

The Association between Subclinical Hypothyroidism and Components of Metabolic Syndrome

Khalid S Aljabri^{1*}, Samia A Bokhari¹, Bandari K Aljabri² and Turki A Alharthi³

¹Department of Endocrinology, Saudi Arabia

²Faculty of Medicine, Saudi Arabia

³College of Medicine, Saudi Arabia

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***Corresponding author:** Khalid S Aljabri, Department of Endocrinology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

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Abstract

Background and objective: The burden of thyroid diseases in the general population and patients with Metabolic Syndrome (Mets) is enormous. Therefore, the present study was an effort to investigate the association between Subclinical Hypothyroidism (SCH) and components of Mets in a selected group of patients with Mets in Saudi Arabia.

Design: We analyzed retrospectively 798 participants with Mets between the age 20 to 89 years. All patients were from the population of the Primary health center at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. Patients with Serum Thyroid Stimulating Hormone (TSH) level >4.2 mIU/L and normal free Thyroxine (FT4) level were taken as SCH. Metabolic risk factors were defined using the 2006 IDF criteria.

Result: 798 patients with Mets were included. Patients with SCH were non-significantly older than without SCH, 55.0 ± 12.6 vs. 53.3 ± 12.4 , $p=0.07$. There were 242 (30.3%) cases with SCH where female was found in 180 cases (74.4%) and male was 62 cases (25.6%), $p=0.009$. Patients in the age group of ≥ 60 years had non-significantly higher prevalence of SCH (36.8%) compared to <40 years (12%), 40-49 years (20.2%) and 50-59 years (31%), $p=0.2$. Cases with $HbA1c > 5.6$ or T2DM, HTN, TG (≥ 1.7 mmol/l) and low HDL-C were significantly more prevalent in patients with than without SCH (87.4 vs. 80.5%, $p=0.03$), (56.6 vs. 47.8%, $p=0.03$), (52.7 vs. 34.0%, $p<0.0001$) and (58.7 vs. 49.7%, $p=0.03$) respectively. SCH with $HbA1c > 5.6$ or T2DM, HTN and low HDL-C were increased significantly with advanced ages and non-significantly increased with advanced ages in patients with SCH and TG (≥ 1.7 mmol/l). Regression analysis of odd ratio of risk factors for patients with SCH and Mets showed that gender, $BMI \geq 30$ kg/m², HTN, TG (≥ 1.7 mmol/l) and low HDL-C were associated with higher likelihood of SCH.

Conclusion: Our study suggests that SCH might be a risk factor for Mets and its components. Further investigations are needed to evaluate the mechanism of this correlation.

Keywords: Subclinical hypothyroidism; Components of metabolic syndrome

Introduction

The Metabolic Syndrome (Mets) includes central obesity, Hyperglycemia Plus Insulin Resistance (IR), Hypertension (HTN), Dyslipidemia [1]. Thyroid Hormones play an important role in regulating Carbohydrate, Lipids and Protein metabolism. There are several studies about the correlation between thyroid function and components of Mets, but the results are disputed. A cross-sectional study of 1581 Euthyroid subjects found that there was positive correlation between Thyroid Stimulating Hormone (TSH) and index of IR as well as Triglyceride (TG) [2]. About one sixth of the Mets patients in Turkey were found to have Subclinical Hypothyroidism (SCH) [3]. Hypothyroidism affects Mets parameters including high density lipoprotein (HDL-C), TG and Fasting Blood Glucose (FBS). Thyroid hormones are major regulatory hormones and may be associated with metabolic syndrome [4,5].

The common pathogenic factor in both the disorders is IR. Many studies have reported a role of IR in causing a significant overlap in diagnosis in Mets population and Hypothyroidism as well [6]. IR subjects are more susceptible to the increased levels of high LDL-C at increasing TSH levels even within the normal range [7]. Among older women, high TSH levels were

associated with deleterious changes in serum lipids and that women with multiple lipid abnormalities were twice as likely to have increased TSH level [8]. However, studies that evaluate the relation between SCH and these metabolic disturbances are limited; therefore, the purpose of this study was to analyze the association between SCH and Mets components in a selected group of Mets from Jeddah City, Saudi Arabia.

Method

We analyzed retrospectively 798 participants with Mets between the age 20 to 89 years. All patients were from the population of the Primary health center at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. All data were collected based on a review of electronic medical data. Patient who are pregnant were excluded. The reference range values of TSH 0.22-4.2 μ U/L and Free T4 12.0-22.0 μ mol/L. Patients with serum TSH level >4.2 μ U/L and normal FT4 level were taken as SCH. Metabolic risk factors were defined using the 2006 IDF criteria that define elevated TG as \geq 150mg/dL (\geq 1.7mmol/L) and reduced HDL-C as <40mg/dL (<1.03mmol/L) for male and as <50 mg/dL (<1.29mmol/L) for female [9]. HTN was defined when the systolic blood pressure was \geq 130mm Hg and/or diastolic blood pressure was \geq 85mm Hg in addition to receiving any medication for HTN. Abnormal glucose metabolism was considered when HbA1c (\geq 5.7) or when patients were known to have type 2 diabetes mellitus (T2DM). The total

number of cohort were separated on basis of age values into four groups: <40 years, 40-49 years, 50-59 years and \geq 60 years.

Statistical Analysis

Continuous variables were described using means and Standard Deviations. Univariate analysis of baseline demography both between groups, were accomplished using unpaired t-test and nonparametric and Chi square test were used for categorical data comparison. Regression analysis was performed to assess for Odd Ratio (OR). P value <0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

Result

798 patients with Mets were included. There were 158 cases (19.8%) male and 640 cases (80.2%) were female with mean age 53.8 \pm 12.5 with mean body mass index (BMI) 32.5 \pm 6.3 kg/m^2 , (Table 1). HbA1c>5.6 or T2DM, HTN, TG (\geq 1.7mmol/l) and low HDL-C were present in 82.6%,51.0%, 39.7% and 52.4% respectively. The mean TSH and FT4 values were 3.6 \pm 2.3MIU/l and 15.3 \pm 2.1 μ mol/l respectively. Patients with SCH were non-significantly older than without SCH, 55.0 \pm 12.6 vs. 53.3 \pm 12.4, $p=0.07$. There were 242 cases (30.3%) cases with SCH where female was found in 180 cases (74.4%) and male was 62 cases (25.6%) with male to female ratio of 1 to 2.9, $p=0.009$, (Table 1).

Table 1: Base-line characteristics and bivariate analysis for patients with Subclinical hypothyroidism

Parameters	Total Present	Subclinical Hypothyroidism		P Value
		Absent		
Numbers	798	242 (30.3)	556 (69.7)	
Age (Years)	53.8 \pm 12.5	55.0 \pm 12.6	53.3 \pm 12.4	0.07
Gender	Male	158 (19.8)	62 (25.6)	0.009
	Female	640 (80.2)	180 (74.4)	
Body mass index (kg/m^2)	Mean \pm SD	32.5 \pm 6.3	33.3 \pm 6.3	0.02
	\geq 30	516 (65.4)	171 (70.7)	0.04
HbA1c>5.6 or Type 2 diabetes	607 (82.6)	195 (87.4)	412 (80.5)	0.03
Hypertension	346 (51.0)	137 (56.6)	2.9 (47.8)	0.03
Triglyceride (\geq 1.7mmol/l)	315 (39.7)	127 (52.7)	188 (34.0)	<0.0001
High density lipoprotein (<1.29mmol/l)	398 (52.4)	131 (58.7)	267 (49.7)	0.03
TSH (MIU/l)	3.6 \pm 2.3	6.3 \pm 2.2	2.4 \pm 1.1	<0.0001
FT4 (μ mol/l)	15.3 \pm 2.1	15.0 \pm 2.1	15.4 \pm 2.1	0.02

[mean \pm standard deviation (SD) or number (%)].

Patients in the age group of \geq 60 years had higher prevalence of SCH (36.8%) compared to <40 years (12%), 40-49 years (20.2%) and 50-59 years (31%), $p=0.2$, (Figure 1). Patients with SCH were significantly have higher BMI than without SCH, 33.3 \pm 6.3 vs. 32.1 \pm 6.3, $p=0.02$. Cases with HbA1c>5.6 or T2DM, HTN, TG (\geq 1.7mmol/l) and low HDL were significantly more prevalent in patients with SCH compared to Euthyroid patients (87.4 vs. 80.5%, $p=0.03$), (56.6 vs. 47.8%, $p=0.03$), (52.7 vs. 34.0%, $p<0.0001$) and (58.7 vs. 49.7%, $p=0.03$) respectively. SCH with HbA1c>5.6 or T2DM, HTN and low HDL were increased significantly with

advanced ages ($p=0.003$, $p<0.0001$ and $p=0.003$ respectively) and non-significantly increased with advanced ages in patients with SCH and TG (\geq 1.7 mmol/l) ($P=0.6$), (Table 2). Regression analysis of odd ratio of risk factors for patients with SCH and Mets showed that gender, BMI \geq 30 kg/m^2 , HTN, TG (\geq 1.7mmol/l) and low HDL-C were associated with higher likelihood of SCH, (OR=1.62; 95% confidence interval [CI]=1.01-2.59), $p=0.04$), (OR=2.26; 95% CI=1.48-3.45), $p<0.0001$), (OR=2.27; 95% CI=1.46-3.52), $p<0.0001$), (OR=2.67; 95% CI=1.81-3.94), $p<0.0001$) and (OR=3.49; 95% CI=2.30-5.31), $p<0.0001$) respectively, (Table 3).

Table 2: Comparison between metabolic syndrome components and age groups for patients with subclinical hypothyroidism [Number (%)].

Parameters	Age (Years)				P value
	<40	40-49	50-59	≥60	
Numbers	99 (12.4)	189 (23.7)	255 (32.0)	255 (32.0)	
HbA1c>5.6 or Type 2 diabetes	16 (8.2)	40 (20.5)	59 (30.3)	80 (41.0)	0.003
Hypertension	6 (4.4)	20 (14.6)	45 (32.8)	66 (48.2)	<0.0001
Triglyceride (≥1.7 mmol/l)	12 (9.4)	26 (20.5)	42 (33.1)	47 (37.0)	0.6
High density lipoprotein (<1.29 mmol/l)	18 (13.7)	29 (22.1)	40 (30.5)	44 (33.6)	0.003

Table 3: Regression analysis for odd ratio of risk factors for patients with subclinical hypothyroidism in patients with metabolic syndrome

Parameters	Odd Ratio	P value
Age (years)	1.00 (0.99-1.02)	0.4
Gender	1.62 (1.01-2.59)	0.04
Body mass index (kg/m ²) ≥30	2.26 (1.48-3.45)	<0.0001
HbA1c>5.6 or Type 2 diabetes	1.37 (0.82-2.30)	0.2
Hypertension	2.27 (1.46-3.52)	<0.0001
Triglyceride (≥1.7 mmol/l)	2.67 (1.81-3.94)	<0.0001
High density lipoprotein (<1.29 mmol/l)	3.49 (2.30-5.31)	<0.0001

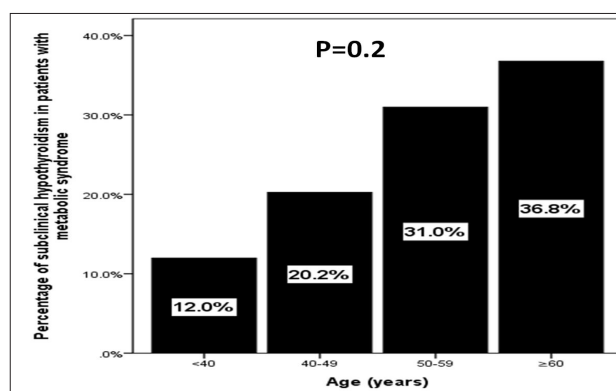


Figure 1: The prevalence of hypothyroidism in patients with metabolic syndrome in correlation to age groups..

Discussion

High prevalence of Mets is a global phenomenon. Hypothyroidism and Mets are recognized risk factors for atherosclerotic cardiovascular disease. The aim of the present study was to analyze the association between SCH and Mets components in adult population from Jeddah City, Saudi Arabia. In the present population-based study of 798 patients with Mets, we found a significant association between SCH and components of Mets. The above results agree with previous studies showing an association between Mets and SCH [2,3,10-16]. Garcia et al. [11] reported that there was no association between Mets or its components and subclinical Thyroid Dysfunction. A study in Taiwan explored the serum TSH levels and Mets components and concluded that even slight increases in TSH, as in SCH, may be a Mets risk factor.

Lai [14] Another study concluded that Higher TSH levels in SCH with a TSH>10MIU/l are associated with increased odds

of prevalent Mets [15]. Moreover, even high normal TSH levels and low normal free T4 levels were significantly associated with increased prevalence of Mets, which may be of importance when evaluating such subjects [2,16]. Mets is increased in patients with hypothyroidism and suggested that hypothyroidism be considered in newly diagnosed Mets patients [12]. In accordance with the above-mentioned studies, we have found increased risk of Mets in SCH.

We found that patients with SCH were non-significantly older than without SCH, 55.0±12.6 vs. 53.3±12.4, p=0.07. SCH with HbA1c>5.6 or T2DM, HTN and low HDL were increased significantly with advanced ages (p=0.003, p<0.0001 and p=0.003 respectively) and non-significantly increased with advanced ages in patients with SCH and TG (≥1.7mmol/l) (P=0.6), (Table 2). Among the study population, the prevalence of SCH is significantly more in female (74.4% vs. 25.6%, p=0.009) and earlier

studies shows that the thyroid dysfunction was common in females with mets [17,18]. Previous studies reported a high prevalence of subclinical hypothyroidism among female with Metabolic Syndrome [17].

In our study, like the Virta study the prevalence of obesity with subclinical hypothyroid was higher than in euthyroid cases [19]. 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, a mechanism which may explain the correlation between TSH levels and obesity [20]. The current analyses suggest that HTN was the metabolic factor that significantly associated with the occurrence of SCH. This relationship may reflect the observation that HTN is the most common manifestation within the myriad of at-risk phenotypes associated with atherosclerotic cardiovascular disease. Furthermore, among all the possible pathological pathways leading to HTN, several share a link with hypothyroidism including changes in circulating catecholamines, disturbances in the Renin-Angiotensin-Aldosterone system, and increased peripheral vascular resistance [21-23].

In this study, the HbA1c>5.6 or T2DM, TG (≥ 1.7 mmol/l) were significantly higher and low HDL-C levels were significantly lower in the SCH patients with Mets than in the patients without SCH. These findings were similar to those obtained in the studies on Hispanic population by Garcia et al. [11] and on Chennai urban population by Shantha et al. [11,24] 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 reductions in HDL-C [25-27]. However, the results of population studies about the correlation between Thyroid function and Lipid profiles are controversial. Association of SCH with components of Mets was assessed by multiple logistic regression analysis in the present study. Gender, BMI ≥ 30 kg/m², HTN, TG and HDL-C showed significant association with SCH in persons with Mets whereas there was no statistically significant association with age and HbA1c>5.6 or T2DM, (Table 3).

In a retrospective study, Razvi et al. [28] found treatment of SCH with levothyroxine was associated with fewer ischemic heart disease events in the younger individuals, supporting a beneficial effect of thyroid hormone on cardiovascular risk factors in hypothyroid patients [28]. Whether Thyroid Dysfunction has a major direct effect, or is just an intermediate mediator, or simply a "Bystander" in these many pathways leading to coronary atherosclerosis needs to be continuously monitored. Thus, exploring the reverse relationship between Mets and thyroid dysfunction as well as the temporal sequence of association of Mets, thyroid dysfunction, and cardiovascular diseases may be a worthwhile topic for future research. Furthermore, the efficacy of hypothyroidism medicine to prevent the development of Mets should also be investigated in future studies we aimed to identify the prevalence of SCH in patients with Mets in primary health care setting.

Furthermore, due to the retrospective nature of this study, the observed population reflects a selected yet comprehensive group of patients rather than the general population. Our study

could be limited by the question of clustering of cases within the study region and the effect that might have on our estimates, in addition, the current study population may appear limited in size and therefore may underestimate the true frequency of SCH in the general population. In addition, the study shares the limitations of all retrospective studies. In conclusion, our study suggests that SCH might be a risk factor for Mets and its components. Further investigations are needed to evaluate the mechanism of this correlation.

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