

Correlation between Subclinical Hypothyroidism and Metabolic Syndrome: A Retrospective Study

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Abstract

Background: Several studies worldwide have studied the correlation between subclinical hypothyroidism (SCH), and metabolic syndrome (MetS), but have reported inconsistent findings.

Objectives: To assess the correlation between SCH and MetS in a population from Saudi Arabia.

Methods: This retrospective study was conducted at King Abdulaziz University Hospital and analyzed all thyroid function tests conducted between January 1, 2019, to December 31, 2021. A predesigned checklist was used to collect data about patients' characteristics such as age, gender, nationality, TSH, FT4 level, and MetS components.

Results: A total of 41,519 thyroid function tests were conducted during the study period. From this, 1303 (3.1%) patients were found to have SCH, with the majority being females (74.4%). The prevalence did not differ according to gender but increased to 3.5% among those aged >60 years. MetS components between mildly and markedly elevated TSH were significant for total cholesterol ($P < 0.001$) and high-density lipoprotein cholesterol ($P < 0.05$). Male patients with SCH were at a higher risk of developing diabetes ($P < 0.001$) and hypertension ($P < 0.02$), than female patients with SCH. After adjusting for age, in the multiple stepwise linear regression analysis, a significant association was found between TSH levels and ALT (odds ratio: 0.77) and SBP (odds ratio: 0.35).

Conclusion: The study demonstrated that the prevalence of SCH is similar between both genders but increases with age. MetS components were abnormal in patients aged >50 years and in males with SCH. SCH and MetS components were found to be correlated, and thus monitoring these variables in patients with SCH is advisable.

Keywords: Body mass index, cardiovascular risk factors, diabetes, dyslipidemia, hypertension, metabolic syndrome, obesity, subclinical hypothyroidism

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INTRODUCTION

Subclinical hypothyroidism (SCH) is characterized by an increase in blood thyroid-stimulating hormone (TSH) levels above the normal range despite normal serum total thyroxin T4 or free T4 levels.^[1] The upper limit for TSH is debatable, but the most common cutoff is 4 mIU/L; 90% of those with SCH having mild TSH levels (4.0–10.0 mIU/L).^[2] A significant increase in TSH (i.e., >10.0 mIU/L) has been found to be a reasonable threshold for initiating treatment in patients with SCH,^[3] while a cut-off of 7 mIU/L is associated with a greater risk of overt hypothyroidism.^[4]

SCH is a common condition, with a prevalence range of 7.5–8.5% in females and 4.4% in males.^[5,6] In Saudi Arabia, the prevalence of SCH is 9.8% and 10.7% in males and females, respectively.^[7] However, the prevalence of SCH varies according to the population, age, gender, race, demographic area, and TSH measurements.^[8] SCH is significantly higher in women, older adults, and iodine-sufficient populations.^[9,10] The prevalence of SCH in women has also been linked to increased age and obesity, affecting up to 35% of women aged >50 years.^[11] A study from Saudi Arabia showed that body mass index (BMI) was not associated with thyroid dysfunction among type 2 diabetic patients,^[12] which contradicts the findings of another study that found a positive association between obesity and increased TSH levels.^[13]

Numerous studies have studied the link between SCH, metabolic syndrome (MetS), and cardiovascular risk factors. Although the contributing role of SCH to cardiovascular disease (CVD) is yet unclear, several studies have found that the presence of SCH increases the risk of CVD.^[14,15] Similarly, MetS has been found to increase the risk of CVD by twofold and type 2 diabetes mellitus by fivefold.^[16] A rise in TSH levels has also been linked to an increase in the prevalence of MetS.^[17,18]

Central adiposity, hypertension, low high-density lipoprotein cholesterol (HDL-C), and high triglycerides levels have been found to be strongly associated with SCH.^[19] In addition, a positive relationship has been found between total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and TSH levels.^[20] On the other hand, hypertension and HDL-C have been found to be the only components associated with SCH.^[21] A high normal TSH level is linked with a higher occurrence of MetS.^[22] Individuals with SCH have a higher prevalence of hypertension than those with euthyroid, and this association is stronger in females.^[23] Even within the

reference range, TSH levels were found to have positive linear associations with systolic and diastolic blood pressure in a population-based study.^[24]

Patients with T2DM are at higher risk of developing SCH than the general population. Females with T2DM have 1.7 times higher risk of developing SCH than males.^[25] In Saudi Arabia, data from a recent study showed that 46% of patients with SCH had diabetes mellitus.^[26] In addition, MetS components such as obesity, diabetes, hypertension, and dyslipidemia are common in the Middle East, especially in Saudi Arabia. Most SCH patients do not receive treatment because they are undiagnosed or because their primary physician did not take any additional steps to reduce the risk. Exploring the link between SCH and MetS will guide future approaches to the treatment of SCH. Accordingly, the purpose of this study was to explore the correlation between SCH and MetS in a population from Saudi Arabia.

METHODS

Study design, setting and participants

This retrospective chart review was conducted at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, between January to March 2022. KAUH is one of the largest tertiary care public hospitals in the region. The study was conducted after obtaining approval from the Bioethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia.

All thyroid function tests that were conducted from January 1, 2019, to December 31, 2021, were reviewed and those that met the criteria of SCH were included in the analysis.^[1] Accordingly, adults aged ≥ 18 years with elevated TSH levels and normal levels of free thyroxin (FT4) were included in the study. The study excluded patients with hypothyroid, who underwent thyroidectomy, those on levothyroxine treatment, and pregnant women. A predesigned checklist was used to collect data about patients' characteristics such as age, gender, nationality, TSH level, FT4 level, and MetS components.

Measurements and laboratory tests

BMI was classified as follows: underweight, <18.5 kg/m²; normal, 18.5–24.99 kg/m²; overweight, 25–29.99 kg/m²; and obese, ≥ 30 kg/m².^[27] Diagnosis of diabetes was based on the Diagnosis and Classification of Diabetes Mellitus by the American Diabetes Association: symptoms of diabetes plus a random plasma glucose concentration (RBG) of ≥ 200 mg/dL (11.1 mmol/L) or fasting blood glucose (FBG) of ≥ 126 mg/dL (7.0 mmol/L) or HbA1c of $\geq 6.5\%$.^[28] The presence of dyslipidemia was confirmed

if TC >6.18 mmol/L.^[29] A TSH level between 4 and 6.9 mIU/L was considered as mild elevation and between 7 and 10 mIU/L as marked elevation. The patient was considered positive for each component of MetS if either the diagnosis was confirmed on the chart or the patient had been prescribed medications for these components. For these tests, the normal reference ranges are shown in Table 1.

Data analysis

The data were analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequency and proportion, while continuous variables were presented as mean and standard deviation. Independent sample *t*-test was used to compare the means of the groups and Chi-square test was performed for nominal variables. Patients with mildly and markedly elevated TSH were compared. After adjusting for age, linear regression analysis was used to study the relationship between TSH levels and other variables. The odds ratio was calculated by unit for alanine transaminase (ALT) and systolic blood pressure (SBP) (1 IU/L and 1 mmHg, respectively). *P* ≤ 0.05 was considered statistically significant.

RESULTS

A total of 41,519 thyroid function tests were performed in adults over the study period. The mean age (SD) of the patients was 45.5 (±17.8) years. The prevalence of SCH among the study population was 3.1% (*N* = 1303), with the majority being female (74.4%); however, there was no difference in prevalence between males and females (3% vs. 3.2%, respectively). The prevalence increased to 3.5% among patients aged ≥60 years. A total of 30.6% had diabetes mellitus and 29.2% had hypertension. In addition, a considerable proportion of the study subjects had dyslipidemia and coronary artery disease (CAD) (23.3% and 11.7%, respectively). The demographic, clinical and laboratory characteristics of the study population are given in Table 2.

Thyroid function and MetS components

The normal concentration of TSH ranged from 0.5–4 mIU/L and FT4 from 12 to 25 pmol/L. The comparison of biochemical characteristics and disease states in mildly elevated TSH and markedly elevated TSH are shown in Table 3. Among patients aged >50 years, markedly elevated TSH was found in about half of the patients and 42% showed mildly elevated TSH. The MetS components were significant for TC, FBG, HDL-C, and aspartate transaminase (AST) levels. Patients with markedly elevated TSH had higher FBG levels than those with mildly

Table 1: Normal reference range of the studied variables

Laboratory test	Normal reference range
Hemoglobin (male:female) (g/dL)	14.0–17.5:12.3–15.3
HbA1c (%)	4.8–5.5
ALT (U/L)	0–41
AST (U/L)	0–40
TC (mmol/L)	<5.17
HDL-C (mmol/L)	0.9–1.68
LDL-C (mmol/L)	2.59–3.34
TG (mg/dL)	0.5–2.26

HbA1c – Glycated hemoglobin; ALT – Alanine transaminase; AST – Aspartate transaminase; TC – Total cholesterol; HDL-C – High-density lipoprotein cholesterol; LDL-C – Low-density lipoprotein cholesterol; TG – Triglyceride

Table 2: General characteristics of the study participants (N=1303)

Variables	n (%)
Gender	
Male	334 (25.6)
Female	969 (74.4)
Nationality	
Saudi	921 (70.7)
Non-Saudi	382 (29.3)
DM (<i>n</i> =967)	399 (30.6)
HTN (<i>n</i> =995)	380 (29.2)
Dyslipidemia (<i>n</i> =876)	303 (23.3)
CAD (<i>n</i> =1298)	140 (11.7)
Obesity (<i>n</i> =901)	346 (38.4)

Variables	Mean±SD
Age (years)	45.49±17.8
SBP (mmHg)	138.30±19.0
DBP (mmHg)	76.75±10.4
MAP (mmHg)	97.15±14.6
BMI (<i>n</i> =901)	29.07±7.4
TSH (mIU/L)	5.37±1.3
FT4 (pmol/L)	13.46±1.8
FT3 (pmol/L)	4.29±0.8
LDL-C (mmol/L)	3.29±1.4
TC (mmol/L)	4.51±1.3
TG (mmol/L)	1.51±0.6
HDL-C (mmol/L)	1.11±0.3
RBG (mmol/L)	7.60±4.1
FBG (mmol/L)	7.84±4.1
HbA1c (%)	7.13±2.4
AST (IU/L)	23.35±12.5
ALT (IU/L)	27.75±18.6
Bilirubin (µmol/L)	8.53±3.9
Hemoglobin (g/dL)	12.91±1.7

SD – Standard deviation; DM – Diabetes mellitus; HTN – Hypertension; CAD – Coronary artery disease; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MAP – Mean arterial pressure; BMI – Body mass index; TSH – Thyroid-stimulating hormone; FT4 – Free thyroxine; FT3 – Free triiodothyronine; LDL-C – Low-density lipoprotein cholesterol; TC – Total cholesterol; TG – Triglyceride; HDL-C – High-density lipoprotein cholesterol; RBG – Random blood glucose; FBG – Fasting blood glucose; HbA1c – Glycated hemoglobin; AST – Aspartate transaminase; ALT – Alanine transaminase

elevated TSH. After adjusting for age, multiple stepwise linear regression analysis between TSH levels and other metabolic risk factors showed significance for ALT and SBP with odds ratios of 0.77 and 0.35, respectively. The association between TSH levels and other variables are represented in Table 4.

Table 3: Comparison of biochemical characteristics and disease states between mildly elevated and markedly elevated thyroid-stimulating hormone groups

Variables	Mildly elevated TSH	Markedly elevated TSH	P
	TSH (4–6.9 mIU/L)	TSH (7–10 mIU/L)	
Gender, n (%)			
Male	289 (25.3)	45 (28)	0.44
Female	852 (74.7)	116 (72)	
Age above 50 years, n (%)	464 (42)	79 (50)	0.05*
Obesity, n (%)	297 (26)	45 (28)	0.18
DM, n (%)	350 (42)	45 (39)	0.57
HTN, n (%)	327 (38)	49 (38)	0.89
Dyslipidemia, n (%)	268 (35)	34 (34)	0.87
CAD, n (%)	117 (10)	22 (14)	0.19
BMI (kg/m ²), mean±SD	29.39±0.36	29.5±0.71	0.41
FT4 (pmol/L), mean±SD	14.28±1.69	13.98±1.53	0.15
FT3 (pmol/L), mean±SD	4.56±1.16	4.42±1.13	0.93
SBP (mmHg), mean±SD	131.3±19.88	131.4±19.15	0.67
DBP (mmHg), mean±SD	75.6±12.54	76.7±13.78	0.24
LDL-C (mmol/L), mean±SD	3.05±1.09	3.28±1.27	0.84
TC (mmol/L), mean±SD	4.44±1.19	4.65±1.48	<0.001*
HDL-C (mmol/L), mean±SD	1.27±0.36	1.31±0.42	0.05*
TG (mmol/L), mean±SD	1.49±1.92	1.48±0.82	0.64
FBG (mmol/L), mean±SD	6.6±2.66	6.8±3.31	0.08
HbA1c (%), mean±SD	6.53±1.73	6.50±1.76	0.03*
AST (IU/L), mean±SD	26.98±43.829	43.19±126.008	0.00
ALT (IU/L), mean±SD	29.81±89.384	39.30±94.786	0.198
Hemoglobin (g/dL), mean±SD	12.33±2.047	12.19±3.145	0.004

*Indicates significance at $P < 0.05$. n (%). Student's *t*-test, Chi-square test were done for continuous and categorical variables respectively.

SD – Standard deviation; DM – Diabetes mellitus; HTN – Hypertension; CAD – Coronary artery disease; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; BMI – Body mass index; TSH – Thyroid-stimulating hormone; FT4 – Free thyroxine; FT3 – Free triiodothyronine; LDL-C – Low-density lipoprotein cholesterol; TC – Total cholesterol; TG – Triglyceride; HDL-C – High-density lipoprotein cholesterol; FBG – Fasting blood glucose; HbA1c – Glycated hemoglobin; AST – Aspartate transaminase; ALT – Alanine transaminase

Table 4: Association between thyroid-stimulating hormone level and metabolic risk factors

Variables	B coefficient	SE	OR	P	95% CI
ALT (IU/L)	0.031	0.006	0.768	0.00	0.019–0.045
SBP (mmHg)	0.013	0.006	0.349	0.03	0.001–0.026

SE – Standard error; CI – Confidence interval; OR – Odds ratio; ALT – Alanine transaminase; SBP – Systolic blood pressure

Gender and age-based subgroup analysis of metabolic syndrome components

The comparison of metabolic syndrome components based on the two age groups (≤ 50 vs. > 50 years) are shown in Table 5. Patients aged > 50 years were significantly affected by diabetes, hypertension, dyslipidemia, obesity, and CAD compared with the younger age group.

In terms of gender, male patients with SCH had a significantly higher prevalence of diabetes, hypertension, and CAD than female patients. However, obesity and the mean BMI were comparable between females and males. In addition, SBP, DBP, and MAP did not differ significantly between the two groups. However, both LDL and HDL levels were higher in females. The gender-wise comparison of the biochemical characteristics and diseased states is given in Table 6.

DISCUSSION

This study found that the prevalence of SCH is 3.1% among a population within Saudi Arabia. This was lower than that reported by Al-Geffari *et al.*, who only included diabetic patients and those with a higher mean age.^[12] Therefore, difference is expected, as both age and diabetes are associated with an increased risk of SCH; the latter possibly because insulin influences thyrotropin-releasing hormone and TSH.^[25] The prevalence was also lower than reported in the study published by Al Eidan *et al.*, and this can be attributed to the inclusion of severe SCH with higher TSH levels than in our study.^[7] The prevalence of the components of MetS among SCH subjects (diabetes, obesity, high blood pressure, and dyslipidemia) in our study population was 30.6%, 38.4%, 29.2%, and 23.3%, respectively; these rates are similar to the prevalence of SCH of 22% in a MetS group in an internal medicine outpatient clinic in India.^[30]

A significant effect of age on the severity of SCH was found. Half of the participants with markedly elevated TSH were > 50 years old. This is consistent with a previous study, which found a higher prevalence of SCH in older aged people,^[9] and is possibly due to declining thyroid

Table 5: Comparison of metabolic syndrome components according to age and gender

Components	Age-wise comparison			Gender-wise comparison		
	Age >50 years, n (%)	Age <50 years, n (%)	P	Males, n (%)	Females, n (%)	P
DM	289 (60)	110 (23)	0.000	141 (52)	258 (37)	<0.001
HTN	271 (59)	109 (20)	0.000	116 (44)	264 (36)	0.02
CAD	116 (21)	24 (3)	0.000	95 (38)	208 (33)	0.18
Dyslipidemia	191 (42)	112 (26)	0.000	55 (17)	85 (9)	<0.001
Obesity	177 (32)	169 (22)	0.001	94 (28)	252 (26)	0.1

DM – Diabetes mellitus; HTN – Hypertension; CAD – Coronary artery disease

Table 6: Gender-wise comparison of body mass index, blood pressure, and biochemical characteristics

Patient characteristics	Mean±SD		P
	Male	Female	
BMI (kg/m ²)	29.61±7.257	29.25±10.572	0.209
SBP (mmHg)	131.40±19.531	131.23±19.841	0.968
DBP (mmHg)	76.07±12.993	74.16±12.611	0.605
LDL-C (mmol/L)	3.00±1.253	3.13±1.052	0.007
TC (mmol/L)	4.22±1.244	4.56±1.216	0.133
TG (mmol/L)	1.59±1.043	1.44±2.067	0.845
HDL-C (mmol/L)	1.06±0.263	1.36±0.373	0.000
FBG (mmol/L)	7.01±2.786	6.47±2.675	0.346
HbA1c (%)	6.79±1.918	6.40±1.630	0.004
AST (IU/L)	30.88±60.639	28.14±59.424	0.785
ALT (IU/L)	41.67±150.407	26.73±45.913	0.027

BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; LDL-C – Low-density lipoprotein cholesterol; TC – Total cholesterol; TG – Triglyceride; HDL-C – High-density lipoprotein cholesterol; FBG – Fasting blood glucose; HbA1c – Glycated hemoglobin; AST – Aspartate transaminase; ALT – Alanine transaminase; SD – Standard deviation

function with age. Therefore, it is important to factor the patient’s age when deciding on initiating treatment for SCH, as, conversely, it can contribute to an extended lifespan.^[31]

Our results of significantly higher levels of diabetes, hypertension, CAD, dyslipidemia, and obesity in participants >50 years old was similar to that of another study, which concluded that declining thyroid function leads to increased serum lipid levels, thereby explaining the increased prevalence of dyslipidemia.^[9] The increased prevalence of the other components could be related to increased obesity with age^[32] and because the cardiovascular system is a crucial target of the thyroid hormone.

There was also an effect of gender on SCH: diabetes, hypertension, and CAD were significantly higher in males with SCH. This contradicts a previous study, which found that females with SCH were more likely to develop hypertension than males and suggested that this may be due to a decrease in circulating estrogen.^[33] Our study found significantly higher LDL-C and HDL-C levels in females. The finding contrasts with a previous study in India, which found no gender effect on HDL and LDL levels.^[34] However, that study had suggested that women in the

perimenopausal years are at a higher risk of dyslipidemia. In contrast to a previous study in a large Chinese cohort, which found TSH levels to be lower in males, our mean TSH level did not differ statistically between males and females.^[35] The differences between our study and others may be due to the differing study population ages or levels of iodine in drinking water.

In the present study, the MetS components (diabetes, obesity, high BP, and dyslipidemia) were not substantially altered between the groups, mildly and markedly elevated TSH, in contrast to previous findings.^[17,18,22,24] This difference may be due to the values used to designate participants into the mild and severe SCH groups; therefore, care must be taken when assigning participants to groups. However, some of the individual MetS components had considerable variances: markedly elevated TSH group had higher levels of TC, HDL-C, hemoglobin, and AST and lower levels of HbA1c.

The finding for TC is consistent with a previous study,^[20] which reported that the level increased with TSH level. In addition, compared with euthyroid controls, another study found higher levels of TC and HDLC in patients with SCH and concluded that the hypothyroid state might be responsible for dyslipidemia because thyroid hormone has a significant impact on lipid metabolism.^[22] This could explain our study’s findings. Another reason for the higher level of HDL in the severe SCH group could be that severe short-term hypothyroidism is linked with impaired cholesterol efflux capacity, where the excretion of cholesterol via bile is decreased.^[36] The higher levels of AST observed in the severe SCH group are consistent with a recent report that found a positive correlation with TSH levels, which decreased after LT4 treatment.^[37] The higher levels found are also parallel with those in an SCH group compared with euthyroid controls.^[38] The reason for this association is not clear, but they may be linked to the change in lipid peroxidation, a major cause of liver cell damage in obesity-related SCH. A correlation between SCH and HbA1c levels has been reported previously and has been suggested to be linked to insulin resistance in SCH.^[39,40] Our finding that the HbA1c level was lower in those with

severe SCH contrasted with a previous study (with similar TSH values used to define SCH) that found lower levels in euthyroid controls.^[41] However, HbA1c values depend on various factors, including the glycemic level, which may have differed between these studies.

In terms of the risk factors for MetS identified using stepwise linear regression, there was a low but significant positive correlation between TSH and ALT levels and SBP, particularly the former. ALT is a marker for fatty liver, which has recently been found to be associated with MetS,^[38] and this could explain our findings. In addition, we found that TSH levels enhanced the odds ratio of cardiovascular risk variables, providing further evidence that severe SCH is a risk factor for CVD and should be closely monitored.

We analyzed >41,000 thyroid function tests done over a 3-year period to determine the correlation between SCH and MetS in Saudi Arabia. Although we found no difference between mildly and markedly elevated TSH in terms of MetS, there were differences in the two of the component variables of MetS (TC and FBG), possibly because declining thyroid function is associated with dyslipidemia and insulin resistance. There was also a difference in levels of AST and hemoglobin, which has recently been implicated in linking fatty liver or nonalcoholic steatohepatitis with SCH. Our findings indicate that these variables should regularly be monitored in patients with SCH, especially in older patients who are more likely to be affected by conditions such as diabetes and obesity. It is particularly important to account for gender when monitoring because the prevalence of some risk factors differs between males and females.

Strengths and limitations

This study has several strengths, including the substantial number of study participants, the wide range of ages studied, and the relatively longer study period. In addition, the study included both Saudi and non-Saudi patients.

The study has few limitations, such as having been conducted in a single center and the inherent limitations of a retrospective study design. Therefore, longitudinal studies with a wider representative sample are required to validate the findings of this study. Furthermore, as there are no definitive criteria for SCH, another limitation is that the values used to define SCH may differ from those used in previous studies, thereby negating direct comparisons.

CONCLUSION

The study found that the prevalence of SCH is about 3%, which increases in those aged >60 years. In addition, MetS

components were abnormal in patients aged >50 years and in males with SCH. Monitoring these variables in SCH patients is recommended, especially in older patients and particularly in females because the protective effect of estrogen weakens with age.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Ethical considerations

The study was approved by the Bioethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia (Ref. no.: 473-21; date: January 5, 2022). The requirement for patient consent was waived owing to the retrospective study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: S.H.; methodology and data analysis: A.H.A., S.B.A., S.A.A., S.A.Albeladi, A.M.S.A., S.M.A., and W.A.A.; writing – original draft preparation: S.A. and K.G.; writing – review and editing: S.A. and K.G.; supervision: M.B. and S.A.

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Conflicts of interest

There are no conflicts of interest.

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