothyroid subjects had higher BMI, TG than euthyroid subjects. Neither hyperthyroid nor hypothyroid subjects showed significant difference in BP, pulse pressure (PP), and baPWV compared with euthyroid subjects. The prevalence of hypertension in different thyroid status was similar with no statistical significance. For electrophysiological parameters, we found that QT interval and T_{p-e} interval shortened significantly in hyperthyroid subjects, but T_{p-e} /QT ratio did not show significant differences in the euthyroid group. On the other hand, the hypothyroid group had a longer

QT interval, a shorter T_{p-e} interval, and a smaller T_{p-e} /QT ratio than euthyroid group. In addition, RaVL did not show obvious and significant differences between hyperthyroid and euthyroid subjects. However, RaVL was slightly higher in hyperthyroid subjects, though the difference did not reach statistical significance ($P=0.08$).

With regard to glucose metabolism, we found that the prevalence of abnormal glucose tolerance (impaired glucose tolerance (IGT) and diabetes mellitus (DM)) in hyperthyroidism was 55.7% (45.2 and 10.5%

Table 2 Characteristics of the subjects categorized by thyroid status. Data are expressed as mean $\pm$ S.D. or %.

	Euthyroidism (<i>n</i> =4465)	Hyperthyroidism (<i>n</i> =124)	Hypothyroidism (<i>n</i> =491)
Age (years)	46.87 $\pm$ 12.28	48.44 $\pm$ 11.47	46.457 $\pm$ 13.89
BMI (kg/m ²)	22.76 $\pm$ 3.07	22.42 $\pm$ 3.24	23.26 $\pm$ 3.53 [†]
WC (cm)	78.04 $\pm$ 8.84	78.01 $\pm$ 8.78	78.52 $\pm$ 8.93
SBP (mmHg)	134.2 $\pm$ 23.04	137.18 $\pm$ 24.86	135.52 $\pm$ 26.25
DBP (mmHg)	79.86 $\pm$ 13.28	80.63 $\pm$ 13.75	80.18 $\pm$ 13.66
PP (mmHg)	54.33 $\pm$ 13.95	56.54 $\pm$ 14.44	55.34 $\pm$ 17.07
baPWV (cm/s)	1447 $\pm$ 388	1490 $\pm$ 383	1472 $\pm$ 386
HR (bpm)	74.36 $\pm$ 14.27	86 $\pm$ 19.59 [†]	73.5 $\pm$ 13.07
T_{p-e} (ms)	0.116 $\pm$ 0.024	0.110 $\pm$ 0.024 [†]	0.113 $\pm$ 0.025*
QT interval (ms)	0.401 $\pm$ 0.041	0.377 $\pm$ 0.047 [†]	0.406 $\pm$ 0.042 [†]
T_{p-e} /QT ratio	0.289 $\pm$ 0.055	0.291 $\pm$ 0.057	0.279 $\pm$ 0.058 [†]
RaVL (mV)	0.263 $\pm$ 0.243	0.269 $\pm$ 0.270	0.280 $\pm$ 0.249
TG (mmol/l)	1.07 (0.77–1.57)	0.98 (0.7–1.41)*	1.15 (0.79–1.69)*
TC (mmol/l)	4.95 $\pm$ 1.4	4.65 $\pm$ 1.17*	4.97 $\pm$ 1.1
HDL-C (mmol/l)	1.48 $\pm$ 0.33	1.43 $\pm$ 0.36	1.48 $\pm$ 0.32
LDL-C (mmol/l)	3.19 $\pm$ 0.87	2.96 $\pm$ 0.89*	3.2 $\pm$ 0.91
TSH (mIU/l)	1.38 (0.97–1.9)	0.01 (0.01–0.17) [†]	3.89 (3.33–5.1) [†]
Positive TPOAbs (%)	8	56.6 [†]	25.4 [†]
Hypertension (%)	37.3	37.9	41.1
IGR (%)	32	45.2 [†]	33
DM (%)	5.9	10.5 [†]	4.1

HR, heart rate; IGR, impaired glucose regulation. *Compared with euthyroidism, $P<0.05$; [†]Compared with euthyroidism, $P<0.01$; [‡]Compared with euthyroidism, $P<0.001$. TG and TSH are shown as median and interquartile range.

Table 3 Blood glucose, insulin, indices of insulin resistance, and β -cell function among different thyroid status.

	<0.3 (mIU/l)		0.3–0.99 (mIU/l)		1.0–1.99 (mIU/l) (reference)		2.0–2.99 (mIU/l)		3.0–10 (mIU/l)		>10 (mIU/l)		P
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	
FBG	5.57 (5.45–5.69)	5.55* (5.43–5.67)	5.37 (5.33–5.41)	5.39 (5.35–5.42)	5.34 (5.32–5.37)	5.35 (5.33–5.38)	5.37 (5.33–5.41)	5.36 (5.32–5.40)	5.39 (5.32–5.45)	5.38 (5.32–5.44)	5.30 (5.14–5.47)	5.28 (5.11–5.45)	0.024
PBG	7.40 (7.07–7.74)	7.392* (7.09–7.69)	7.19 (7.09–7.31)	7.20* (7.10–7.29)	6.99 (6.92–7.06)	7.01 (6.94–7.07)	6.97 (6.87–7.08)	7.00 (6.90–7.11)	6.98 (6.81–7.14)	7.02 (6.86–7.17)	6.73 (6.37–7.08)	6.69 (6.24–7.14)	0.003
FINS	5.74 (4.78–6.88)	6.04† (5.26–6.94)	4.09 (3.89–4.30)	4.52* (4.78–6.88)	4.16 (4.02–4.31)	4.23 (4.10–4.36)	4.41 (4.19–4.64)	4.17 (3.97–4.38)	4.37 (4.04–4.72)	4.09 (3.81–4.39)	3.23 (2.43–4.29)	2.71† (2.20–3.31)	<0.001
PINS	20.44 (16.95–24.65)	21.67† (17.96–26.15)	14.85 (13.9–15.87)	15.81 (14.89–16.79)	15.74 (15.08–16.44)	16.07 (15.41–16.79)	16.46 (15.44–17.55)	15.96 (14.95–17.05)	17.2 (15.53–19.07)	17.01 (15.47–18.71)	14.99 (11.63–19.35)	11.83* (8.98–15.60)	0.007
HOMA-IR	1.39 (1.15–1.67)	1.45† (1.26–1.68)	0.97 (0.92–1.02)	1.07* (1.03–1.12)	1.02 (0.94–1.01)	1.00 (0.96–1.03)	1.04 (1.01–1.10)	0.98 (0.94–1.04)	1.03 (0.95–1.12)	0.96 (0.90–1.04)	0.75 (0.57–1.00)	0.63* (0.51–0.78)	<0.001
Gutt index	82.43 (75.26–90.31)	80.88† (73.92–88.41)	99.58 (96.74–102.51)	96.93* (94.16–100.08)	100.78 (98.69–102.82)	100.78 (98.69–102.92)	98.10 (95.11–101.29)	101.70 (98.39–105.21)	96.35 (91.93–101.29)	99.88 (94.82–105.32)	106.80 (93.13–122.36)	123.1* (105.74–143.45)	<0.001
HOMA- β	57.60 (47.94–69.19)	60.34† (51.99–69.47)	46.58 (44.25–49.03)	50.86* (48.62–53.25)	47.29 (45.70–48.93)	47.99 (46.48–49.60)	49.99 (47.38–52.76)	47.75 (45.42–50.25)	48.75 (44.96–52.86)	45.29 (42.01–48.76)	38.20 (27.6–52.01)	30.29† (24.44–37.48)	<0.001

FBG, fasting blood glucose; PBG, 2-h postload blood glucose; FINS, fasting insulin; PINS, 2-h postload insulin; Gutt index, and HOMA- β were logarithmically transformed and subsequently back transformed for presentation. Adjustment: sex, age, BMI, WC, serum lipids, smoking status, systolic and diastolic blood pressure. Compared with the group with serum TSH 1–1.99 mIU/l, * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

respectively), much higher than in euthyroidism, but there was no significant difference between hypothyroidism and euthyroidism. To avoid confusion, diabetic patients and those subjects on therapy that could interfere with glucose and lipid metabolism were excluded when we investigated the relationship between IR, β -cell function and thyroid function. To study the glucose metabolism morespecifically, we divided the nondiabetic participants into six groups according to the levels of serum TSH, i.e. TSH < 0.3, 0.3–0.99, 1.0–1.99, 2.0–2.99, 3.0–10, and > 10 mIU/l (Table 3). Group with a TSH between 1.0 and 1.99 mIU/l had the largest number of subjects ($n = 2329$). By using covariance analysis, blood glucose, insulin, HOMA-IR, Gutt index, and HOMA- β were measured after adjusting for age, sex, blood lipids, BMI, and smoking status. The results showed that hyperthyroid subjects (TSH < 0.3 mIU/l) had higher levels of blood glucose, insulin, HOMA-IR, HOMA- β , and lower Gutt index than any other group, whereas subjects with TSH > 10 mIU/l had lower levels of insulin, HOMA-IR, HOMA- β , and higher Gutt index than any other group. All variables regarding glucose metabolism in subjects with moderately elevated TSH (3.0–10 mIU/l) did not show significant differences from the group with serum TSH of 1.0–1.99 mIU/l.

A multivariate linear regression analysis for the associations between TSH and IR, β -cell function is shown in Table 4. There was a significant negative correlation between TSH and HOMA-IR, HOMA- β after adjustment for sex, age, BMI, serum lipids, smoking status, and systolic (SBP) and diastolic BP (DBP).

Discussion

In this study, the total prevalence of thyroid dysfunction based on an abnormal TSH alone was 12.1% (14.1% in women and 9.5% in men), and the prevalence of positive TPOAbs was 10.8% (7.4% of males and 13.5% of females). As expected, the prevalence of hypothyroidism and positive TPOAbs in females was higher than that in males. The prevalence of hypothyroidism increased with age among the females (but not in males) aged > 40 years, which was similar to other studies (1–3). Increasing serum thyroid antibody prevalence with age had been reported in other studies (1, 4), but in this study, the prevalence of positive TPOAbs did not change significantly with age ($P > 0.05$).

In this study, the levels of TG, TC, and LDL-C in hyperthyroid subjects were decreased, while the TG level was higher in hypothyroid subjects than in euthyroid subjects. These changes in the lipid profile are explained by the regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism (12). Hypothyroid subjects had higher BMI than euthyroid subjects, which was consistent with the results of many other studies (13).

Table 4 Full multiple linear regression models examining associations of TSH with indices of insulin resistance and β -cell function in nondiabetics.

Independent variable	Dependent variable					
	Log HOMA-IR			Log HOMA- β		
	β	<i>t</i>	<i>P</i> value	β	<i>t</i>	<i>P</i> value
Log TSH	-0.096	-6.244	<0.001	-0.073	-4.67	<0.001

Linear regression models adjusted for age, sex, BMI, WC, TC, TG, HDL-C, LDL-C, smoking status, and systolic and diastolic blood pressure.

In this study, we demonstrated that neither hyperthyroid nor hypothyroid subjects showed significant difference in BP, PP, and baPWV compared with euthyroid subjects. PP and baPWV, which reflect arterial stiffening, have prognostic value for cardiovascular disease. It has been reported that thyroid dysfunction, even in the subclinical stage, was associated with increased arterial stiffness (14–16). However, we found that vascular function assessed by baPWV and PP did not change in hyperthyroidism or hypothyroidism in this study, which probably is because the course of thyroid disorder was not long enough to impair the vascular function or probably due to the limit of sample size.

An increasing number of studies have suggested that the T_{p-e} interval may correspond to the transmural dispersion of repolarization, and that prolonged T_{p-e} interval and greater T_{p-e}/QT ratio are associated with malignant ventricular arrhythmias (17). In this study, we used the T_{p-e} interval and the T_{p-e}/QT ratio as electrocardiographic indices of ventricular arrhythmias. The most likely explanation for shortened T_{p-e} interval and QT interval in hyperthyroid subjects may be due to accelerated heart rate, and because both QT interval and T_{p-e} interval were shortened, the T_{p-e}/QT ratio did not change significantly compared with the euthyroid group. On the other hand, interestingly, hypothyroid subjects show a shortened T_{p-e} interval and a smaller T_{p-e}/QT ratio than the euthyroid group. As mentioned above, prolonged T_{p-e} interval and greater T_{p-e}/QT ratio are associated with ventricular arrhythmias, but whether shortened T_{p-e} interval and smaller T_{p-e}/QT ratio are associated with ventricular arrhythmias is uncertain. This study showed a shortened T_{p-e} interval and a smaller T_{p-e}/QT ratio in the hypothyroid group.

With regard to RaVL, a very recent prospective study (18) focused on the R wave voltage in lead aVL as being rather closely associated with left ventricular mass (LVM), and additionally being predictive of incident cardiovascular events in hypertensive patients. In this study, we also used this electrophysiological parameter to study the association between LVM and thyroid function. We found that neither hyperthyroid nor hypothyroid subjects showed significant difference in RaVL compared with euthyroid subjects.

However, RaVL was slightly higher in hyperthyroid subjects, though the difference did not reach statistical significance ($P=0.08$). Many studies (19, 20) have found that hypothyroidism, even in the subclinical stage, was associated with ischemic heart disease (IHD). As we know, the latter can lead to left ventricular hypertrophy, which is an important prognosis factor for IHD, so hypothyroid subjects may increase the risk of cardiovascular events. The lack of statistical significance ($P=0.08$) in RaVL of hypothyroid subjects was probably due to the limited sample size.

It is well known that hyperthyroidism is frequently associated with impaired glucose tolerance. The prevalence of abnormal glucose tolerance in subjects with hyperthyroidism (55.7%) observed in this study was much higher than that observed in subjects with hypothyroidism or euthyroidism. In nondiabetic subjects, we found that those with serum TSH <0.3 mIU/l showed higher levels of glucose and insulin both in the fasting state and after load, higher HOMA-IR and HOMA- β , and lower Gutt index than any other group in this study. We believe that the increase in blood glucose observed in this study might be the initial step of action of thyroid hormone excess. It is well known that thyroid hormones can increase gluconeogenesis, glycolysis, intestinal glucose absorption, and so on. The insulin levels were increased in this study partly because of increased glucose-stimulated insulin secretion (GSIS). Another important reason for the increase was IR. IR is common in hyperthyroidism (21, 22), and hepatic IR in hyperthyroidism is a rather consistent finding (21). Besides, IR in peripheral tissues (adipose tissue or skeletal muscle) is also reported in hyperthyroidism (23, 24). In hyperthyroidism, pancreatic β -cells secrete more insulin to compensate for the increased demand of insulin when plasma glucose increases and IR exists, which leads to an apparent increase in β -cell secretory function (a higher HOMA- β) in this study. However, in one study in rats, it has been reported that thyroxine (T_4) treatment increased the rate of β -cell apoptosis and then reduced insulin in pancreas and GSIS (25), and in another study, it was found that thyroid hormones reduced insulin content of β -cells, probably through inhibition of proinsulin mRNA which results in delayed inhibition of GSIS (26). However in this study, we did not find the effects of impaired β -cell function in hyperthyroidism. We think that it is in a stage of compensatory hyperfunction of β -cell. As reported in a recent follow-up study (27), HOMA β -cell function increased between years 4 and 3 before diagnosis and then decreased until diagnosis of diabetes, which suggested that it would take several years before the impairment of β -cell function. Hyperthyroid subjects usually receive treatment in time, so the course of thyroid disorder is not long enough to impair β -cell function.

On the other hand, the hypothyroid patients with moderately elevated TSH values (3.0–10 mIU/l) did not

show differences in glucose, insulin, HOMA-IR, and HOMA- β compared with the reference group with serum TSH values (1.0–1.99 mIU/l), while those with markedly elevated TSH values (>10 mIU/l) showed lower insulin levels both in the fasting state and after load, lower HOMA-IR and HOMA- β than any other group. In most other studies, the concentration of insulin in hypothyroidism is reported to be normal (28) or decreased (29, 30), which is similar to our result. Insulin sensitivity in hypothyroid patients has been found to be normal (31) or decreased (32–34). Hypothyroidism, even in the subclinical stage, has been shown to be associated with IR (35, 36). Our findings were different from these studies. A significant lower HOMA-IR (associated with a lower HOMA- β) was observed when we analyzed the participants with markedly elevated TSH values (>10 mIU/l), suggesting that insulin sensitivity was increased in this group. Only one study reported an increased sensitivity of glucose disposal to insulin in hypothyroidism (37), which was somewhat similar to this study.

In order to further understand the relationship between thyroid function and IR and insulin secretion of β -cells, a multivariate linear regression analysis with HOMA-IR or HOMA- β as the outcome was used. We found a significant negative correlation, albeit weak, between TSH and IR assessed by HOMA-IR index, which was contrary to other studies (38–40). In a trial with thyroid hormones in obesity, a positive correlation between IR parameters and serum TSH was significantly influenced by the BMI (40). In fact, most of the IR parameters were related to obesity and dyslipidemia. Some studies also suggested that thyroid function might cause dyslipidemia through altered insulin sensitivity in healthy subjects (41) and patients with type 2 diabetes mellitus (42). However, we found that HOMA-IR was diminished in the group with serum TSH >10 mIU/l, even though TG, LDL levels, and BMI were significantly higher in this group (data not shown), suggesting that obesity and dyslipidemia in hypothyroidism were not associated with IR in this study. There are some other mechanisms that may be responsible for these observations. Generally, there is a negative correlation between TSH and thyroid hormones. The higher serum TSH usually means the lower thyroid hormones via negative feedback. HOMA-IR decreased as TSH increased, which may be interpreted as a negative correlation between insulin sensitivity and thyroid hormones. It is well known that thyroid hormones have insulin-antagonistic effects. As TSH increased, thyroid hormones decreased and insulin-antagonistic effects weakened. It may be the main mechanism for these results. Besides, it is also possible that the course of thyroid disorder in this study was not long enough to impact the insulin sensitivity in hypothyroidism. On the other hand, the negative correlation between serum TSH and HOMA- β in this

study could be interpreted as an influence of the altered insulin sensitivity on the secretion of β -cells.

After all, further study on the magnitude of contribution of thyroid hormones, either tri-iodothyronine (T_3) or T_4 , to the insulin action and development of glucose intolerance is needed.

This study has several limitations. First, due to insufficient serum, T_3 and T_4 levels were not measured, which may have resulted in some misclassification (e.g. pituitary disease). And it was not able to subclassify accurately persons with an abnormal TSH as having subclinical versus overt disease. Secondly, this study was cross-sectional, so its ability to infer causality is limited. Thirdly, we did not detect TgAb and also TgAbs to have prevalence of thyroid antibodies only for TPOAbs. However, TPOAbs are now considered as a more important marker for autoimmune thyroid disease than TgAbs. Fourthly, because HOMA uses fasting values for estimation, it mostly describes hepatic IR and steady-state insulin secretion in this study. Moreover, we did not have access to direct measures of IR and β -cell function. Although euglycemic hyperinsulinemic clamp technique (Clamp-IR) is the standard method for the measurement of insulin sensitivity, its invasiveness and high cost have limited its use in clinical practice. The OGTT is less precise (43) but simpler to perform and is often used in large epidemiological or intervention studies.

In conclusion, this survey investigated the prevalence of thyroid disorders and its associations with cardiovascular risk, IR, and β -cell function. Vascular function did not show difference among different thyroid states. Thyroid dysfunction was associated with some ECG changes, suggesting that hypothyroid subjects may carry higher cardiovascular risk than euthyroid subjects. We also found a significant negative correlation, albeit weak, between IR, insulin secretion and TSH, which may be explained by the decreasing insulin-antagonistic effects of thyroid hormones along with increasing TSH.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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