

A Population Based Study on the Association of Thyroid Status with Components of the Metabolic Syndrome

Fahimeh Ramezani Tehrani^{1*}, Maryam Tohidi², Marzieh Rostami Dovom¹ and Fereidoun Azizi³

¹Reproductive Endocrinology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Prevention of Metabolic Disorders Research Center, Iran

³Endocrine research center, Iran

Abstract

Introduction: Although overt hypothyroidism is a known risk factor for cardiovascular disease, there is no consensus regarding the impact of subclinical hypothyroidism (SCH) on metabolic syndrome (MetS). A positive association between overt hypothyroidism and hypercholesterolemia is well documented. This study investigated whether there is any association between (SCH) and MetS components.

Material and Methods: In a community based population using the stratified, multistage probability cluster sampling method, 1126 women aged 18-45 years, were randomly selected from four urban areas of Iran. After considering the exclusion criteria, 914 subjects were enrolled. Multiple logistic regression analysis was used to investigate the simultaneous effect of different variables on MetS and each of its components.

Results: In this study the prevalence of euthyroid women with MetS was 16.9%, which was similar to its prevalence among women with SCH (19.2%). The average estimated total score of Mets in women with SCH was significantly higher than the euthyroid women ($p=0.006$). We found that TSH levels in SCH subjects were negatively and positively correlated with HDL-C and diastolic blood pressure respectively, even after adjustment for age, BMI and HOMA-IR. There was no significant correlation between TSH level in SCH subjects and other MetS components. The prevalence of obesity/overweight in women with SCH was higher than that in euthyroid women.

Discussion: Although there is no evidence of any association between thyroid status and all Mets components, but thyroid dysfunction can be considered a risk factor for metabolic syndrome.

Abbreviations: SCH- Sub Clinical Hypothyroidism; MetS- Metabolic Syndrome

Introduction

Metabolic syndrome (Mets), a complex of disorders including the abdominal obesity, dyslipidemia, hypertension and impaired fasting glucose, is one of the known risk factors for cardiovascular disease (CVD) [1-3]. Despite the controversy on its definition it is estimated that one out of four people around the world suffers from this syndrome [4,5]. The prevalence of Mets in Iran is reported to be 30.1 %, using the ATP III definition [6].

Overt hypothyroidism acts as a CVD risk factor through several mechanisms, as a result of which the incidence of heart attack can increase over two fold in hypothyroid subjects [7-11]. A positive association between overt hypothyroidism and hypercholesterolemia is well recognized [12]. In addition it is reported that thyroid hormones influence vascular smooth muscles, consequently reducing arterial resistance, and causing a decline in diastolic blood pressure[13]. Moreover, insulin sensitivity can be affected by thyroid function and a positive association between overt hypothyroidism and BMI has been well documented [14,15] .

The correlation between subclinical hypothyroidism (SCH) and Mets and its components varies in different studies and seems to be influenced by age, gender and race of study participants[9,10,16]. A significant correlation between SCH and Mets was reported in a study from India [17]. Park *et al.* found that the serum concentration of TSH in menopausal women with SCH was a powerful predictor of Mets and its components [18]. However in contrast to these studies, the prevalence of Mets among Turkish subjects with subclinical thyroid disorders was similar to normal subjects (0.35% compared with 0.33%) [19]; in the Manji *et al.* study there was no significant association

between BMI and serum TSH levels in subjects with no apparent impairment of thyroid function [20].

We aimed to investigate whether there was any association between SCH with Mets or its components in a community based population of Iranian reproductive aged women.

Material and Methods

Using the stratified, multistage probability cluster sampling method, a total of 1126 women, aged 18-45 y, were recruited from among reproductive aged women, living in urban areas of four randomly selected provinces of different geographic regions of Iran, i.e. Ghazvin (Central), Kermanshah(East), Golestan (North) and Hormozgan (South). The Iranian household list available from the Health Department was used to identify the frame for the selection of the sampling units.

***Corresponding author:** Prof. Fahimeh Ramezani Tehrani M, Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Parvaneh, Yaman Street, Velenjak, P.O.Box:19395-4763, Tehran, I.R.Iran, Postal Code: 1985717413, Tel: 98-21-22409309; Fax: 98-21-22402463; E-mail: ramezani@endocrine.ac.ir, framezan@post.harvard.edu

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Before data collection, trained interviewers explained in detail the purpose and procedure of the study to subjects at their homes and obtained their written consent, following which a questionnaire including demographic and reproductive histories, family history and a personal history of thyroid diseases, diabetes, hypertension and dyslipidemia and their treatment was completed. All participants underwent clinical examinations, where body weight, height, waist (WC), hip circumferences (HC) and blood pressure were measured. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height and waist circumference (WC) were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. Body mass index was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). Blood pressure was measured twice, with a 3-min interval, after 30 minutes of rest and the mean value of the two measurements was used. An overnight fasting venous blood sample was obtained from each subject and stored at -80°C , until the time of measurements.

Menopausal women, those who had undergone hysterectomy or bilateral oophorectomy, participants having a personal history of thyroid disease and had been taking thyroxine or anti-thyroid drugs for treatment, those taking medication affecting thyroid function, and any pregnant or lactating women were excluded ($n=105$). Furthermore women with incomplete clinical information or those whose blood samples were not available ($n=107$) were also excluded from the present study.

Fasting serum glucose, triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured using the enzymatic colorimetric method (Pars Azmon Inc., Tehran, Iran) using a Selectra 2 auto-analyzer (Vital Scientific, Spankeren, The Netherlands). The Friedewald equation was used to calculate low-density lipoprotein cholesterol (LDL-C); samples with $\text{TG} > 400 \text{ mg/dl}$ were assayed by the direct method. In all the biochemical analyses, the intra- and inter-assay coefficients of variation (CV) were less than 2.5% and 3.2% respectively.

Free thyroxine (FT4) was measured by radioimmunoassay and the thyroid-stimulating hormone (TSH) was assayed by immunoradiometric assay (Izotop, Budapest, Hungary) with a Wallac Wizard gamma counter (Turku, Finland); the intra- and inter-assay CVs were 3.4% and 4.6% for FT4 and 1.7% and 3.4% for respectively TSH determinations.

We measured insulin by immune-enzymometric assay using commercial kits (Mercodia, Upssala, Sweden and the Sunrise ELISA reader (Tecan Co., Salzburg, Austria), the intra- and inter-assay CV being 2.4 and 5.8%, respectively. HOMA-IR was calculated according to the formula: $\text{HOMA-IR} = [(\text{Fasting insulin level (mU/L)} \times \text{Fasting plasma glucose (mmol/L)}) / 22.5]$.

Definitions

SCH (SCH) is defined as serum free T4 level within the reference range in the presence of elevated serum TSH level (4.5 mIU/L).

We used the definition of the NCEP ATPIII modified in 2005 by the American Heart Association (AHA) and the national Heart, Lung, and Blood Institute [21]. We adjusted the waist circumference cut off value, 91.5 cm , as it suggested for Iranian women [22]. According to this definition, Metabolic Syndrome was suggested as the following criteria: the presence of any three of five risk factors of the following: (1) Abdominal obesity as $\text{WC} \geq 91.5 \text{ cm}$ for women (2) $\text{FPG} \geq 100 \text{ mg/}$

dl or drug treatment; (3) Fasting $\text{TG} \geq 150 \text{ mg/dl}$ or drug treatment; (4) Fasting $\text{HDL-C} < 50 \text{ mg/dl}$ in women or drug treatment; (5) Raised blood pressure defined as systolic blood pressure (SBP) $\geq 130 \text{ mmHg}$, diastolic blood pressure (DBP) $\geq 85 \text{ mmHg}$ or antihypertensive drug treatment or antihypertensive drug treatment.

For each MetS criteria we considered 1 point for any woman who had the criteria; the individual MetS risk score was calculated by sum of points that were gained from the 5 MetS criteria.

Statistical analysis

Continuous variables were checked for normality using the one-sample Kolmogorov-Smirnov test; they are expressed as mean \pm standard deviation and/or median and inter quartile ranges, as appropriate. The categorical variables are expressed as percentages. Two-sample comparisons were used by Fisher's exact test, Student's *t* test, or Mann-Whitney U test, as appropriate. Multiple linear regression analysis was performed to identify relationships between serum lipid parameters, systolic and diastolic blood pressure as dependent variables and thyroid function after adjusting for BMI, age and HOMA-IR. Multiple logistic regression analysis using the enter procedure was performed to investigate the simultaneous effect of different variables on Mets and each of its components. The interactions between all of covariates included in the final models were tested. Data analysis was performed using the SPSS 15.0 PC package (SPSS Inc., Chicago, IL).

Results

Of the 1126 women, aged 18-45, recruited for the present study, 914 subjects met our inclusion criteria; of these 720 participants (78.8%) were euthyroid and 194 women (21.2%) had sub-clinical hypothyroidism.

Clinical characteristics, anthropometric and biochemical parameters of participants with SCH in comparison to those with normal thyroid function are summarized in Table 1. There was a significant difference between the means of body mass index (BMI), age, systolic and diastolic blood pressure, waist circumference and HDL serum levels of women with SCH in comparison to these values in euthyroid women. There was no significant difference between serum insulin and HOMA-IR in hypothyroid women compared to their euthyroid counterparts. Of the 914 women participants, 159 (17.5%) had Mets, among these women, 11.3% had three, 5.1% had four and only 1% had all of the five components of Mets. The prevalence of Mets among hypothyroid women was 19%, and of these, 10.3%, 8.2% and 0.5% had three, four and five criteria of Mets. Prevalence of Mets in subjects with normal thyroid function was 16.9%; 11.4% had three components 4.3% had four and 1.1% had five Mets criteria.

After adjustment for BMI there were no statistically significant associations between TSH and total cholesterol, LDL or FBS, but there was a significant negative association between TSH and HDL ($p=0.001$, $r=-0.115$) and between TSH and diastolic blood pressure ($p=0.001$, $r=0.001$). Table 2 demonstrates the predictive coefficient (standardized beta) of Mets before and after further adjustment for other variables. There was a positive, statistically significant correlation between serum cholesterol and TSH levels (Standardized $B=0.001$, $p=0.02$) but it ceased to exist after further adjustment for age, BMI and HOMA-IR, in spite of mild increase in its standardized beta. Multivariate logistic regression analysis revealed that increasing TSH levels were associated with an increase in diastolic blood pressure and decrease in HDL-C.

	Euthyroid N=720	SCH N=194	P value
Age	34±7.6†	35.8±7.4†	0.003
Obesity			
Waist(cm)	84.5±12.2†	86.9±12†	0.01
BMI(Kg/M2)	26.9±5.1†	27.9±5.1†	0.002
Abdominal obesity Prevalence (%)	20.7	26.3	0.05
BMI>30(Kg/M2)	23.1	28.9	0.06
High blood Pressure			
Systolic(mmHg)	109±13.9†	111.2±14.1†	0.012
diastolic(mmHg)	69.3±11†	71.1±11†	0.008
High blood pressure prevalence (%)	2.1	3.6	NS
HBP treatment prevalence (%)	2.8	3.61	NS
BP>130/85 prevalence (%)	5.3	7.61	NS
Blood Lipid			
Total cholesterol(mg/dl)	184.8±41.7†	185±38.2†	NS
TG(mg/dl)	140.2±97.7†	148.8±100.1†	NS
LDL cholesterol(mg/dl)	111.2±35.8†	111.6±33.9†	NS
HDL cholesterol(mg/dl)	45.7±13.2†	43.9±12†	0.01
Chl≥150mg/dl (%)	80.6	85	NS
Chl≤50 mg/dl (%)	64.1	71	0.04
TG≥150mg/dl (%)	30.5	40.4	0.006
Blood sugar			
FBS(mg/dl)	85.9±27.2†	89.3±21.7†	NS
Insulin	9.2±9.9†	8.2±5.4†	NS
HOMA-IR	2.2±3.1†	1.9±1.8†	NS
Diabetic Mellitus (%)	4.6	5.2	NS
FBS>100mg/dl (%)	17.6	16.6	NS
Metabolic Syndrome	76.6	23.4	NS
Metabolic syndrome score	1.3±1.6†	1.6±1.2†	0.013
Metabolic Syndrome prevalence (%)	16.9	19.2	NS

SCH: Women with subclinical hypothyroidism; † mean ± SD

Table 1: The basic and metabolic characteristics of study subjects according to the thyroid status.

	Model		TSH			Free T4	
		β	P value*	R ²	β	P value	R ²
Total Cholesterol	1	0.001	*0.025	0.001	0.126	-	0.015
	2	- 0.031	0.339	0.065	0.161	-	0.09
	3	-0.032	0.315	0.099	0.156	-	0.123
	4	- 0.028	*0.0371	0.109	0.153	-	0.132
Waist circumference	1	0.047	0.16	0.001	- 0.01	0.752	- 0.001
	2	- 0.004	0.888	0.18	0.044	0.143	0.181
	3	- 0.005	0.804	0.672	0.023	0.224	0.673
	4	- 0.004	0.847	0.675	0.022	0.247	0.676
TG	1	0.053	0.108	0.002	0.008	0.82	- 0.001
	2	0.032	0.337	0.033	0.031	0.346	0.032
	3	0.031	0.344	0.07	0.025	0.43	0.07
	4	0.042	0.174	0.168	0.015	0.628	0.166
HDL-C	1	- 0.111	*0.001	0.011	0.05	0.133	0.001
	2	- 0.097	*0.004	0.024	0.034	0.344	0.016
	3	- 0.095	*0.003	0.078	0.041	0.205	0.072
	4	- 0.1	*0.002	0.091	0.045	0.158	0.083
FBS	1	0.05	0.12	0.001	0.045	0.172	0.001
	2	0.03	0.371	0.029	0.069	*0.037	0.033
	3	0.029	0.377	0.035	0.066	0.044	0.039
Systolic BP	1	0.062	0.063	0.003	- 0.002	0.987	- 0.001
	2	0.028	0.374	0.078	0.035	0.28	0.079
	3	0.028	0.368	0.106	0.03	0.35	0.106
	4	0.031	0.326	0.114	0.022	0.489	0.114
Diastolic BP	1	0.111	*0.001	0.011	0.014	0.675	- 0.001
	2	0.086	*0.008	0.054	0.043	0.19	0.049
	3	0.086	*0.007	0.08	0.038	0.24	0.074
	4	0.088	*0.006	0.082	0.036	0.263	0.076
HOMA_IR	1	- 0.028	0.401	-	0.037	0.264	-
	2	- 0.034	0.309	0.001	0.044	0.191	0.002
	3	- 0.035	0.286	0.038	0.038	0.246	0.038

*P< 0.05 is significant; β: standardized regression coefficients; R²: coefficient of determination. Model 1, crude; Model 2, after adjustment for age; Model 3, after adjustment for age and BMI; Model 4, after adjustment for age, BMI and HOMA-IR

Table 2: Association of thyroid function tests with metabolic parameters.

Discussion

In the present population based study of over 900 reproductive aged women, we found no evidence of an association between thyroid status and the prevalence of Mets, but subclinical thyroid dysfunction was related with two components of Mets (low HDL and high TG). In addition, the average estimated total score of Mets in women with SCH was significantly higher than the euthyroid women. We found that TSH levels were negatively correlated with HDL-C and positively with diastolic blood pressure independently of well-known MetS risk factors (age, BMI, HOMA-IR).

In this study, 21.2% of women had subclinical thyroid dysfunction. It is estimated that about 2-20% people in the world are suffering from SCH and its prevalence is influenced by the geographic location, sex, diet and race [23]. The prevalence of hypothyroidism in Turkey (16.4%), United States of America (5.9%) and Finland (9.5%) are less than the estimated prevalence in the present study [19,24,25] and our prevalence is similar to the 21.9% reported by Shantha in India [26].

In the present study, 16.9% of euthyroid women had Mets that was similar to its prevalence among women with SCH (19.2%). The prevalence of Mets in our study was less than that reported in the Tehran Lipid and Glucose Study (25%) [6] which may be explained by their excluding postmenopausal and ageing women. Similar to the our study, the prevalence of Mets in Turkish women with SCH was similar to the healthy euthyroid women (35% compared to 33%) [26]; furthermore Garcia *et al* reported that there was no association between Mets or its components and subclinical thyroid dysfunction [24]; despite these findings, Uzunlulu *et al* observed that the Mets in women with SCH is about three times higher than in healthy women (16.4% compared with 5.8%) [19].

Studies have shown that acute administration of TSH to euthyroid subjects caused endothelial dysfunction and increased serum levels of C-reactive protein, TNF- α , several indices of oxidative stress and IL-6 [27,28]. In the present study, despite no difference in the prevalence of Mets, we found a statistically significant difference in the average total scores of Mets between women with SCH and euthyroid women ($p=0.006$). Moreover, TSH levels were positively correlated with triglycerides and negatively with HDL-C, which may confirm that TSH levels may have long-term harmful effects on cardiovascular health through the association with serum lipids. It has been shown that as a result of decline in the number hepatocytes cell-surface receptors for LDL, resulting in reduced LDL catabolism in women with overt hypothyroidism leads to increased levels of cholesterol and LDL-C and reductions in HDL-C [29,30]. However, the results of population studies about the correlation between thyroid function and lipid profiles are controversial [10,31].

In this study there is a negatively significant association between TSH and HDL-C, an association that exists even after adjustment with BMI, age and HOMA-IR. A negative association between HOMA-IR and TSH was reported by Roos *et al* [8]. However some studies have shown that the association between TSH and serum lipids in women with normal thyroid function is regulated via insulin sensitivity [14]. Similar to our results, Lie *et al* found no difference in serum insulin levels and HOMA-IR of hypothyroid women in comparison to euthyroid ones [10]; however these levels of insulin in Kuwaiti women with SCH were higher than women with normal thyroid function, despite no discrepancy in their HOMA-IR, [32].

In our study, similar to the Virta study the prevalence of obesity/

overweight in women with subclinical hypothyroid was higher than in euthyroid women [25] whereas Manji reported no correlation between thyroid function status and body mass index in subjects without overt thyroid dysfunction [18,20]. It has been shown that in adipocytes and pre adipocytes expressed TSH receptors, TSH binds with its receptors and induces pre adipocytes to produce and release adipokines [33], a mechanism which may explain the correlation between TSH levels and obesity.

There was no consensus regarding the association between increasing systolic or diastolic blood pressures and TSH serum concentrations in women, without overt thyroid dysfunction [8,34,35]. In the present study, there was a statistically significant difference between the means of systolic and diastolic blood pressure of women with sub clinical hypothyroidism in comparison to euthyroid participants; however it was not clinically important and the prevalence of hypertension or high blood pressure, as a component of metabolic syndrome, was similar among our study groups. In contrast to the study conducted among Chinese women [10], we observed a positive significant correlation between serum level of TSH and diastolic blood pressure, a correlation that remained after further adjustment for age, BMI and HOMA-IR.

This large community-based study provided us with a unique opportunity to study the association between TSH and the Mets components in an ethnically homogenous population of reproductive aged women. As reported by Janghorbani *et al*, following a large national survey [36], the educational status and the prevalence of obesity in the present study could justify and confirm our population as being representative of Iranian reproductive aged women [36]. Also the amount of intra-assay variability in our data is likely to be minimal because all laboratory measurements were done at the same laboratory, by the same person. This study does have some limitations. First, its cross-sectional design allowed us to assess only the association rather than causal relationship. Second, since the study population included only Iranian reproductive aged women, results are not applicable to other races, men, post menopausal women or other countries with different iodine intakes.

Conclusion

In conclusion we found no evidence of an association between thyroid status and Mets, but TSH levels were associated with Mets components, independent of the well-known risk factors of this syndrome. Further investigations are needed to determine the comprehensive mechanism of this correlation.

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Details of Ethics Approval

The ethical review board of the Research Institute for Endocrine Sciences has approved the study proposal and informed consent was obtained from all subjects.

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