Original Research Paper

Volume - 12 | Issue - 04 | April - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medical Biochemistry

METABOLIC SYNDROME AND INSULIN RESISTANCE IN SUBCLINICAL HYPOTHYROID FEMALES: BEFORE AND AFTER THERAPY

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ABSTRACT **Background:** There is increasing evidence that subclinical hypothyroidism is significantly associated with metabolic syndrome and insulin resistance. However, these studies did not comment regarding the status of metabolic syndrome and insulin resistance before and after therapy. **Methods:** Fifty subclinical hypothyroid female patients between the ages of 18-45 years were recruited for the study. Metabolic syndrome and insulin resistance (HOMA-IR) were evaluated in these patients before and after therapy (irrespective of therapy). **Results:** Diastolic hypertension, triglycerides, and fasting plasma glucose were significantly decreased; however, systolic blood pressure, waist circumference, and HDL-C did not differ significantly in SCH patients after therapy. **Conclusion:** The frequency of metabolic syndrome (38% to 16%) as well as insulin resistance (40% to 14%) was significantly reduced in females with subclinical hypothyroidism after therapy compared to before therapy, which may reduce the risk of CVD.

KEYWORDS : Subclinical Hypothyroidism, Before and After Therapy, Metabolic Syndrome, Insulin Resistance,

INTRODUCTION:

Hypothyroidism is the most common thyroid disorder in the general population, especially in women. Various studies reported an increased risk of osteosclerotic cardiovascular disease in patients with subclinical hypothyroidism and showed that subclinical hypothyroidism is an independent risk factor for myocardial infarction (MI) and atherosclerosis in elderly women [1,2].

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 prevalence of cardiovascular disease is 2-3 times higher in individuals with metabolic syndrome than in age-matched controls [3,4].

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 [5]. This indicates a possible interplay between thyroid status and insulin sensitivity.

Subclinical hypothyroidism, insulin resistance, and metabolic syndrome are independent risk factors for atherosclerotic cardiovascular disease. The presence of metabolic syndrome and insulin resistance in subclinical hypothyroidism may result in a higher risk of cardiovascular disease in patients with subclinical hypothyroidism. Previous studies reported that subclinical hypothyroidism is significantly associated with metabolic syndrome [6-8] and insulin resistance [9,10]. However, these studies did not comment regarding the effect of replacement therapy on metabolic syndrome and insulin resistance.

Various studies showed the effect of replacement therapy on traditional lipid profiles and other cardiovascular risk factors with controversial data [1,11-15]. Recently there are two studies one in Serbia [16] on metabolic syndrome and insulin resistance and another one in Turkey [17] which is only on insulin resistance in SCH patients before and after therapy.

However, searching PubMed concerning the effect of replacement therapy on metabolic syndrome and insulin resistance in SCH patients, we did not find any study in India at the time of our study design. Hence due to very limited and conflicting data available, we decided to evaluate metabolic syndrome and insulin resistance in female patients with SCH before and after therapy.

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 subclinical hypothyroid (SCH) females attending the outpatient department of Medicine and Endocrinology were selected and enrolled in the study. All the anthropometric, clinical, and biochemical parameters were evaluated and compared in these patients before therapy and 4-6 weeks after therapy (irrespective of therapy), on the restoration of euthyroidism. The selection of cases was done based on inclusion and exclusion criteria. All the cases belong to the age group 18 to 45 years. 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. 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.

Subclinical hypothyroidism: 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 NCEP - ATP III (National Cholesterol Education Program Adult Treatment Panel III) [18,19], 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) 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:

1) Blood Pressure (mmHg): was measured by using a standard sphygmomanometer on the left upper arm with the patient in a sitting position.
2) 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 FT4) and insulin were estimated by chemiluminescence immunoassay (CLIA) using commercially available Acculite CLIA microwells from Monibind 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. LDL-C was calculated using the friedwards formula[20] (LDL-C = Total-C- (HDL+ TG/5)

HOMA-IR:
Insulin resistance was estimated using homeostasis model assessment (HOMA-IR) from fasting glucose and insulin using the formula [21,22]

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

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

Statistical Analysis:
Data are expressed as mean + SD and proportion (%) of patients. Comparison of mean values of parameters between before therapy and after therapy was done using the paired t-test. McNemar's test was used for the comparison of qualitative data between before therapy and after therapy. Statistical analysis was performed using free Open-Epi software and Microsoft excel worksheet. P > 0.05 was considered non-significant and P < 0.05 was considered as significant.

RESULTS:
Table-1 shows that the mean values of thyroid hormones FT3 and FT4 were significantly increased, whereas TSH was significantly decreased in SCH patients after therapy. As shown in Table-2, the mean values of components of metabolic syndrome, namely-diastolic blood pressure, triglyceride, and fasting glucose were significantly decreased as well as Insulin and HOMA-IR were also found to be significantly decreased in SCH patients after therapy. There was no significant change observed in mean values of waist circumference, systolic blood pressure, and HDL-C in SCH patients after therapy. Total cholesterol and LDL-C were also significantly decreased in SCH patients after therapy.

The frequency of metabolic syndrome (38% to 16%) as well as its components and insulin resistance (40% to 14%) were found to be significantly decreased in SCH patients after therapy (Table-3), as compared to before therapy.

Table-1: Baseline characteristics of subclinical hypothyroid patients: before and after therapy

Subclinical hypothyroid patients (n=50)			
Variables	**Before Therapy**	**After Therapy (n=50)**	**P-value**
FT3 (pg/ml)	2.66 ± 0.39	2.78 ± 0.38	P < 0.05
FT4 (ng/dl)	1.28 ± 0.13	1.33 ± 0.14	P < 0.001
TSH (µIU/ml)	12.45 ± 3.24	2.93 ± 0.46	P < 0.0001

Values are expressed as mean ± SD P < 0.05: considered significant.

Table-2. Clinical and biochemical parameters in Subclinical hypothyroid patients:before and after therapy

Parameters	Subclinical hypothyroid patients (n=50)		p-value
	Before therapy	After therapy	
WC (cm)	81.87 ± 4.71	81.59 ± 4.56	NS
SBP (mmHg)	121.44 ± 5.36	121.20 ± 3.61	NS
DBP (mmHg)	82.72 ± 4.97	80.84 ± 3.25	P < 0.001
Total Cholesterol(mg/dl)	191.18± 20.95	182.30±20.78	P <0.0001
HDL-C (mg/dl)	46.75 ± 6.60	48.64 ± 7.46	NS
LDL-C (mg/dl)	116.28±22.97	106.60±22.95	P <0.0001
TG (mg/dl)	140.67 ± 18.43	135.47 ± 14.19	P < 0.001
Fasting glucose (mg/dl)	91.88 ± 12.5	85.32 ± 8.68	P < 0.0001
Insulin(µIU/ml)	9.25 ± 2.44	8.34 ± 1.94	P < 0.05
HOMA-IR	2.14 ± 0.78	1.78 ± 0.57	P < 0.001

Values are expressed as mean ± SD WC: waist circumference
NS: non-significant SBP: Systolic blood pressure
p < 0.05: considered significant DBP: Diastolic blood pressure

Table-3: Frequency of metabolic syndrome, its components, and insulin resistance in subclinical hypothyroid patients before and after therapy

Subclinical hypothyroid patients (n=50)			
Parameters	**Before therapy No. (%)**	**After therapy No. (%)**	**p-value**
Metabolic Syndrome	19 (38%)	08 (16%)	P < 0.001
WC ≥ 80cm	24 (48%)	18 (36%)	P < 0.05
Blood Pressure ≥ 130/85mmHg	16 (32%)	05 (10%)	P < 0.001
Fasting Glucose ≥ 100mg/dl	20 (40%)	06 (12%)	P < 0.001
TG ≥ 150mg/dl	17 (34%)	10 (20%)	P < 0.01
HDL-C < 50mg/dl	21 (42%)	10 (20%)	P < 0.001
Insulin Resistance (HOMA-IR ≥ 2.5)	20 (40%)	07 (14%)	P < 0.001

Values are expressed as No. (%) of patients. P < 0.05: considered as significant. WC: waist circumference, TG: Triglycerides

Figure: 1. Components of Metabolic Syndrome in SCH patients: Before and After Therapy

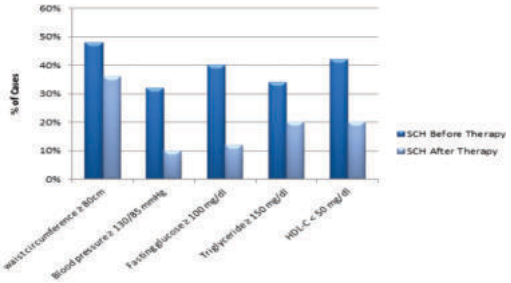
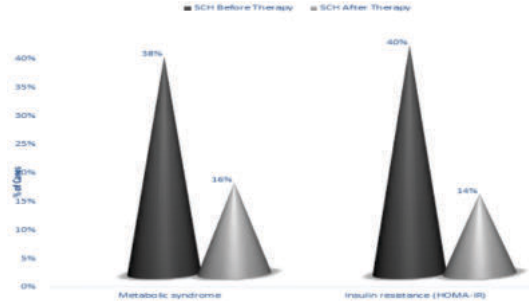


Figure: 2. Frequency of Metabolic syndrome and Insulin Resistance in SCH Women: Before and After Therapy



DISCUSSION:
Subclinical hypothyroidism has been associated with atherosclerosis and myocardial infarction in elderly women [23]. Association between subclinical hypothyroidism and metabolic syndrome has been reported in previous studies [6-8]. A study in Taiwan explored the relationship between serum TSH levels and components of metabolic syndrome, concluded that even a slight increase in TSH as in subclinical hypothyroidism may be a risk factor for metabolic syndrome [8]. Insulin resistance, the main pathophysiological basis for metabolic syndrome contributes to increased incidence of metabolic abnormalities. The presence of metabolic syndrome and insulin resistance in patients with subclinical hypothyroidism may result in an increased risk of CVD.

However, due to limited published data, it is unclear whether the status of metabolic syndrome and insulin resistance improves after the restoration of euthyroidism in these patients. In the present study, we found that the frequency of metabolic syndrome decreased significantly (38% to 16%) in subclinical hypothyroid female patients after therapy (Table-3; Figure-2). This is in agreement with the recent study in Serbia [16], which showed that normalization of TSH led to

the decrease of the frequency of metabolic syndrome in SCH patients after therapy.

On examining individual components of metabolic syndrome, it was observed that waist circumference was not decreased significantly in SCH patients after therapy (Table-2) However (Table-3; Fig.-1) the frequency of patients having waist circumference ≥80 cm significantly decreased after therapy (48% to 36%). In agreement with our findings, a non-significant decrease in waist circumference was shown in the previous studies in SCH patients after therapy [13,17].

A significant decrease was observed in the mean values of systolic and diastolic blood pressure (table-2) as well as in the frequency of hypertension (BP≥ 130/85mmHg) in SCH patients (table-3) after therapy (32% to10%). This finding is in agreement with the recent study [16] whereas another study [1] did not find any change in blood pressure in SCH patients after therapy.

In contrast to the findings of studies [16,17], in our study (Table-2, Table-3; Fig.1) fasting glucose levels, as well as the frequency of hyperglycemia(≥100mg/dl), were significantly decreased (40% to 12%). in SCH patients after therapy.

In agreement with the previous studies [11,16], total cholesterol and LDL-C were also found to be significantly decreased in SCH patients after therapy. Triglyceride levels (table-2) as well as the frequency (Table-3, figure-1) of hypertriglyceridemia (TG≥150mg/dl) were found to be significantly decreased in SCH patients after therapy (34% to 20%). Similarly, various studies [11,16,24] showed decreased TG levels whereas in contrast to these few studies did not observe any change in TG levels in SCH patients after therapy [1,12,25-27].

An increase in HDL-C level was observed (Table-2) in SCH patients after therapy, but it was not statistically significant. However, the frequency of patients with low HDL-C (<50 mg/dl) was significantly decreased (42% to 20%) in SCH patients after therapy. Few previous studies [1,11] showed increased HDL-C levels, another study [28] showed a significant decrease in HDL-C level, whereas others [16,17,25] showed no significant change in HDL-C in SCH after therapy.

In recent times, tremendous interest has been raised in the influence of thyroid hormone action on insulin levels. The association between subclinical hypothyroidism and insulin resistance has been reported in various studies [5,9,10,29]. In the present study, the mean value of insulin resistance as assessed by the HOMA-IR index (Table-2) was found to be significantly decreased in SCH patients after therapy. In agreement with our findings, a recent study [16] reported significantly decreased HOMA-IR values and in contrast to these other studies [17,30] did not observe a significant change in HOMA-IR values in SCH patients after therapy. We also observed that (Table-3; Figure-2) the frequency of insulin resistance (HOMA-IR≥2.5) was significantly decreased (40% to 14%) in SCH patients after therapy. Our study demonstrated a significant improvement in the components of metabolic syndrome as well as the status of insulin resistance in SCH female patients after therapy.

CONCLUSION:

The frequency of metabolic syndrome, its components, and insulin resistance has been significantly decreased in females with subclinical hypothyroidism after therapy. Further long-term follow-up studies are required to confirm whether these short-term benefits will translate into a significant reduction in the risk of cardiovascular disease in these patients.

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