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Association of Subclinical Hypothyroidism with Metabolic Syndrome in Young Adult Egyptians

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) and metabolic syndrome (MetS) are two common medical conditions. Thyroid dysfunction, prominently SCH has been described more frequently in MetS patients than general population. SCH affect MetS parameters including high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), plasma glucose and blood pressure. The relation between the two conditions looks like a bi-directional relationship.

Objectives: The aim of this study was to investigate the association between SCH and MetS in Egyptian young adults and to study the prevalence of MetS and its components in SCH subjects.

Patients and methods: The study was conducted at Zagazig University Hospitals. 602 freshman-year students with no history of medical disease were included in the study. General examination, anthropometric, and routine investigations plus thyroid function tests were done for all.

Results: Diastolic hypertension (DBP) and impaired fasting glycaemia (IFG) showed significant differences between SCH and EUT. Among the 602 participants, 23.9 % were diagnosed with MetS and 8.9 % with SCH. MetS was found in 22.4 % in the euthyroidism (EUT) group and in 39 % in the SCH group. SCH was found in 14.6 % in subjects with MetS and in 7.2% in non- MetS subjects. There was a significant association between MetS and SCH ($\chi 2=7.3$, $p<0.05$). Weight, BMI, and DBP were the significant predictors for SCH in patients with MetS.

Conclusions: It could be concluded that there is a significant association between MetS and SCH. DBP and IFG show significant difference between SCH and EUT**.**

Keywords: Subclinical hypothyroidism, Metabolic syndrome.

INTRODUCTION

One of the most common medical issues, particularly in women, is thyroid dysfunction. Subclinical hypothyroidism (SCH), which is the initial biochemical aberration in hypothyroidism, is characterized by a rise in blood thyroid stimulating hormone (TSH) concentration in conjunction with normal serum free thyroxine (FT4) concentration **(1)**.

The prevalence of SCH varies by gender and age, with women over 60 years of age experiencing rates as high as 20% in certain studies. Worldwide the prevalence ranges from 1 to 10% **(2)**.

The term "Metabolic Syndrome" (MetS) refers to a "constellation" of cardiometabolic risk factors that together raise the risk of developing type 2 diabetes mellitus (DM) and cardiovascular disease **(3)**. Although it has been linked to coronary and carotid artery disease, the link between SCH and MetS and each of its components is still up for debate **(4)**.

In relation to this topic, numerous researches have shown a correlation between rising TSH levels and increasing body mass index (BMI) and percentage of body fat **(5)**.

Although visceral obesity and insulin resistance are thought to be key factors in the etiology of MetS, an imbalance of other hormones, such as thyroid and glucocorticoids, may hasten metabolic problems and raise the risk of MetS **(6)**.

On the other hand, thyroid dysfunction, prominently SCH is found more frequently in MetS patients than general population **(7).**

MetS appears to be a risk factor for subclinical hypothyroidism **(4).**

The relation between the two conditions looks like a bi-directional relationship.

The aim of this study was to investigate the association between SCH and MetS in young adult Egyptians and to study the prevalence of MetS and its components in SCH subjects.

PATIENTS AND METHODS

This cross-sectional study included a total of 602 freshman-year students with no history of medical disease, examined at Zagazig University Hospitals.

All participants were new faculty students doing medical examination as a part of undergraduate admission requirements. Data were collected from them, and they were subjected to history taking and physical examination.

Physical examination included waist circumference, WC (defined as the midpoint from the lower costal margin to the iliac crest, standing and at the end of normal expiration), and BMI (kg/m^2) was done to all participants. Body weight was taken while wearing the less amount of clothes.

Personal and family medical history was gathered, with stress on endocrine, metabolic, and cardiovascular diseases history. Blood samples were taken for routine checkup after 8 hours fasting plus TSH and FT4. The MetS was defined according to the International Diabetes Federation (IDF) by presence of WC > 94 cm (men) or > 80 cm (women) in addition to the presence of two at least from the following: 1. Fasting blood

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glucose (FBG) higher than 5.6 mmol/L (100 mg/dl) or having treatment for DM -2. High-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or taking medications for low HDL-C -3. Blood triglycerides (TG) > 1.7 mmol/L (150 mg/dl) or taking medications for hypertriglyceridemia (HTG) -4. Blood pressure > 130/85 mmHg or taking medications for hypertension [8].

Although MetS can be diagnosed if patients are taking medications for dyslipidemia, DM, or hypertension, we excluded any participant on medications to better investigate the MetS components and their associations with other factors while eliminating the effect of medications. SCH was defined as TSH more than 4.5 mIU/l with normal FT4 [9]. Patients were considered euthyroid (EUT) if thyroid hormones levels are normal.

Patients with history of any medical disease or on medications for hypertension, dyslipidemia, thyroid, or DM were excluded. Also, those on any medications affecting thyroid function (e.g. amiodarone and iodide) were excluded.

Ethical approval:

This study was ethically approved by Zagazig University's Research Ethics Committee. Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Statistical analysis was made by using SPSS software package. All quantitative data were expressed as median ± standard deviation.

While comparing between two groups, student t test was applied. Chi square test was used for the comparison of qualitative data. p level < 0.05 was considered significant. Multivariate logistic regression analysis was used to predict the relationships between dependent and independent variables and 95% confidence interval was calculated.

RESULTS

A total of 602 people was enrolled in this study (281 males and 321 females). 54 SCH subjects and 144 with MetS were found. The clinical characteristics of all are summarized in **Table 1**.

Between SCH and EUT subjects only TSH, FT4, FBG, and diastolic blood pressure (DBP) showed significant differences.

Table (1): Demographic, anthropometric, clinical, and biochemical characteristics of study subjects (EUT and SCH).The quantitative variables are expressed as means ± standard deviation, and the qualitative variables are expressed as percentages (%)

	EUT (548)	**SCH (54)**	**P**
Age (years)	18.4 ± 0.3	18.3 ± 0.4	0.17
Gender -Female - Male	 287(52.4 %) 261(47.6 %)	 34(63.0 %) 20 ((37.0 %)	0.137
Waist circumference (cm)	86.7 ± 9.6	87.6 ± 8.2	0.508
BMI (kg/m^2)	24.4 ± 3.6	25.1 ± 2.4	0.165
Weight (kg)	74.2 ± 6.7	76.2 ± 9.5	0.135
SBP (mmHg)	126.5 ± 8.2	128.6 ± 7.4	0.068
DBP (mmHg)	76.6 ± 5.0	80.3 ± 4.5	**0.000**
T. cholesterol (mg/dl)	183.9 ± 41.1	192.2 ± 27.6	0.27
LDL-C (mg/dl)	107.8 ± 27.6	111.7 ± 28.1	0.68
TG (mg/dL)	136.1 ± 23.9	137.0 ± 24.9	0.765
HDL-C (mg/dL)	52.8 ± 9.5	52.7 ± 9.7	0.912
FBG (mg/dL)	94.2 ± 9.3	97.9 ± 8.3	**0.005**
TSH (mIU/l)	2.6 ± 0.7	7.4 ± 1.7	0.000
FT4 (pmol/L)	16.5 ± 2.4	14.3 ± 1.1	0.000

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. TG: triglycerides. LDL-C: low-density lipoprotein cholesterol. HDL-C: high-density lipoprotein cholesterol. FBG: fasting blood glucose. TSH: thyroid stimulating hormone. FT4: free thyroxine.

According to the IDF criteria, MetS has one fixed component (high WC) and four variable components. We tested the proportions of the five components of MetS in SCH and EUT either they have or do not have MetS (**table 2)**. The highest percentage in both groups was the high WC.

Table (2): Comparing the percentage of MetS and its components between EUT and SCH subjects

	EUT (548)	**SCH (54)**	**p**
MetS	123 (22.4)	21 (39 %)	**< 0.05**
HWC	288 (52.6%)	30 (55.6 %)	0.673
HTG	125 (22.8%)	14 (25.9%)	0.604
Low HDL-C	147 (26.8 %)	17 (31.5 %)	0.463
Hypertension	108 (19.7 %)	18 (33.3 %)	**0.019**
IFG	139 (25.4 %)	24 (44.4 %)	**0.003**

HWC: high waist circumference. HTG: hypertriglyceridemia, HDL-C: High-density lipoprotein cholesterol. IFG: impaired fasting glucose.

To study correlation between FT4 and TSH level with different patient parameters a Perason correlation test was done **(Table 3)**. TSH level showed +ve correlation with FBG and DBP. FT4 showed a +ve correlation with HDL-C and a –ve correlation with all other parameters.

Table (3): Correlation between FT4 and TSH level with other parameters in all subjects

	TSH		FT4	
	r	P	r	p
BMI (kg/m^2)	0.013	0.751	-0.353	**< 0.05**
Weight (kg)	-0.044	0.276	-0.344	**< 0.05**
Waist (cm)	0.055	0.179	-0.240	**< 0.05**
TG (mg/dL)	0.014	0.735	-0.184	**< 0.05**
HDL-C (mg/dL)	-0.023	0.567	0.0183	**< 0.05**
SBP (mmHg)	0.078	0.055	-0.250	**< 0.05**
DBP (mmHg)	0.147	**< 0.05**	-0.174	**< 0.05**
FBG (mg/dL)	0.106	**0.009**	-0.304	**< 0.05**

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. TG : triglycerides. HDL-C: high-density lipoprotein cholesterol. FBG: fasting blood glucose.

Multivariate logistic regression analysis of predictors for SCH in patients with MetS was done **(Table 4).** Weight, BMI, and DBP were the significant predictors for SCH in patients with MetS.

Table (4): Multivariate logistic regression analysis of predictors for subclinical hypothyroidism in patients with metabolic syndrome

Parameters	OR (95% C.I.)	P value
Age (years)	0.523 (0.109-2.523)	0.420
Gender	1.850 (0.248- 13.829)	0.549
BMI (kg/m^2)	0.588 (0.410- 0.843)	**0.004***
Weight (kg)	0.914 (0.838- 0.998)	**0.044***
Waist (cm)	1.033 (0.923 - 1.156)	0.575
SBP (mmHg)	0.918 (0.829 - 1.017)	0.102
DBP (mmHg)	1.211(1.066 - 1.376)	**0.003***
TG (mg/dL)	0.985 (0.961- 1.009)	0.223
DL-C (mg/dL)	1.082 (0.985- 1.188)	0.100
FBG (mg/dL)	0.992 (0.920 - 0.920)	0.832

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. TG : triglycerides. HDL-C: high-density lipoprotein cholesterol. FBG: fasting blood glucose.

The prevalence of MetS and SCH in all subjects is shown in **(figure 1).** The results of the Chi square of association (2x2) showed that there is a significant association between MetS and SCH ($\chi 2$=7.3, p<0.05).

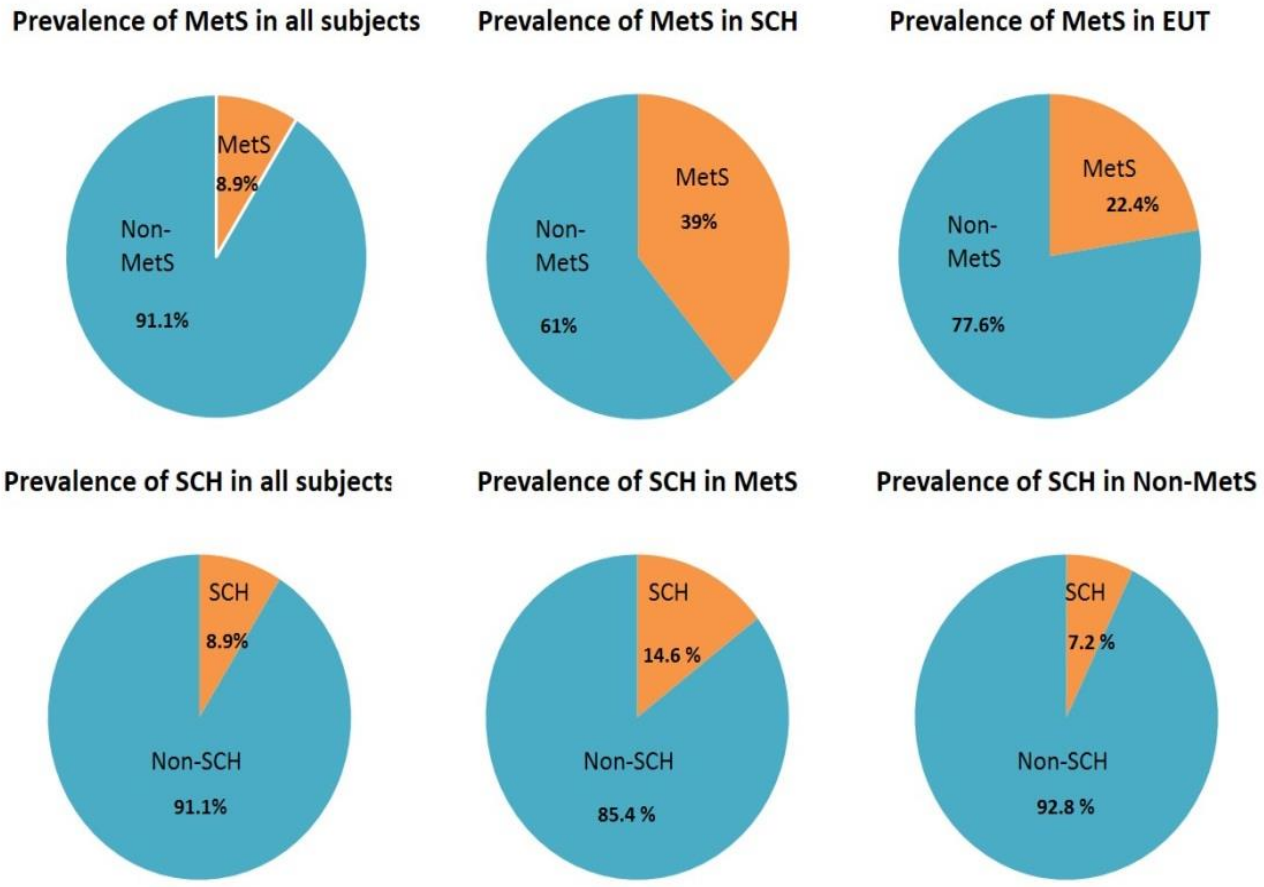

Figure (1): Prevalence of SCH and MetS in study populations.

DISCUSSION

SCH is a common thyroid disorder with different prevalence rates in different populations. Our results showed that the overall rate was 8.9 %, in the female (10.6%) and in the males (7.1%). In the United States it was found to be (4.3%), much less than in Denmark (19.7 %) [10]**.** Different results are due to age group differences, geographical area, iodine intake, plus ethnicity factors. As regard MetS, the overall prevalence was 23.9 %, in the females (26.5%) and in the males (21%). The prevalence from different populations differs greatly. In adult Brazilians it was (33.0%) **[11]**, in United States adults it was (31.9%) in Mexican Americans and (23.8%) among whites, (21.6%) in African Americans and in people reporting an "other" race or ethnicity it was (20.3%) **[12]**. Different lifestyles, ethnicity, and even the definition used to diagnose MetS all contribute to different rates.

SCH and EUT subjects showed significant differences regarding DBP, FBG, TSH, and FT4.

Due to increased systemic vascular resistance, hypothyroidism is recognized to cause diastolic hypertension; however, the impact of SCH on blood pressure has not received enough research. A meta-analysis conducted in 2011 found that DBP was higher in SCH compared to controls **[13]**. In our study the percentage of subjects with hypertension was higher in SCH vs EUT (33.3 % vs 19.7 %). In another cross-sectional study**,** there was no association between SCH and hypertension **[14]**. Our finding of a significant difference in FBG between the two groups is supported by **Bermúdez *et al.* [15]** who stated that hyperglycemia was the only metabolic parameter with a positive correlation with SCH. Carbohydrate metabolism is affected by thyroid hormones as evidenced by affecting the translocation of glucose transporters and hence the ability of cells to use glucose. Also, regulating fatty acids metabolism, glycogen synthesis, and protein kinases expression in skeletal muscles **[16].**

There was no significant differences in TG and HDL-C between SCH and EUT subjects. Also, the percentage of subjects with either high TG or low HDL-C showed no significant difference between the two groups. Although the level of TG was higher in the SCH subjects with lower level of HDL-C, the difference was non-significant statistically. There was no correlation between TSH level and HDL-C or TG.

The hepatic expression of hydroxymethylglutaryl coenzyme A reductase is induced by thyroid hormones, which increases cholesterol synthesis. The absorption of cholesterol by intestine increases in hypothyroidism due to thyroid hormone actions on Niemann-Pick C1-like 1 protein in the gut **[17]**. The results of observational studies of serum lipid levels in patients with SCH have been inconsistent. In a study of 7000 outpatients, the levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) were elevated in overt hypothyroidism patients but not in SCH **[18].** In a study conducted on 25,862 subjects in Colorado, total cholesterol, TG, and LDL-C levels were significantly higher in individuals with hypothyroidism, with higher levels in SCH subjects than in EUT subjects**[2]**.

There was no significant difference in the obesity parameters (BMI, WC, and weight) between SCH and EUT.

Khan *et al.* [19] found that SCH was found more in obese subjects though there was no significant difference. In our study, both the TSH level and the presence of SCH did not show correlation with BMI, WC, or weight. Other studies found a positive correlation of SCH with WC (p= 0.004) **[20]**.

Thyroid hormones level can be affected by obesity as well, in addition to the role of thyroid hormones in regulating body weight but several reports failed to find a link between obesity and SCH, and their results were conflicting **[21]**.

The prevalence of MetS in all subjects was 144/602 (23.9 %), in SCH was 21/54 (39 %), and in the EUT was 123/548 (22.4 %). **Bermúdez *et al.* [15]** found that 56.1 % of SCH subjects has MetS while a less percentage was found in those with EUT (38.3 %). The percentages were (25.7%) and (21.3 %) respectively in another study **[20].** The prevalence of SCH in all subjects was 54/602 (8.9 %), in MetS was 21/144 (14.6 %) and in non-MetS was 33/458 (7.2 %). **Khan *et al.* [19]** studied the prevalence of SCH in a group of 173 subjects with MetS, of them, (16.0%) had SCH. In another study, the prevalence was (16.4%) in patients with MetS and (5.8 %) in non-MetS subjects**[22]**.

Thyroid dysfunction may be one intermediate link between MetS and cardiovascular disease. These cross-sectional interrelations are obviously multifactorial including increased inflammation, pro thrombosis, defective fibrinolysis, endothelial dysfunction **[23]**, insulin sensitivity and endothelium-dependent vasodilatation **[24, 25].**

We studied the percentage of positive metabolic syndrome components in both SCH and EUT subjects. All components showed a higher percentage in the SCH group with a significant difference in hypertension and impaired FBG. Thyroid dysfunction can affect all components of MetS, not only in overt disease, but also in the setting of SCH. FT4 showed significant correlations with all obesity and metabolic parameters while TSH level showed +ve correlation with FBG and DBP only. In a similar comparison conducted by **Saroj *et al.* [26]**, they found a significant negative correlation between TSH and HDL while FT4 did not show any significant correlation. Thyroid functions affect MetS parameters including HDL-C, TG, blood pressure and plasma glucose and even in the studies who failed to find a clear association between SCH and MetS risk**,** there was a correlation between loss of thyroid function and some MetS parameters (i.e. higher cholesterol and impaired FBG) **[27].** Insulin resistance is a major player in the development of MetS. It has been proposed that the elevated TSH in obesity is a phenomenon similar to insulin resistance, in which leptin is the responsible for

increased resistance in TSH receptors leading to rising levels of TSH [28]. The higher incidence of SCH in MetS and vice versa as observed in our study makes an important question: are patients with either SCH or MetS must be investigated for the presence of the other condition? And whether early thyroxine therapy in SCH can delay the progression of MetS?

The cross-sectional design of our study makes stabling causality in analyzed data difficult. Prospective studies, with bigger sample size, are needed to confirm our findings and better understanding the link between the two conditions.

CONCLUSIONS

It could be concluded that there is a significant association between MetS and SCH. DBP and IFG show significant difference between SCH and EUT. BMI, and DBP are the significant predictors for SCH in patients with MetS. TSH level is positively correlated with FBG and DBP. The relation between SCH and MetS may be bidirectional with presence of one condition may justify the investigations for the other one. More research is needed to evaluate role of thyroxine therapy in delaying development of MetS in patients with SCH.

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