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RESEARCH ARTICLE

ASSOCIATION BETWEEN SUBCLINICAL HYPOTHYROIDISM AND METABOLIC SYNDROME

Nehal Hamdy[1], Noha Adly[1],Yasser Bakr[1], Abeer Salem[1] and Sahar Abdel Aty[2]

1.Department of Internal Medicine and Centre of endocrinology and diabetes, AL kasr Al Ainy hospital, Faculty of Medicine, Cairo University, Egypt

2.Department of clinical pathology, AL kasr Al Ainy hospital, Faculty of Medicine, Cairo University, Egypt

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Corresponding Author

Noha Adly

Abstract

Background: sub-clinical Hypothyroidism and metabolic syndrome are recognized risk factors for atherosclerotic cardiovascular disease.

Aim: This study aimed to investigate associations between subclinical thyroid disease, insulin resistance, and metabolic syndrome.

Methods: A cross-sectional study from a tertiary care Kasr Al Ainy teaching hospital in Cairo, Egypt. 30 patients with subclinical hypothyroidism and 30 healthy age matched euthyroid control subjects were included in the study. TSH, FT4 were measured for both the groups using electrochemiluminescence immuno assay. The metabolic syndrome criteria according to the National Cholesterol Education Program/ATP III were sought for in both groups. Fasting plasma Insulin levels were measured and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated.

The baseline characteristics between the groups were compared with Student's' test. Chi-square test was used to analyze the association between metabolic syndrome and sub-clinical hypothyroidism. Logistic regression analysis was applied to identify the association between sub-clinical hypothyroidism and the patient characteristics in the study group.

Results: Of the 30 patients in the study group, 20 were females (66.7%), 10 were males (33.3%) with mean age 44.8 ± 11.0 years. Of the 30 subjects in the control group, 10 were females (33.3%), 20 males (66.7%) with mean age 47 ± 11.6 years. In the study group, 26 had metabolic syndrome (86.7%), 4 had no metabolic syndrome (13.3%). In the control group 9 subjects had metabolic syndrome (30%), 21 subjects had no metabolic syndrome (70%) ($P<0.001$).Data showed that insulin resistance is significantly higher in the subclinical hypothyroid patient group than in the control group ($P = 0.05$), so there is positive correlation between TSH and insulin resistance (HOMA-IR) but not with the insulin level ($P = 0.124$). Logistic regression analysis recognized the association between female gender ($P = 0.021$) and metabolic syndrome

Conclusion: Subclinical hypothyroidism was associated with metabolic syndrome and females were more at risk. Metabolic syndrome patients with insulin resistance (HOMA- IR) are at significant risk of having sub-clinical hypothyroidism.

INTRODUCTION

Metabolic syndrome (MetS), a cluster of disorders including central obesity, glucose intolerance, hypertension and dyslipidemia, has been used to identify individuals at risk of cardiovascular disease (CVD) [1, 2].

Subclinical hypothyroidism (SCH) is diagnosed based on laboratory evaluation with few or no definitive clinical signs or symptoms and defined as an elevation in serum thyroid-stimulating hormone (TSH) above the upper limit of the reference range (0.45-4.5mIU/L) with normal serum free T4 and T3 concentration [3]. Subclinical hypothyroidism has also been suggested as a risk factor for atherosclerotic cardiovascular disease. Thyroid functions affect metabolic syndrome parameters including HDL cholesterol, triglycerides, blood pressure and plasma glucose. On the other hand, the relationship between thyroid dysfunction and metabolic syndrome is not clearly identified yet [4].

Thyroid dysfunction is a risk factor for CVD mediated by the effects of thyroid hormones on lipid metabolism and blood pressure [5-7].

Some studies have shown that insulin resistance (IR) or hyperinsulinemia is associated with overt or subclinical hypothyroidism and metabolic syndrome (MetS) [7-9]. The prevalence of subclinical hypothyroidism and metabolic syndrome tend to increase with age [1, 10].

CVD risk increases markedly in the postmenopausal period because of the sudden decline in the protective effect of estrogen in women [9]. Many studies have revealed an association between subclinical hypothyroidism and metabolic syndrome or cardiovascular risk factors in postmenopausal women [11-13] but there are a few similar studies in children or adolescents [14, 15]. However, no studies have examined the association between thyroid hormone levels and metabolic syndrome in young women of reproductive age.

Some studies recommended lowering the upper reference limit of TSH to 2.5 mU/L based on a large-scale epidemiological survey that revealed that more than 95% of normal individuals have TSH levels < 2.5 mU/ L and that those with higher TSH levels are likely to have various thyroid disorders [10,16-18].

We aimed to investigate whether there was any association between SCH with MetS or its components in a case controlled study in patients attending the tertiary care of Al Kasr Al Ainy teaching hospital in Cairo, Egypt.

PATIENTS AND METHODS

Subjects:

The study was performed from January 2013 to November 2013. Thirty patients with subclinical hypothyroidism who had attended the internal medicine and endocrinology outpatient clinic of Al Kasr al Ainy Hospital and 30 healthy age matched euthyroid control subjects were included in the study. None of the subjects had been prescribed any medications for hypertension, dyslipidemia, thyroid, or estrogen replacement therapy.

Exclusion Criteria:

Any patient with:

- Other causes of an elevated TSH level, such as recovery from non thyroidal illness, Cushing disease and syndrome, and certain cases of central hypothyroidism before diagnosis of SCH
- significant chronic diseases: renal disease, hepatic disease, or having a myocardial condition
- immobile
- Pregnancy
- Patients with history of chronic drug usage (steroid treatment, antidepressant and/or anti-psychotic drug users, oral contraceptives).

Ethical aspects

Research protocols were approved by the medical ethics committee of the Kasr al Ainy medical school, Cairo University. All participants provided a written informed consent after the research protocols were carefully explained to them. Informed consent was obtained from all the study participants and their approval taken by signature.

Procedures and definitions

All of the subjects underwent a complete screening panel, including history taking, physical examination. Weight and height were measured while the subjects wearing light clothes and no shoes; the body mass index (BMI) was also calculated (kg/m2). The waist circumference was measured on bare skin during mid respiration at the narrowest indentation between the 10th rib and iliac crest to the nearest 0.1 cm. Serum TSH and FT4 was assessed using a

microparticle enzyme immunoassay (Architect; Abbott Laboratories, Abbott Park, IL). The fasting plasma glucose (FPG) and 2-hour post-load plasma glucose (2 hr-PG) levels were obtained. Triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured using the enzymatic colorimetric method. Low-density lipoprotein cholesterol (LDL-C) was calculated. The fasting plasma insulin (FPI) concentrations were measured using the DRG Insulin ELISA kit.

Calculation of IR

All of the patients were on an unrestricted diet. After an overnight fasting period of 12 h, glucose (mg/dl) and insulin (mIU/ml) levels were measured and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated according to the formula: HOMA-IR= [(Fasting insulin level (mU/L) × Fasting plasma glucose (mmol/L)]/ 22.5 [18]. HOMA-IR cut-off value used was 2.7 (>2.7 was considered insulin resistant and <2.7 was considered insulin sensitive) [19].

Definition of metabolic syndrome (MetS)

The metabolic syndrome criteria according to the 2001 National Cholesterol Education Program/ATP III [20]:

Current ATP III criteria define the metabolic syndrome as the presence of any three of the following five traits:

1. Abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in)
2. Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
3. Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C
4. Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure
5. Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Statistical analyses

The data analysis was performed using SAS SPSS 12 (SPSS, Inc., Chicago, IL) and Excel (Microsoft Corp., Redmond, WA). All data were expressed as means ± standard deviation (SD). Student's t test was used to compare differences between various parameters. Pearson's correlation coefficients were calculated to determine the strength of the associations. Multiple linear regression analysis was performed to evaluate the association of TSH and metabolic parameters. The p values are based on logarithmic data, while the mean values are presented as untransformed data. All p values were 2-tailed, and statistical significance was defined as $p \leq 0.05$.

RESULTS

Participants in both groups were age matched. In the control group: The mean age was 47.26 ± SD 11.64, while in patients with subclinical hypothyroidism group: The mean age was 44.8± SD 11.00. (Table-1)

Table-1: Comparison of age in the studied groups

Groups	Age		T-Test	
	Range	Mean ± SD	T	P-value
Controls	20.000 - 70.000	47.267 ± 11.647	0.843	0.402

Patients	27.000 - 66.000	44.800 ± 11.000		

Our study revealed that the prevalence of subclinical hypothyroidism was more among the females. The control group subjects were: 10 Females (33.33 %) and 20 Males group (66.67%), while the patients with subclinical hypothyroidism were 20 Females (66.666%) and 10 Males (33.333%).The difference in sex distribution between the two groups was statistically significant , P-value: <0.001. The reason may be that our primary selection was based on TSH only in classifying both groups and the fact that SCH affect the females more than males. (Table-2) and (Figure-1)

Table-2: Comparison of sex in the studied groups

sex	Groups						Chi-Square	
	Controls		Patients		Total			
	N	%	N	%	N	%	X2	P-value
Female	10	33.33	20	66.666	30	50	23.254	<0.001*
Male	20	66.67	10	33.33	30	50		
Total	30	100.00	30	100.00	60	100.00		

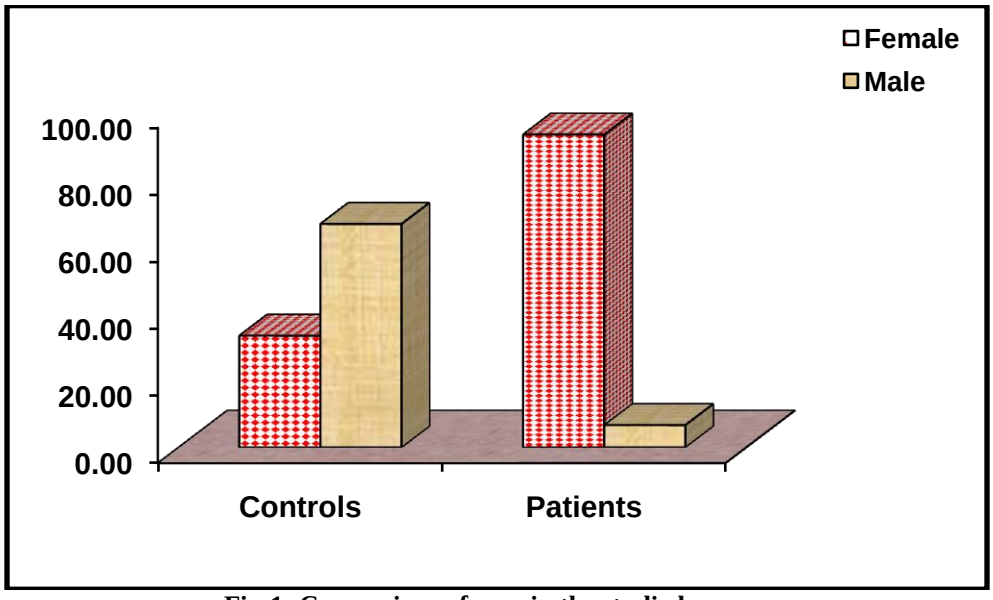

Fig-1: Comparison of sex in the studied groups

Comparing between the presence of metabolic syndrome components in both groups (Table-3) and (Figure-2) our data showed that metabolic syndrome is significantly higher in SCH patient group than in the control group, the P-value: <0.001. The metabolic syndrome prevalence in subclinical hypothyroidism was 86.67% [26 patients] vs. only 30 % [9 patients] of the control group.

The total number of those who were found to fulfill the metabolic syndrome criteria according to the 2001 National Cholesterol Education Program/ATP III in this study was 35 individual (58.33% of total). Their mean age was 45.077± SD 10.859 in subclinical hypothyroidism and was 41.222±13.103 in the control group.

Table-3: Comparison between the presence of metabolic syndrome in the studied groups

Metabolic S	Groups						Chi-Square	
	Controls		Patients		Total			
	N	%	N	%	N	%	X2	P-value
Negative	21	70.00	4	13.33	25	41.67	19.817	<0.001*
Positive	9	30.00	26	86.67	35	58.33		
Total	30	100.00	30	100.00	60	100.00		

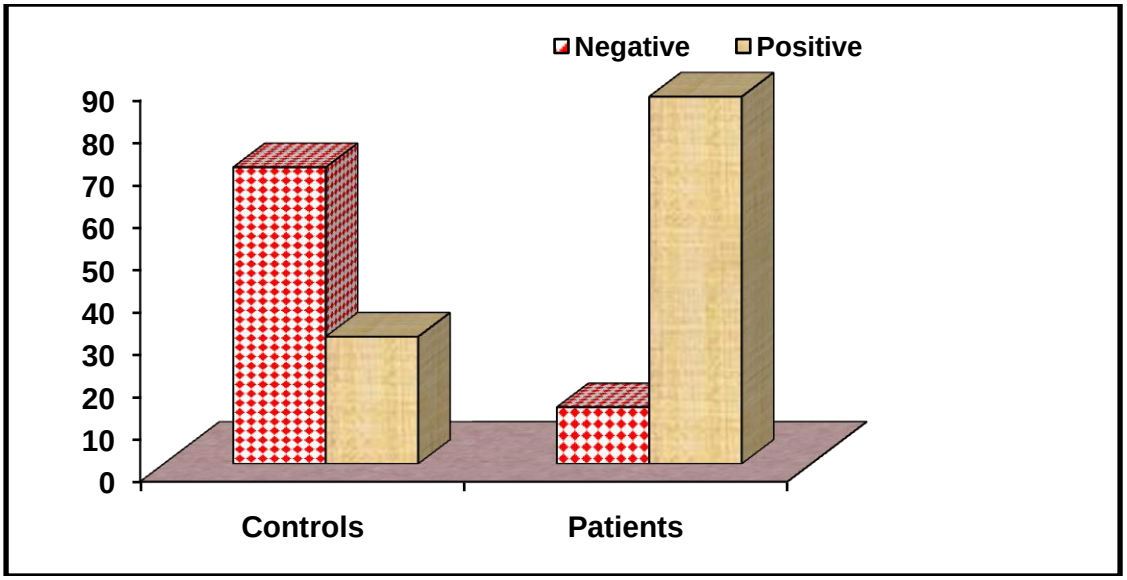

Fig.2: Comparison between the presence of metabolic syndrome in the studied groups

Our study revealed that the prevalence of metabolic syndrome was more among the females with thyroid dysfunction. This conclusion was withdrawn from: 66.6 % of SCH patients were females and that metabolic syndrome is significantly higher in SCH patient group. A higher prevalence in women might be related to their higher rate of obesity.

Our study showed that the waist circumference is significantly higher in SCH patient group than in the control group. P-value: < 0.001. The mean waist circumference in the control group was: 92.40 ± SD 18.237, while, the mean waist circumference in Patients with subclinical hypothyroidism was: 110.000±13.901.

Also our results showed that waist circumference is significantly higher in patients with both subclinical hypothyroidism and metabolic syndrome group than in patients with subclinical hypothyroidism without metabolic syndrome group. The mean waist circumference in patients with both subclinical hypothyroidism and metabolic syndrome group was: 112.077 ± SD 13.508, [P-value: < 0.034]. While, the mean waist circumference in patients

with metabolic syndrome alone but without subclinical hypothyroidism group was: 97.889 ± SD 18.510. The difference in waist circumference was not significant despite being one of the major criteria in diagnosing metabolic syndrome. [P-value = 0.288]. The reason of this finding might be that the presence of SCH may augment the effect of metabolic syndrome on waist circumference.

Our results showed that the Triglycerides (TG) level is significantly higher in SCH patient group than in the control group. In the control group, the mean TGs: 135.567± SD 41.779, while, in patients with subclinical hypothyroidism group, the mean TGs: 175.967± SD 89.838; P-value 0.029. (Table-4) and (Figure-3)

Table-4: Comparison between triglyceride levels in the studied groups

Groups	TGs		T-Test	
	Range	Mean ± SD	t	P-value
Controls	47.000 - 222.000	135.567 ± 41.779	-2.233	0.029*
Patients	50.000 - 356.000	175.967 ± 89.838		

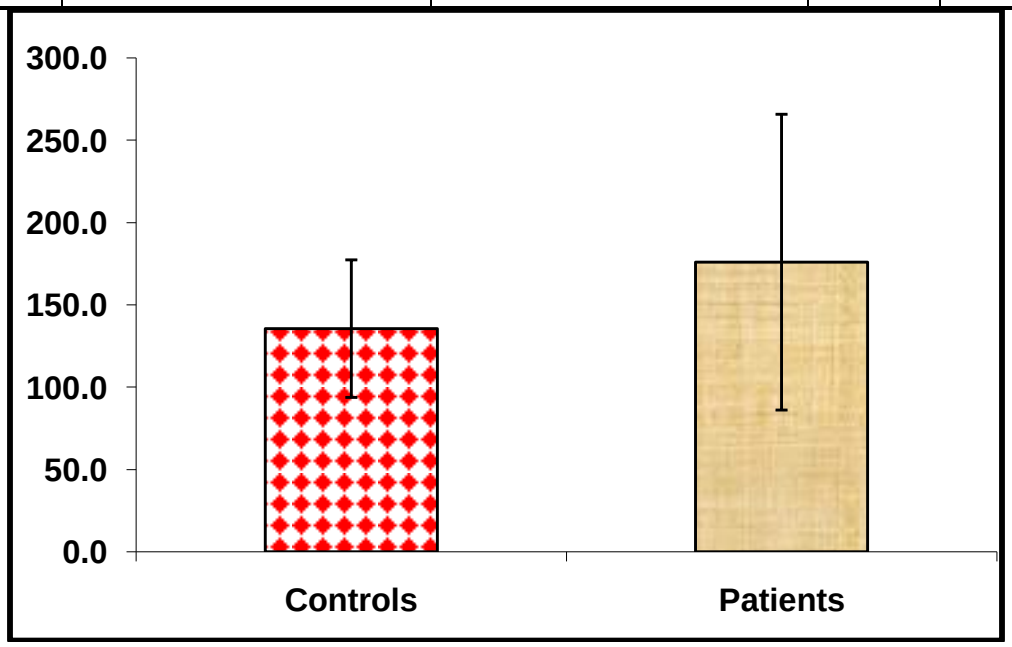

Fig.3: Comparison between triglyceride levels in the studied groups

Our results showed that HDL level is significantly lower in SCH patient group than in control group. In the control group, the mean HDL 39.600± SD 5.360, while, in patients with subclinical hypothyroidism group, the mean HDL: 32.833 ± SD 10.062; P-value 0.002. (Table-5)

Table-5: Comparison between HDL levels in the studied groups

Groups	HDL	T-Test

	Range	Mean ± SD	t	P-value
Controls	30.000 - 49.000	39.600 ± 5.360	3.251	0.002*
Patients	11.000 - 57.000	32.833 ± 10.062		

Also, our data showed that total Cholesterol level is significantly higher in SCH patient group than in control group. Total Cholesterol in Control: 150.600±36.909. Total Cholesterol in patients with subclinical hypothyroidism group: 195.067 ± 41.688. P-value<0.001

Also, in this study, our results showed that within SCH patients group, those who had metabolic syndrome, had a significantly higher TG level (P-value 0.047), while HDL and total cholesterol did not reach a significant difference. Again this difference was not seen in the control group between those with and without metabolic syndrome.

Our results showed that there was no significant difference between the 2 groups in Fasting Blood Sugar (FBS) level. Mean Fasting Blood glucose (FBG) in the control group: 107.900 ± 31.217. Range: 66 – 190. Mean Fasting Blood glucose [FBG] patients with subclinical hypothyroidism group: 116.133±41.964. Range: 72-250. P-value 0.392

We had noticed that the there was a statistically significant difference in the level of TSH within the control group between those with and without the metabolic syndrome. The mean TSH in those with metabolic syndrome was 2.862 ± SD 0.643 which was significantly higher than those without the metabolic syndrome. The mean TSH was 2.280 ± SD 0.643. P value: 0.031

Our results showed that Cutoff value of serum TSH of 3.2 can predict the presence of metabolic syndrome with sensitivity of 80%,Specificity of 84%, Positive Predictive value (PPV): 87., Negative Predictive value (NPV): 75, and accuracy of 80%. (Table-6)

ROC curve between Metabolic and TSH in all data:

ROC curve between Metabolic and TSH in all data					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
> 3.2	80.0	84.0	87.5	75.0	80.1

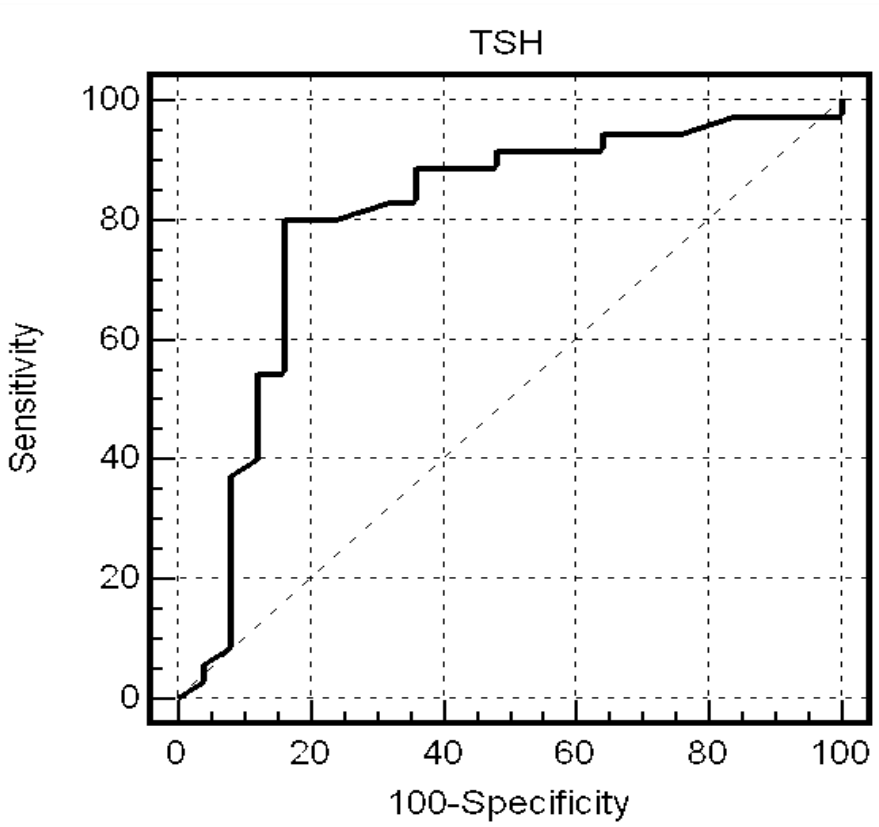

Fig.4A: Sensitivity and specificity of TSH in predicting Metabolic Syndrome

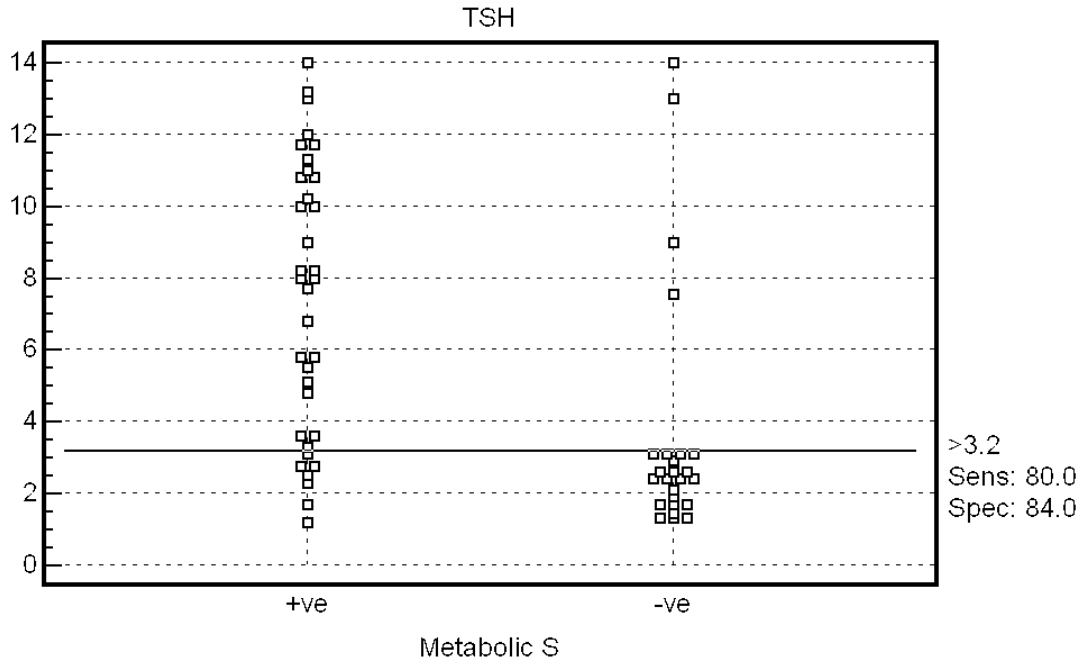

Fig.4B: Sensitivity and specificity of TSH in predicting Metabolic Syndrome

According to the insulin levels in both groups our data showed that insulin level is significantly higher in SCH patient group than in control group. Mean insulin level in the controls was: 10.600 ± SD 10.648, range: 0.200 - 34.800. Mean insulin level in patients with subclinical hypothyroidism group: 18.333 ± SD 11.897, range: 1.300-52.100. P-value: 0.010 (Table-7)

Table-7: Comparison between insulin levels in the studied groups

Groups	INSULIN LEVEL		T-Test	
	Range	Mean ± SD	t	P-value
Controls	0.200 - 34.800	10.600 ± 10.648	-2.653	0.010*
Patients	1.300 - 52.100	18.333 ± 11.897		

In our study, the comparison between insulin resistance (by HOMA-IR) in both groups showed that insulin resistance is significantly higher in SCH patient group than in the control group (Table-8) and (Figure-5).
Mean insulin resistance in the control Group: 47.420 ± 45.598. Mean insulin resistance in patients with subclinical hypothyroidism group: 95.157 ± 69.710. P-value was 0.003
Our data showed a positive correlation between TSH and insulin resistance (by HOMA-IR) P-value: 0.05, but, not insulin level: P-value 0.124

Table-8: Comparison between insulin resistance (by HOMA-IR) in the studied groups

Groups	HOMA-IR		T-Test	
	Range	Mean ± SD	t	P-value
Controls	0.978 - 163.044	47.420 ± 45.598	-3.139	0.003*
Patients	5.604 - 276.111	95.157 ± 69.710		

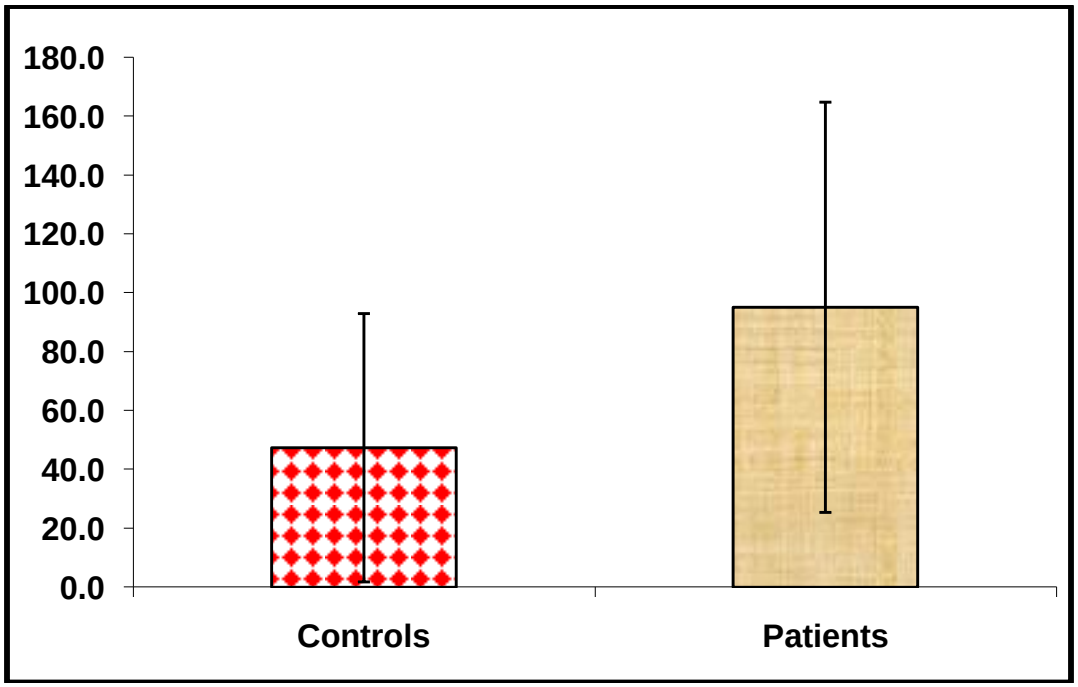

Fig.5: Comparison between insulin resistance (by HOMA-IR) in the studied groups

Our data showed a positive correlation between TSH and insulin resistance (by HOMA-IR) but not with insulin level (Figure-6)

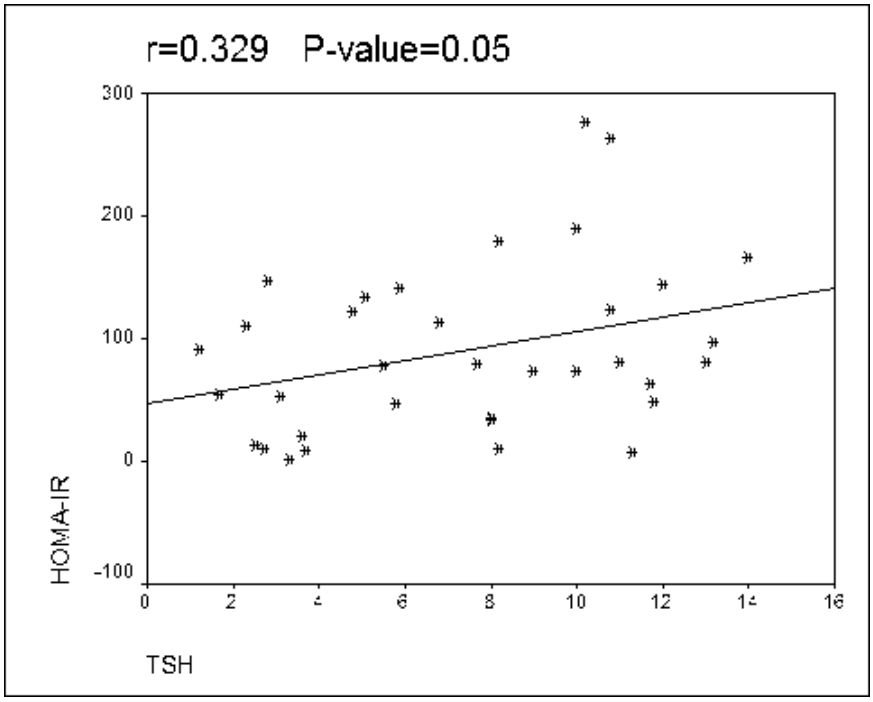

Fig.6: correlation between TSH and insulin resistance (by HOMA-IR)

DISCUSSION

Our data showed that metabolic syndrome is significantly higher in SCH patient group than in the control group. The P-value: <0.001. The metabolic syndrome prevalence in subclinical hypothyroidism was 86.67% [26 patients] vs. only 30 % [9 patients] of the control group.
The total number of those who were found to fulfill the metabolic syndrome criteria according to the 2001 National Cholesterol Education Program/ATP III in this study was 35 individual (58.33% of total). Their mean age was 45.077± SD 10.859 in subclinical hypothyroidism and was 41.222±13.103 in the control group.

Our results showed that Cutoff value of serum TSH of 3.2 can predict the presence of metabolic syndrome with sensitivity of 80%,Specificity of 84%, Positive Predictive value (PPV): 87., Negative Predictive value (NPV): 75, and accuracy of 80%.

We had also noticed that the there was a statistically significant difference in the level of TSH within the euthyroid control group between those with and without the metabolic syndrome. The mean TSH in those with metabolic syndrome was 2.862 ± SD 0.643 which was significantly higher than those without the metabolic syndrome. The mean TSH was 2.280 ± SD 0.643. P value: 0.031
This could be explained by the finding in studies showing that adipocytes and preadipocytes express TSH receptors and that TSH induces preadipocytes to produce and release adipokines, some of them such as leptin play a very important role in the onset of metabolic syndrome and cardiovascular diseases[21].

This association may be explained by argue that both conditions are prevalent in the population. Some experts have suggested that the true upper limit of TSH is only 2.5 or 3 mU/L in healthy individuals without thyroid disease, while others argue that the serum TSH distribution shifts towards higher values with age, independent of the presence of antithyroid antibodies. Both conditions spring from a common soil, i.e., cytokines. In subclinical hypothyroidism, cytokines play a role in the inflammation; similarly, cytokines play an important role in the metabolic syndrome (because of insulin resistance). Also both have a common end point which is atherosclerotic cardiovascular disease. Metabolic syndrome patients with SCH may have systemic inflammation and conversely, metabolic syndrome patients with raised high sensitivity C reactive protein HsCRP are at risk for SCH.

Our results were consistent with Ashizawa et al., [22]. They published a study conducted in Japanese people; and found a significant increase in a cluster of metabolic cardiovascular disease risk factors among people with subclinical hypothyroidism. Also Erdogan, et al.,[23] study aim was to investigate the frequency of metabolic syndrome in hypothyroid patients. One hundred overt hypothyroid patients, 100 subclinical hypothyroid patients and 200 healthy controls were enrolled in this study. NCEP-ATP III criteria was used for metabolic syndrome diagnosis. Metabolic syndrome prevalence was 44% in the hypothyroid group, 35% in the subclinical hypothyroid group and 33% in the control group. (p=0,016 for hypothyroid group versus controls and p=0,002 for hypothyroid group versus subclinical hypothyroid group). They concluded that: Metabolic syndrome increased in patients with hypothyroidism and therefore hypothyroidism should be considered in newly diagnosed metabolic syndrome patients.

Lai et al., [24] explored the relationship between serum thyrotropin and components of metabolic syndrome in a Chinese cohort included 1534 adults. They found the level of TSH in metabolic syndrome group was obviously higher than that in non metabolic syndrome group (2.54 mIU/L vs. 2.22 mIU/L, p<0.05) and that the serum TSH within the reference range was positively related with the prevalence of overweight/obesity. They concluded that slight increase in serum TSH may be a risk factor for metabolic syndrome.

On the other hand Liu et al., [25] concluded that subclinical hypothyroidism did not appear as an independent risk factor for the metabolic syndrome.

Our study revealed that the prevalence of metabolic syndrome was more among the females with thyroid dysfunction. This conclusion was withdrawn from: 66.6 % of SCH patients were females and that metabolic syndrome is significantly higher in SCH patient group. A higher prevalence in women might be related to their higher rate of obesity.This finding was consistent with the study done by Shantha et al., [26] who found that females with metabolic syndrome had significant association with SCH. The study by Uzunlulu et al; [27] had also shown females to be more associated with SCH and metabolic syndrome.

Our data showed that insulin level is higher in SCH patient group than in control group.Mean insulin level in the controls was: 10.600 ± SD 10.648. Range: 0.200 - 34.800 .Mean insulin level in patients with subclinical hypothyroidism group: 18.333 ± SD 11.897 Range: 1.300-52.100 P-value: 0.010

In our study, insulin resistance (by HOMA-IR) in both groups showed that insulin resistance is significantly higher in SCH patient group than in euthyroid control group. Mean insulin resistance in the control Group: 47.420 ± 45.598. Mean insulin resistance in patients with subclinical hypothyroidism group: 95.157 ± 69.710. P-value was 0.003.

These results were consistent with Tuzcu et al., [28] that showed that SCH has been associated with fasting hyperinsulinemia and Al Sayed et al., [29] who found that the level of insulin in subclinical hypothyroid group was obviously higher than that in normal controls; however no difference was found in HOMA-IR. Also Roos et al., [30] study showed that both FT4 and TSH were significantly associated with HOMA-IR ($\beta = -0.133$; $P < 0.001$ and $\beta = 0.055$; $P = 0.024$, respectively), and Median HOMA-IR increased from 1.42 in the highest tertile of FT4 to 1.66 in the lowest tertile of FT4.

Our data showed a positive correlation between TSH and insulin resistance (by HOMA-IR) P-value: 0.05, but, not insulin level: P-value 0.124 these matches with Singh et al., [31] who found a significant positive correlation between the TSH and insulin levels, as well as between the TSH and HOMA IR (Homeostasis model of assessment) levels in the female population who was suffering from SCH.

Our results showed that there was no significant difference between the 2 groups in Fasting Blood Sugar (FBS) level. Mean Fasting Blood glucose (FBG) in the control group: 107.900 ± 31.217. Range: 66 – 190. Mean Fasting Blood glucose [FBG] patients with subclinical hypothyroidism group: 116.133±41.964. Range: 72-250. P-value 0.392

The degree of hypothyroidism that contributes to insulin resistance may not be enough to elevate FBS, but, it was enough to make a statistically significant difference between the two groups regarding insulin level and insulin resistance (by HOMA-IR).

FPG was not statistically different between groups in study done by Erdogan, et al., [23]. The differences, also, did not reach statistical significance in study by Lui et al., [25].

RECOMMENDATIONS

Subclinical Hypothyroidism is associated with metabolic syndrome and females are more at risk.
Early identification of the metabolic abnormality and appropriate intervention may be of importance in patients with subclinical hypothyroidism. Primary importance might be in those populations who are considered having a high risk as being a female, with central obesity. Early thyroxin replacement could reduce the significant cardiovascular risk in these patients. However, there is still a controversy whether the patients with subclinical hypothyroidism would benefit from thyroxin replacement.Metabolic syndrome patients with insulin resistant (HOMA- IR) are at significant risk of having sub-clinical hypothyroidism and should be assessed for thyroid dysfunction.High TSH was associated with deleterious changes in serum lipids which may increase the cardiovascular mortality and morbidity in patients with subclinical hypothyroidism and metabolic syndrome.

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