ORIGINAL ARTICLE

Metabolic syndrome and insulin resistance in women with subclinical hypothyroidism

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Abstract

Background: Hypothyroidism is found to be more prevalent in women than men. There is an increasing evidence that subclinical hypothyroidism and metabolic syndrome are independent risk factors for cardiovascular disease and insulin resistance is the main pathophysiological basis for metabolic syndrome. Limited and conflicting data are available regarding the status of metabolic syndrome and insulin resistance in female patients with subclinical hypothyroidism. *Aim and Objectives:* The current study was conducted to evaluate metabolic syndrome and insulin resistance in women with subclinical hypothyroidism. *Material and Methods:* Fifty newly diagnosed subclinical hypothyroid women between the age group 18-45 years and fifty age-matched healthy women volunteers as controls were selected and enrolled for the study. *Results:* The mean values of diastolic blood pressure, total cholesterol, Low Density Lipoprotein-C (LDL-C), Triglycerides (TG), fasting glucose, insulin, and Homeostasis Model Assessment-Estimated Insulin Resistance (HOMA-IR) were significantly increased, whereas waist circumference, systolic blood pressure, and High Density Lipoprotein-C (HDL-C) were not significantly changed in women with subclinical hypothyroidism as compared to control group. *Conclusion:* Women with subclinical hypothyroidism are having a significantly higher prevalence of metabolic syndrome and insulin resistance which may result in a compounded risk of cardiovascular disease in these patients.

Keywords: Subclinical Hypothyroidism, Metabolic Syndrome, Insulin Resistance, HOMA-IR

Introduction

Thyroid disorders are the most common endocrine disorders worldwide with a prevalence of 42 million in India [1]. Hypothyroidism is a frequent disorder in the general population, especially in women. Subclinical Hypothyroidism (SCH) is defined as an asymptomatic condition with raised levels of Thyroid Stimulating Hormone (TSH) and normal levels of free thyroid hormones (FT3 and FT4) [2]. The prevalence of subclinical hypothyroidism ranges between 4 % to 15 % worldwide and is reported to be 11.4% for women and 6.2% for men in India [3]. Thyroid hormones play an essential role in regulating energy balance and appear to serve as a general metabolic controller, co-coordinating many metabolic processes especially the metabolism of glucose and liquids [2].

Hypothyroidism is a well-known cause of dyslipidemia and overt hypothyroidism is widely recognized as a risk factor for atherosclerosis and cardiovascular disease [4-5]. Although asymptomatic, various studies reported an increased risk of

cardiovascular disease in patients with SCH and showed that SCH is an independent risk factor for Myocardial Infarction (MI) and atherosclerosis in elderly women [6-7].

Insulin resistance that leads to many metabolic abnormalities is a cardinal feature of type -2 diabetes and the prevalence of thyroid disorders in patients with diabetes is significantly higher than in the general population [8].This indicates a possible interplay between thyroid status and insulin sensitivity. Association between insulin resistance and subclinical hypothyroidism has been reported in some studies [8-9]. However, few studies reported that there was no significant difference in insulin and insulin resistance when compared with the euthyroid state [10-11] but controversies still exist.

Metabolic syndrome is a cluster of metabolic disorders consisting of obesity, dyslipidemia, elevated blood pressure, and fasting hyperglycemia. It is associated with multiple cardiovascular risk factors and insulin resistance is the central pathophysiological basis underlying this clustering. The presence of metabolic syndrome is a major risk factor for the development of both type-2 diabetes mellitus and atherosclerosis. The prevalence of the cardiovascular disease is 2-3 times higher in individuals with metabolic syndrome than in age-matched controls [12-13]. Few studies showed that SCH is significantly associated with metabolic syndrome and its components [11, 14-15], while other studies did not show such association between SCH and metabolic syndrome [16-18].

Subclinical hypothyroidism, insulin resistance, and metabolic syndrome are independent risk factors for atherosclerotic Cardiovascular Disease (CVD). Association between these three entities may translate into a compounded risk of CVD in these patients. Searching in PubMed, we have observed that there was limited and conflicting data available regarding the status of metabolic syndrome and insulin resistance in women with SCH. Hence, we decided to evaluate metabolic syndrome, its components, and insulin resistance in women with subclinical hypothyroidism.

Material and Methods

The present cross-sectional study, as a part of Ph.D. work was conducted in the Department of Biochemistry, Govt. Medical College and Hospital, Aurangabad during the period from April 2012 to May 2014. For this study, 50 newly diagnosed and untreated SCH women attending the Outpatient Department (OPD) of Medicine were selected and enrolled in the study as cases. Age-matched 50 healthy euthyroid women volunteers were selected and included in the study as controls. The study protocol was approved by the institutional ethics committee of Govt. Medical College and Hospital at Aurangabad and informed consent was obtained from all the study participants.

Study design: The present study was a cross-sectional study. A purposive sampling technique was used to select the participants for the study. The selection of cases and controls was done on the basis of inclusion and exclusion criteria.

Inclusion criteria: All the cases and controls belong to the age group 18 to 45 years. Newly diagnosed and untreated 50 subclinical hypothyroid women attending the OPD of Medicine, GMC, Aurangabad were selected as cases. Healthy euthyroid 50 women volunteers from hospital staff and patient relatives were selected and enrolled in the study as controls.

Exclusion criteria: Women suffering from diabetes, polycystic ovarian disease, liver or renal disorders, other systemic illnesses, intake of oral contraceptive pills, statins, and other medication that alter thyroid function and liquid levels were excluded from the study. Pregnancy and menopause also accounted for exclusion from the study.

Subclinical hypothyroidism: It was defined as patients with raised TSH levels (> 5.45 μIU/ml) and thyroid hormone (FT3 and FT4) levels within their respective reference ranges. Patients with normal levels of TSH, FT_3 and FT_4 were considered euthyroid.

Metabolic syndrome: For this study metabolic syndrome has been diagnosed according to the modified diagnostic criteria published by National Cholesterol Education Program Adult Treatment Panel III(NCEP-ATP III) [19-20]. It requires at least three of the following five risk factors,

1) Waist circumference: ⩾ 90 cm in men and
   ≥ 80 cm in women
2) Triglycerides (TG): ⩾ 150 mg/dl
3) High Density Lipoprotein-C (HDL-C):
   <40 mg/dl in men and
   < 50 mg/dl in women
4) Blood Pressure (BP): Systolic BP > 130 mmHg
   and /or
   diastolic BP > 85 mmHg
5) Fasting Glucose : ≥ 100 mg/dl.

Anthropometric and clinical measurements

Blood Pressure (mmHg) was measured by using a standard sphygmomanometer on the left upper arm with the patient in a sitting position. Triple measurements were taken at intervals of 10 minutes and the mean value calculated was used for further statistical analysis.

Waist circumference (cm) was measured at the midpoint of the distance between the lowest rib and the iliac crest using a standard measuring tape.

Biochemical investigations

In the case of all study participants, under all aseptic conditions, overnight fasting venous blood was collected in fluoride and plain blood collection path tubes. Blood was allowed to clot and serum was separated by centrifugation at 3000 rpm for 10 minutes and used for the estimation of biochemical parameters. Thyroid profile (TSH, FT_3 and FT_4) and insulin were estimated by Chemiluminescence Immunoassay (CLIA) using commercially available Acculite CLIA microwells from Monobind INC, Lake Forest, CA92630, USA. Plasma Glucose (GOD-POD), serum total cholesterol (CHOD-POD), triglyceride (GPO), and HDL-C (PVS/PEGME) were estimated on XL-640 fully automated clinical chemistry analyzer, Transasia Pvt. Ltd. by using commercially available kits from Erba diagnostics. Low Density Lipoprotein-C (LDL-C) was calculated using Friedward's formula:

LDL-C = Total-C- (HDL+ TG/5) [21].

HOMA-IR

Insulin resistance was estimated using Homeostasis Model Assessment-Estimated Insulin Resistance (HOMA-IR) from fasting glucose and insulin using the formula [22-23]

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mg/dl)} \times \text{Fasting insulin (μIU/ml)}}{405}$$

The cut-off value used for HOMA-IR is ⩾ 2.5

Statistical analysis

Data were expressed as mean ± SD and proportion (%) of patients. Comparison of parameters

between cases and controls was done using an unpaired 't-test'. Pearson's correlation coefficient (r) was used to assess the relationship between different variables. The Chi-square test was used for the comparison of qualitative data between cases and controls. Statistical analysis was performed using free OpenEpi software, Microsoft Word and Excel worksheet. P> 0.05 was considered non-significant and P< 0.05 was considered significant.

Results

In the present study, as shown in Table 1, age was not significantly different between the two study groups. Baseline levels of FT3 and FT4 were significantly decreased (p<0.05) whereas TSH was significantly increased (p<0.0001) in the SCH group compared to the control group.

Table 2 shows that waist circumference, systolic blood pressure, and HDL-C were not significantly changed (p>0.05) in SCH patients compared to the control group. A significant increase was observed in diastolic blood pressure (p<0.05), total cholesterol (p<0.01), LDL-C (p<0.05), TG (<0.0001), fasting glucose (p<0.001), insulin (p<0.01) and HOMA-IR (p<0.001) in SCH group as compared to control group.

Bivariate analysis for metabolic syndrome and insulin resistance in SCH patients (Table 3) shows that metabolic syndrome (38 % vs. 16 %) and insulin resistance (40 % vs. 16 %) were significantly more prevalent in SCH women compared to controls. A significantly increased prevalence was observed in the components of metabolic syndrome especially, raised blood pressure (32 % vs. 12 %), hyperglycemia (40 % vs. 10 %), and raised TG (34 % vs. 14 %) in SCH women compared to controls. The proportion of patients with increased waist circumference (48 % vs. 36 %) and low HDL-C (42 % vs. 32 %) did not differ significantly between the study groups.

In SCH patients, (Table 4) TSH was significantly negatively correlated with FT3 and FT4 (p<0.05). HOMA-IR also correlated negatively with FT3 and FT4 but it was not significant (p> 0.05). TSH significantly positively correlated with insulin (p<0.05) as well as HOMA-IR (0.01). Similarly, TSH and HOMA-IR both were significantly positively correlated with waist circumference (p<0.01; p<0.001), diastolic blood pressure (p<0.05; p<0.001), fasting glucose (p<0.01; p<0.001) and TG (p<0.05; p<0.001), whereas both significantly negatively correlated with HDL –C (p<0.01; p<0.001) respectively.

Table 1: Baseline characteristics of study groups

Variables	Control (n=50)	Subclinical hypothyroid (n=50)	P
Age (years)	36.66 ± 6.78	37.04 ± 5.51	0.7591^{NS}
FT_3 (pg/ml)	2.82 ± 0.30	2.66 ± 0.39	P < 0.05
FT_4 (ng/dl)	1.34 ± 0.15	1.28 ± 0.13	P < 0.05
TSH (µIU/ml)	2.17 ± 0.71	12.45 ± 3.24	P < 0.0001

Values were expressed as mean ± SD, NS: non-significant P <0.05: considered significant.

Table 2: Clinical and biochemical parameters of the study groups

Parameters	Control (n=50)	Subclinical hypothyroid (n=50)	P
Waist circumference (cm)	80.4 ± 5.11	81.87 ± 4.71	P=0.1379^{NS}
SBP (mmHg)	120.8 ± 5.88	121.44 ± 5.36	P=0.5708^{NS}
DBP (mmHg)	80.04 ± 6.12	82.72 ± 4.97	P < 0.05
Total cholesterol (mg/dl)	175.6 ±19.13	191.18 ± 20.95	P < 0.01
HDL-C (mg/dl)	47.35 ± 7.6	46.75 ± 6.6	P=0.6743^{NS}
LDL-C (mg/dl)	106.4 ± 21.76	116.28 ± 22.97	P < 0.05
TG (mg/dl)	112.7 ± 21.39	140.67 ± 18.43	P < 0.0001
Fasting glucose (mg/dl)	82.64 ± 10.12	91.88 ± 12.50	P < 0.001
Insulin (µIU/ml)	7.66 ± 2.32	9.25 ± 2.44	P < 0.01
HOMA-IR	1.60 ± 0.71	2.14 ± 0.78	P < 0.001

Values are expressed as mean ± SD. NS: non-significant SBP: systolic blood pressure p <0.05: considered significant. DBP: diastolic blood pressure, HDL-C: high hensity lipoprotein-C, LDL-C: low density lipoprotein-C, TG: Triglycerides, HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table 3: Bivariate analysis for metabolic syndrome, its components and insulin resistance in subclinical hypothyroid patients

Variable	Control (n=50)	Subclinical hypothyroidism(n=50)	Statistical test
Metabolic syndrome	16 %	38 %	$\chi 2$=6.078 P < 0.05
Waist circumference (⩾ 80cm)	36 %	48 %	$\chi 2$=1.463^{NS}
Blood pressure (⩾ 130/85mmHg)	12 %	32 %	$\chi 2$=5.769 P < 0.05
Fasting glucose (⩾ 100mg/dl)	10 %	40 %	$\chi 2$=11.88 P < 0.001
Triglyceride (⩾ 150mg/dl)	14 %	34 %	$\chi 2$=5.428 P < 0.05
HDL-C (< 50mg/dl)	32 %	42 %	$\chi 2$=1.062^{NS}
Insulin resistance (HOMA-IR ⩾ 2.5)	16 %	40 %	$\chi 2$=7.071 P < 0.01

Values are expressed as percent (%) of subjects. NS: non-significant p <0.05: considered significant. HDL-C: high hensity lipoprotein-C, HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table 4: Correlation of TSH and HOMA-IR with thyroid hormones and metabolic parameters in subclinical hypothyroidism

Parameter	TSH Correlation coefficient(r) r- value p-value	HOMA-IR Correlation coefficient(r) r-value p-value
TSH	- -	0.3988 P < 0.01
FT_3	-0.285 P < 0.05	-0.209^{NS}
FT_4	-0.291 P < 0.05	-0.225^{NS}
Waist circumference	0.3848 P < 0.01	0.4937 P < 0.001
Systolic blood pressure	0.0719 NS	0.2249^{NS}
Diastolic blood pressure	0.3126 P < 0.05	0.5321 P < 0.001
Fasting glucose	0.369 P < 0.01	0.6218 P < 0.001
HDL-C	-0.486 P < 0.01	-0.69 P < 0.001
TG	0.2827 P < 0.05	0.6201 P < 0.001
Insulin	0.3171 P < 0.05	- -

NS: non-significant p < 0.05: considered significant. HDL-C: high density lipoprotein-C, TG: Triglycerides.

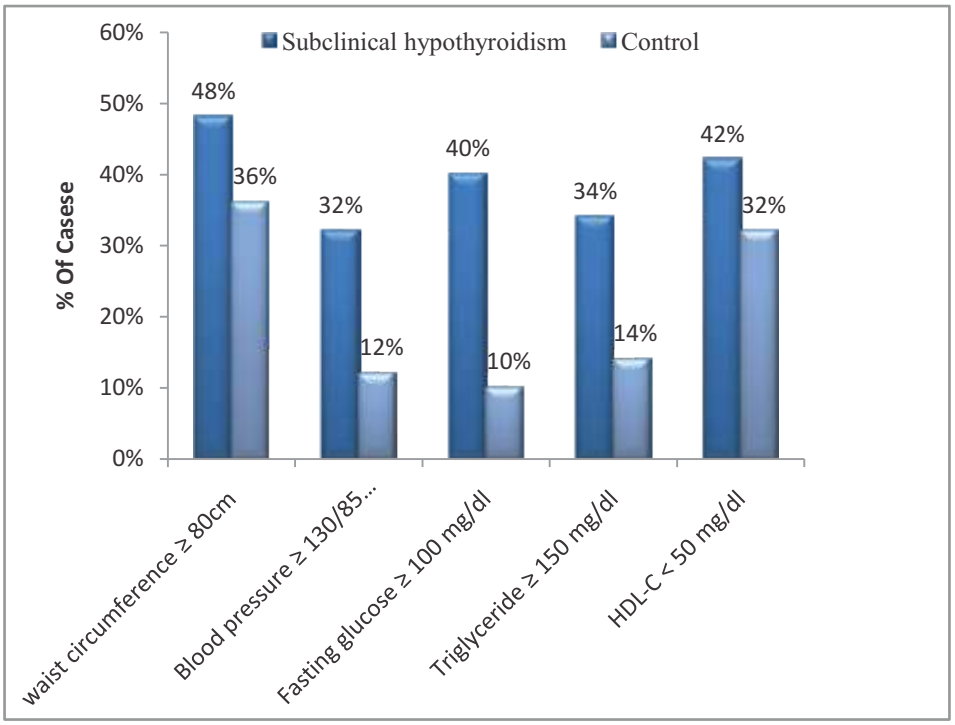

Figure 1: Components of metabolic syndrome in subclinical hypothyroid patients.

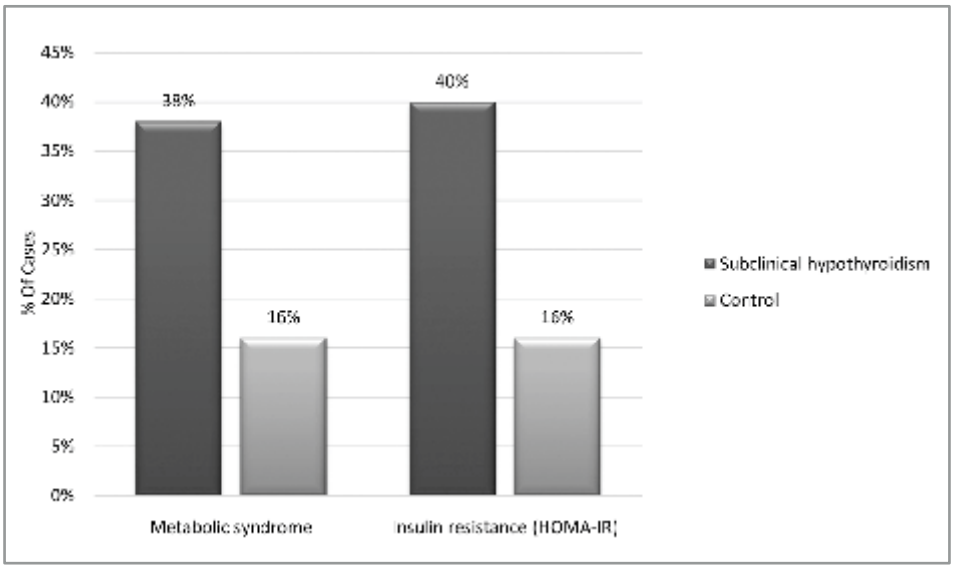

Figure 2: Prevalence of metabolic syndrome and insulin resistance in women with subclinical hypothyroidism

Discussion

Hypothyroidism and metabolic syndrome are independent risk factors for atherosclerotic cardiovascular disease. In the present study, we found that women with SCH are having significantly higher prevalence (Figure 2) of metabolic syndrome (38%) and its components, (Figure 1) especially hyperglycemia (40%) and raised blood pressure (32%). Similarly, the proportion of patients with increased waist circumference (48%) and low HDL-C (42%) was found to be more in the SCH group as compared to the control group but it was not statistically significant. Our findings are in agreement with the previous studies [11, 14-15] who reported, that SCH was significantly associated with metabolic syndrome and would affect each component of metabolic syndrome. In contrast to these, other studies [16-19] did not find any such association between SCH and metabolic syndrome as defined by NCEP-ATP III criteria. In agreement with the previous studies [11] in our study, waist circumference was not significantly different between SCH and control groups. However, a statistically significant positive correlation was observed between TSH and waist circumference in SCH patients.

Hypothyroidism is a well-known cause of secondary hypertension. Previous studies [24-25] have demonstrated elevated blood pressure values and reported a close association between hypothyroidism and hypertension, in particular diastolic hypertension. In agreement with these studies, in the present study, systolic blood pressure did not differ significantly between the study groups whereas diastolic blood pressure was found to be elevated significantly in SCH women as compared to controls. It was also found a significant positive correlation between TSH and diastolic blood pressure in the SCH group.

Thyroid hormones are known to play a key role in regulating the synthesis and mobilization of lipids. In agreement with the previous studies [11, 26-27] in our study, we found that the mean values of total

cholesterol, LDL-C, and TG were significantly elevated in the SCH group compared to the control group. In contrast to these, few studies [28-29], did not find any significant difference in the levels of these lipid parameters between SCH patients and controls. The elevation of triglycerides may be due to the decreased LPL activity observed in hypothyroidism which results in poor clearance of TG-rich lipoproteins as well as endogenous and exogenous TG from circulation [30]. In concurrence with previous studies [11, 26-27], in our study no significant difference was observed in the mean values of HDL-C between SCH and control groups. The normal levels of HDL-C in hypothyroid patients may be due to the reduced activities of Cholesterol Ester Transfer Protein (CETP) and Hepatic Lipase (HL) [31] that results in a reduced transport of cholesteryl esters from HDL2 to VLDL and Intermediate Density Lipoprotein (IDL) as well as reduced transport of HDL-2 to HDL-3.

TSH was found to be significantly positively correlated with total cholesterol, LDL-C as well as TG and negatively correlated with HDL-C.Insulin resistance that leads to many metabolic abnormalities is the central pathophysiological basis underlying glucose intolerance, dyslipidemia, abdominal obesity, and hypertension [32-33]. Arunkumar *et al*. in a recent study demonstrated a higher prevalence of thyroid disorders in diabetic patients compared with the normal population, suggesting a link between thyroid status and insulin sensitivity [34].

Our study demonstrated that (Figure 2) subclinical hypothyroid patients have a significantly higher prevalence of insulin resistance (40%). In the present study, the mean values of fasting glucose, insulin, and HOMA-IR were significantly higher in SCH patients as compared to controls. We also observed that TSH was significantly positively correlated with fasting glucose, insulin as well as HOMA-IR. These findings are in accordance with the previous study [9] which stated that SCH leads to a state of insulin resistance and attributed it to impaired translocation of GLUT-4 transporters on the cell membrane in adipose tissue and muscle. Recently, Chandankhede *et al*. in their study, demonstrated an increase in insulin levels and insulin resistance (HOMA index) as well as a positive correlation between TSH and insulin resistance in hypothyroid patients [35].

In contrast to the above findings, another study reported that insulin and HOMA-IR were not different between SCH and control groups [11]. In our study, HOMA-IR significantly positively correlated with waist circumference, diastolic blood pressure, fasting glucose, and TG, whereas negatively correlated with HDL-C.

The findings in our study suggest that a slight increase in serum TSH might be a risk factor for metabolic syndrome and insulin resistance. Further larger studies are needed to evaluate the complex mechanism behind this association.

Conclusion

In the present study, we conclude that women with subclinical hypothyroidism are having a significantly higher prevalence of metabolic syndrome and insulin resistance. It might result in a compounded risk of cardiovascular disease in these patients. Therefore, subclinical hypothyroid patients should be routinely screened for metabolic syndrome and insulin resistance which may help in the proper treatment and reduce the risk of CVD and improve the quality of life in these patients.

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