ORIGINAL ARTICLE

Association between metabolic syndrome and thyroid function: A study among the hypothyroid population in the northeast of Iran

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Abstract

Background: Hypothyroidism (especially subclinical hypothyroidism) and Metabolic Syndrome (MetS) association have been controversial. *Aim and Objectives:* This study was aimed to examine the MetS components in patients with Clinical and Subclinical Hypothyroidism (CH & SCH) in northeast Iran. *Material and Methods:* In this cross-sectional study, 186 hypothyroid patients were evaluated for MetS using NCEP-ATP III criteria. Thyroid function and lipid profile parameters were measured using ELISA and enzymatic photometric methods. *Results:* MetS was common in 53.2% of hypothyroid patients. The odds of MetS in 50 years and above were about 3.2 times higher than those under 50 ($p = 0.001$). Simple logistic regression analysis showed decreasing one mg/dl High-Density Lipoprotein Cholesterol (HDL-C) increased nearly 10% odds of MetS (OR = 0.916; 95% CI: 0.882–0.951; $p = 0.001$). In addition, rising one unit Waist Circumference (WC) increased about 14% odds of MetS (OR = 1.137; 95% CI: 1.092–1.183; $p = 0.001$). As well as, multiple logistic regression analysis showed low HDL-C ($p = 0.0001$), high SBP ($p = 0.0001$), and high WC ($p = 0.009$) had the most significant effect on developing MetS, respectively. *Conclusion:* This study determined that CH and SCH are significantly associated with MetS. In addition, MetS significantly increased in reduced HDL-C, increased SBP, and age more than 50.

Keywords: Thyroid Function Test, Thyroid Stimulating Hormone, High-Density Lipoprotein, Central Obesity

Introduction

Hypothyroidism is a syndrome characterized by an increase in serum Thyroid Stimulating Hormone (TSH) level with low free T4 (fT4) in Clinical Hypothyroidism (CH) and normal fT4 in Subclinical Hypothyroidism (SCH) [1].

Insufficient production of thyroid hormones leads to an imbalance in the basal metabolic rate and inefficiency in responding to the physiological and metabolic needs of the body [2]. The prevalence of hypothyroidism in an iodine sufficient region in Iran was 4.8% in men and 12.8% in women [3]. The studied area (Golestan province) is located in the iodine-sufficient area [4].

Metabolic Syndrome (MetS) is characterized by a set of metabolic component abnormalities, including central obesity, elevated Triglyceride (TG), decreased High-Density Lipoprotein Cholesterol (HDL-C), increased Low-Density Lipoprotein Cholesterol (LDL-C), hypertension, and hyperglycemia [5]. MetS is related to cardiovascular disease, type 2 diabetes, and some types of carcinoma [6]. Thyroid hormones affect energy homeostasis, glucose, and lipid metabolism.

According to a case-control study performed on women in India, the prevalence of Mets, based on The National Cholesterol Education Program –

Adult Treatment Panel III (NCEP-ATPIII) criteria, in SCH patients (38%) was significantly higher than in the control group (18%) [7]. A population-based study performed on women in some urban areas of Iran (including Golestan) demonstrated that the prevalence of Mets was not significantly different between SCH (19.2%) and euthyroid women (16.9%) [8].

Observational studies on the association between SCH and MetS had conflicting results. Some studies showed that thyroid hormone changes are related to MetS components [9]. The last two systematic review and meta-analysis studies that have been done in this regard did not have the same results. The first systematic review and meta-analysis showed that SCH is positively associated with the prevalence of MetS, especially in Asians. This study was faced with degrees of study heterogeneity that the study design, diagnostic criteria, and location could not explain this heterogeneity [10]. In another systematic review and meta-analysis conducted on the general population, no significant difference was observed in the prevalence of MetS between SCH and euthyroid participants [11]. In recent years, two retrospective studies showed an association between MetS and SCH in the Middle East. Even though, in both studies, the prevalence of MetS in SCH patients was not reported, and in one, no standard definition was used to diagnose MetS [12-13]. Accordingly, this cross-sectional study assessed the relationship between CH and SCH and the components of MetS in an Iranian population living in the northeast of Iran.

Material and Methods

Study population and design

This cross-sectional study was conducted in Golestan province, located in the coastal area of the Caspian Sea in northeast Iran. In this study, 186 consecutive patients with hypothyroidism were recruited from endocrine outpatient clinics in June-November 2020. The diagnosis of CH was defined by an increase in serum TSH level above 4.3 mIU/L and serum FT4 level less than 5.1 pmol/L, and SCH was defined as TSH level above 4.3 mIU/L and FT4 in the normal range (5.1- 14.1).

Sample size

A previous study from a neighboring country demonstrated that the prevalence of metabolic syndrome among hypothyroid patients was 44% [14]. Thus, by the formula $Z^2 pq/d^2$ with a 95% confidence level, an allowable error of 0.07, and a 10% non-respondent rate, the estimated sample size was 186. Simple random sampling was used for selecting participants.

Data collection

MetS was determined according to the NCEP-ATP III criteria. MetS was defined by the presence of at least three of the five following components, including Waist Circumference (WC) $\geqslant$ 102 cm for men or $\geqslant$ 88 cm for women, elevated Blood Pressure (BP) $\geqslant$ 130 mmHg SBP or $\geqslant$ 85 mmHg Diastolic BP (DBP) or on antihypertensive drug treatment, HDL-C < 40 mg/dl for men or < 50 mg/dl for women, TG $\geqslant$ 150 mg/dl or anti-lipid drug treatment history, and Fasting Blood Sugar (FBS) $\geqslant$ 100 mg/dl or previous diagnosis of diabetes mellitus [15].

A measuring tape measured the waist circumference at the midpoint of the distance between the iliac crest and the lowest rib. Body weight was measured with light clothes using a Seca scale (Seca, Reinach, Switzerland) with an accuracy of 0.1 kg. Height was measured using a stadiometer. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). Thyroid hormones

(FT3, FT4, and TSH) and serum MetS components (FBS, HDL-C, and TG) were measured after overnight fasting. Thyroid hormone levels were measured using commercial ELISA kits from Pars Azmoon (Pars Azmoon Inc., Tehran, Iran). Also, lipid profile parameters were evaluated using the enzymatic photometric method with the Pars Azmoon kit.

Statistical analyses

Continuous variables were presented as Mean ± Standard Deviation (SD), and categorical variables were expressed as proportions. The association of each risk factor with MetS was assessed by applying the chi-square test for categorical variables, independent Student t-test for continuous variables, and nonparametric test for continuous variables without normal distribution. The relationship between covariates and MetS was analyzed using univariate simple binary logistic regression to explore the influence of different factors. Then, we used multiple logistic regression analysis to compute adjusted ORs and assess the effect of some variables on MetS. Variables with $p \geqslant 0.20$ in univariate analysis were included in the final multivariate model (except for BMI due to its strong correlation with WC). The dependent variable was MetS, and the covariates were gender, age, BMI, WC, FBS, SBP, DBP, HDL-C, LDL-C, TG, hypothyroid status, and education level. All statistical analyses were conducted using the SPSS (version 16) software. The significance level was set at 0.05 ($\alpha = 0.05$).

Ethical considerations

The study was approved by the Ethics Committee of Golestan University of Medical Sciences (Code: IR.GOUMS.REC.20199207145). All participants signed written informed consent to participate in the study.

Results

Demographic profile and metabolic syndrome in hypothyroid patients

In the present study, 116 (62.4%) participants had CH, and 70 (37.6%) had SCH. The average age of participants was 46.74 ± 14.14 years, and 89.8% were women. The demographic and clinical information of participants is shown in Table 1. The results showed that 53.2% of hypothyroid patients had MetS. Although our study demonstrated that the prevalence of MetS in CH (66.7%) was higher than in SCH (33.3%), this difference was not significant ($p = 0.196$).

Simple logistic regression analysis

The results showed that high WC (93.9%), low HDL-C (84.8%), high FBS (60.6%), high SBP (55.6%), and high TG (53.5%) were the most frequent components in the MetS patients, respectively. The results of univariate simple logistic regression analysis (Table 2) showed that the odds of MetS in hypothyroid patients 50 years and more were about 3.184 times higher than those under 50 (95% CI: 1.734–5.848, $p = 0.0001$). However, there was no gender difference in the odds of developing MetS (95% CI: 0.298–1.992, $p = 0.590$). It could not demonstrate a significant relationship between serum TSH levels and MetS in hypothyroid patients ($p = 0.916$). Also, the categorized TSH (lower and upper 10) was unrelated to MetS ($p = 0.357$). The results showed that older adults ($p = 0.001$), high-BMI ($p = 0.001$), high-WC ($p = 0.001$), high-FBS ($p = 0.001$), high-SBP ($p = 0.001$), high-DBP ($p = 0.001$), low-HDL ($p = 0.001$), high-TG ($p = 0.001$), and lowly educated patients ($p = 0.001$) were at higher risk of MetS.

Multiple logistic regression analysis

In addition, a multiple logistic regression analysis was performed to investigate the simultaneous

effect of MetS components on the odds of developing Mets (Table 3). According to this analysis, the components with the greatest impact on hypothyroid patients (CH and SCH) to develop MetS were decreased HDL-C ($p = 0.0001$), increased SBP ($p = 0.0001$), increased WC ($p = 0.009$), and increased FBS ($p = 0.001$), respectively.

Table 1: Sociodemographic and characteristics of hypothyroid patients

Characteristic	N (%)	Hypothyroid patients		Test Statistics	p
		Subclinical	Clinical		
Gender					
Male	19 (10.2)	8 (42.1)	11 (57.9)	0.180	0.671
Female	167(89.8)	62 (37.1)	105 (62.9)		
Age (y)	186	45.03 ± 15.391	47.77 ± 13.292	-1.282	0.201
Age categories (y)					
<50	103(55.4)	41 (39.8)	62 (60.2)	0.464	0.496
≥50	83 (44.6)	29 (34.9)	54 (65.1)		
BMI (kg/m2)	186	28.73 ± 5.699	29.70 ± 5.835	-1.115	0.266
WC (cm)	186	98.57 ± 12.618	99.79 ± 12.409	-0.644	0.520
FBS (mg/dl)	186	93 (86, 99.5)	98 (91, 111.25)	-2.551	0.011
SBP (mmHg)	186	120 (106.75, 130)	120 (110, 130)	-1.156	0.248
DBP (mmHg)	186	70 (70, 80)	70 (70, 80)	-0.256	0.798
HDL-C (mg/dl)	186	46 (41.75, 52.2)	46 (40.62, 53)	-0.127	0.899
LDL-C (mg/dl)	186	98.5 (76.08, 122.75)	100 (78.95,120.75)	-0.004	0.997
TG (mg/dl)	186	129.5 (99.25, 175)	126.5 (88.25, 170)	-0.676	0.499
TSH (mlu/L)	186	8.16 (5.8, 10.73)	8.23 (5.83, 12.14)	-0.124	0.902
T4 (mlu/L)	186	8.27 (6.47, 9.03)	0.94 (0.61, 2.3)	-3.713	0.001
MetS					
No	87 (46.8)	37 (42.5)	50 (57.5)	1.668	0.196
Yes	99 (53.2)	33 (33.3)	66 (66.7)		
Education level (y)					
0	21 (11.3)	6 (28.6)	15 (71.4)	1.450	0.694
1-11	36 (19.4)	13 (36.1)	23 (63.9)		
12	63 (33.9)	23 (36.5)	40 (63.5)		
12<	66 (35.5)	28 (42.4)	38 (57.6)		

MetS: Metabolic Syndrome, BMI: Body Mass Index, WC: Waist Circumference, FBS: Fasting Blood Sugar, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol, TG: Triglyceride, TSH: Thyroid stimulating hormone, y: year

Table 2: Association between predictors and metabolic syndrome in hypothyroid patients - univariate simple binary logistic regression analysis

Hypothyroid Patients: Odds Ratio (95% C.I for OR)				
Variable (unit)	**Subclinical**	**Clinical**	**Total**	*p*
Gender				
Female	1	1	1	
Male	0.640 (0.141, 2.913)	0.770 (0.298, 1.992)	0.770 (0.298, 1.992)	0.590
Age (y)	1.054* (1.017,1.092)	1.042* (1.011, 1.074)	1.048 (1.024, 1.072)	0.001
Age categories (y)				
<50	1	1	1	
50<=	4.786* (1.717,13.346)	3.184 (1.734, 5.848)	3.184 (1.734, 5.848)	0.001
BMI (kg/m2)	1.396* (1.181, 1.650)	1.283* (1.155, 1.426)	1.320 (1.208, 1.443)	0.001
WC (cm)	1.138* (1.065,1.216)	1.138* (1.080,1.200)	1.137 (1.092, 1.183)	0.001
FBS (mg/dl)	1.135* (1.051,1.225)	1.064* (1.029,1.101)	1.081 (1.047, 1.116)	0.001
SBP (mmHg)	1.082* (1.036,1.131)	1.085* (1.048,1.123)	1.085 (1.055, 1.115)	0.001
DBP (mmHg)	1.037 (0.991,1.085)	1.069* (1.022,1.119)	1.054 (1.021, 1.088)	0.001
HDL-C (mg/dl)	0.875* (0.811, 0.945)	0.933* (0.892, 0.976)	0.916 (0.882, 0.951)	0.001
LDL-C (mg/dl)	1.001 (0.987, 1.014)	0.995 (0.983, 1.006)	0.997 (0.988, 1.006)	0.514
TG (mg/dl)	1.008 (1.000, 1.016)	1.027* (1.016, 1.038)	1.017 (1.010, 1.024)	0.001
TSH (mlu/L)	1.014 (0.925, 1.111)	0.986 (0.921, 1.057)	0.997 (0.944, 1.053)	0.916
TSH categories				
<10 (mlu/L)	1	1	1	
10<= (mlu/L)	1.538 (0.588, 4.025)	1.320 (0.732, 2.380)	1.320 (0.732, 2.380)	0.357
TC (mg/dl)	1.002 (0.991, 1.013)	1.000 (0.991, 1.010)	1.001 (0.994, 1.008)	0.831
Education level (y)				
0	1	1	1	
1-11	2.750 (0.284, 26.607)	0.938 (0.267, 3.292)	0.938 (0.267, 3.292)	0.920
12	0.321 (0.048, 2.133)	0.323 (0.105, 0.988)	0.323 (0.105, 0.988)	0.048
12<	0.237 (0.036, 1.542)	0.179 (0.058, 0.549)	0.179 (0.058, 0.549)	0.003

BMI: Body Mass Index, WC: Waist Circumference, FBS: Fasting Blood Sugar, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, TG: Triglyceride, TSH: Thyroid stimulating hormone, TC: Total Cholesterol, y: year, OR: Odds Ratio, CI: Confidence interval

Table 3: Association between predictors and metabolic syndrome in hypothyroid patients - multiple binary logistic regression analysis

	Hypothyroid patients: OR (95% CI)			
Variable(unit)	**Subclinical**	**Clinical**	**Total**	**p**
Age (y)	1.059 (0.971, 1.156)	0.987 (0.929, 1.048)	1.027 (0.984, 1.071)	0.226
WC (cm)	1.048 (0.926, 1.187)	1.126* (1.024, 1.238)	1.086 (1.020, 1.156)	0.009
FBS (mg/dl)	1.146 (0.997, 1.318)	1.055* (1.001, 1.112)	1.080 (1.032, 1.130)	0.001
SBP (mmHg)	1.135* (1.006, 1.281)	1.128* (1.046, 1.217)	1.090(1.038, 1.144)	0.001
DBP (mmHg)	0.982 (0.886, 1.088)	0.982 (0.895, 1.078)	1.023 (0.964, 1.086)	0.454
HDL-C (mg/dl)	0.774* (0.643, 0.932)	0.939 (0.863, 1.022)	0.870 (0.808, 0.936)	0.001
TG (mg/dl)	1.010 (0.996, 1.025)	1.025* (1.006, 1.045)	1.011 (1.003, 1.019)	0.009
Education level (y)				
0	1	1	1	
1-11	3.517 (0.010, 1282.682)	3.319 (0.245, 45.049)	3.449 (0.436, 27.276)	0.241
12	0.328 (0.002, 66.770)	2.909 (0.206, 40.987)	1.861 (0.241, 14.375)	0.551
12 <	0.114 (0.001, 23.927)	3.578 (0.249, 51.486)	1.485 (0.192, 11.476)	0.705

WC: Waist Circumference, FBS: Fasting Blood Sugar, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL-C: High-Density Lipoprotein Cholesterol, TG: Triglyceride, y: year, OR: Odds Ratio, CI: Confidence interval

Discussion

MetS is a risk factor for cardiometabolic diseases and certain types of cancer and has increasingly become the focus of several studies examining the MetS consequences of hypothyroidism. This study assessed the components of MetS in CH and SCH patients in the coastal area of the Caspian Sea in northeast Iran. We evaluated MetS components, including waist circumference, blood pressure, and BMI, as well as blood sugar and lipid profiles in hypothyroid patients.

The results of the current study revealed that MetS was common in CH (56.9%) and SCH (47.1%). In a research on the Turkish population that used NCEP-ATP III criteria like ours to diagnose MetS, 44% of the CH and 35% of the SCH group had MetS, which was lower than the present study [14]. Another study which was performed in the Syrian population showed that MetS was more common in CH (79.1%) and SCH (71.0%) [16]. This difference could be due to the diagnostic

criteria of MetS. In the Syrian study, a lower WC range (WC ⩾ 94 cm in males and WC ⩾ 80 cm in females) placed people in the MetS group.

Unlike the Turkish study, we did not find the degree of hypothyroidism (clinical and subclinical) having a significant difference in the development of the MetS [14]. Consistent with our study, a case-control study in the Chinese population showed that MetS patterns were similar between SCH and CH [17]. A meta-analysis and systematic review showed that the prevalence of MetS in SCH and euthyroid subjects was not significantly different [11].

However, another meta-analysis showed that the risk of MetS in SCH was related to ethnicity and more common in the Asian population [10]. In contrast to our study, another study among older adults (70–79 years) of SCH participants in the United States found that only marked SCH (TSH > 10) was associated with MetS [18]. This variation could be due to the difference in the age group studied. Unlike the current study, they included just patients over 70 years old.

The current study has also determined that hypothyroid patients who were 50 years and over were at higher risk of developing MetS compared to younger. This finding is in accordance with other studies, which could be explained by a decreased metabolic rate with age [16, 19]. Our study showed that abdominal obesity was the most common component, which placed hypothyroid patients in the MetS group. This finding was in line with the Turkish study [14].

Our study could not demonstrate an association between serum TSH levels and MetS. Contrary to the findings of our study, a cohort study conducted on the US adult population and a large cross-sectional study on the Korean population suggested that elevated TSH levels, even within the normal range are associated with an increased prevalence of MetS [18, 20]. This contrast could be related to the study design. Our study was a cross-sectional study conducted in patients with hypothyroidism.

It could not display gender differences in the odds of MetS in SCH and CH participants. Contrary to this finding, the result of a cross-sectional study in China showed that women with hypothyroidism, especially postmenopausal women, were more at risk of developing MetS than men [21]. Part of this difference could be due to the diagnostic criteria of MetS, which were different in the two studies. In the Chinese study, females with WC ⩾ 85 cm and males with WC ⩾ 90 cm were categorized as MetS, while WC ⩾ 88 in women and WC ⩾ 102 in men were the diagnostic criteria used in our study.

The last systematic review and meta-analysis which assessed the association between SCH and MetS showed that lipid dysfunction in both high TG and low HDL-C levels had a positive correlation with SCH [22]. In this regard, the results of multiple logistic regression analysis in our study showed that decreased HDL-C and increased TG in hypothyroid patients (CH and SCH) had the most and the least significant impact on the development of MetS respectively.

However, this study has some limitations that should be considered when interpreting the findings. First, we did not examine autoimmune thyroid status, which represents an under reported thyroid disease and may influence TSH concentrations. Second, because this study was cross-sectional, a causal relationship between hypothyroidism and Mets could not be determined.

Conclusion

This cross-sectional study indicated that most patients with hypothyroidism, especially CH patients over 50 years of age, faced an increase in MetS. Therefore, it is reasonable to take measures for early diagnosis of thyroid dysfunction and early interventions to treat patients with hypothyroidism, to reduce the risk of MetS. It is also suggested that in future studies, thyroid autoimmune status should be considered in the context of cohort studies.

It is also recommended to assess MeS in hypothyroid patients before and after treatment with thyroid hormones.

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