PREVALENCE OF INSULIN RESISTANCE AND METABOLIC SYNDROME IN WOMEN WITH OVERT HYPOTHYROIDISM.

Medical Biochemistry

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ABSTRACT

Background: Hypothyroidism and metabolic syndrome are independent risk factors for cardiovascular disease, and insulin resistance is the central pathophysiological basis for metabolic syndrome. Limited and conflicting data was available on insulin resistance and metabolic syndrome in overt hypothyroidism. **Objective:** To estimate the prevalence of insulin resistance and metabolic syndrome in women with overt hypothyroidism. **Methods:** Fifty newly diagnosed overt hypothyroid women and fifty healthy women volunteers between the age group 18 – 45 years were selected and enrolled for the study. **Results:** In women with overt hypothyroidism, fasting glucose, insulin, HOMA-IR, waist circumference, systolic and diastolic blood pressure, total-C, LDL-C, and triglyceride (TG) were significantly increased whereas HDL-C was decreased but not significant. **Conclusion:** Women with overt hypothyroidism are having a significantly higher prevalence of insulin resistance and metabolic syndrome which may increase the risk of cardiovascular disease in these patients.

KEYWORDS

Overt hypothyroidism, insulin resistance, metabolic syndrome.

INTRODUCTION:

Hypothyroidism is the most common endocrine disorder worldwide and it is a graded phenomenon extending from mild sub-clinical to overt hypothyroidism The prevalence of hypothyroidism increases with age and is nearly ten times more in women than in men [1]. Overt hypothyroidism is characterized by increased levels of thyroid-stimulating hormone (TSH) and Low levels of free thyroid hormones (FT3 and FT4) [2].The prevalence of overt hypothyroidism has been reported to be 3.5%-4.2% of the population in various studies across India [3,4]. Thyroid hormones play an essential role in regulating energy balance and many metabolic processes especially the metabolism of glucose and lipids [5].Hypothyroidism is a well-known cause of obesity and dyslipidemia and overt hypothyroidism is widely recognized as a risk factor for atherosclerosis and cardiovascular disease [6-8].

Thyroid hormones maintain a fine balance of glucose homeostasis by acting as insulin agonistic and antagonistic. The main pathophysiological basis underlying glucose intolerance, dyslipidemia, abdominal obesity, and hypertension has been attributed to insulin resistance [9]. 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 [10]. This indicates a possible link between thyroid function and insulin sensitivity. Few studies demonstrated that both subclinical and overt hypothyroidism leads to a state of insulin resistance [11-13]. However, another study [14] observed no significant difference in insulin and insulin resistance in hypothyroid patients when compared with the euthyroid state.

Metabolic syndrome is a cluster of metabolic disorders consisting of obesity, dyslipidemia, elevated blood pressure, and fasting hyperglycemia. Insulin resistance is supposed to be the central pathophysiological phenomenon underlying this clustering [15,16]. The prevalence of the metabolic syndrome is increasing all over the world with distinct evidence of high prevalence in India and other south Asian countries. In the western population, the prevalence of Mets is around 20% in adults. In India, the prevalence of Mets is 18.3% according to the NCEP-ATP III definition [17]. The prevalence of the cardiovascular disease is 2-3 times higher in individuals with metabolic syndrome than in age-matched controls [18]. Few studies reported [19,20] an association between hypothyroidism and metabolic syndrome and its components.

Hypothyroidism, insulin resistance, and metabolic syndrome are independent risk factors for the same disease process namely cardiovascular disease, and the association between these three entities may translate into a compounded risk of cardiovascular disease.

Limited and Scanty data was available on insulin resistance and metabolic syndrome in hypothyroidism, at the time of our study design. Hence, we planned to study insulin resistance and metabolic syndrome in women with overt 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 overt hypothyroid (OH) women from the outpatient department of Medicine and Endocrinology and 50 age-matched healthy euthyroid women volunteers were selected and included in the study.

INCLUSION CRITERIA:

All the cases and controls belong to the age group 18 to 45 years.

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. The study protocol was approved by the institutional ethics committee of Govt. Medical College and Hospital, Aurangabad, and informed consent were obtained from all the study participants.

Overt hypothyroidism:

Patients with high TSH levels (>10mIU/ml) and low levels of FT3 (<1.4pg/ml) and /or FT4 (<0.8ng/dl) were considered as overt hypothyroid.

Euthyroidism:

Patients with TSH, FT3, and FT4 levels within their respective reference range were considered as euthyroid.

Metabolic syndrome:

For this study metabolic syndrome was defined according to the modified diagnostic criteria published by NCEP-ATP III (National Cholesterol Education Programme Adult Treatment Panel III)[15,21].

It requires at least 3 of the following 5 risk factors-
1) Waist circumference: ≥ 90 cm in men and ≥ 80 cm in women.

2)   Triglycerides (TG): ≥ 150 mg/dl.
3)   HDL-Cholesterol: < 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:
Waist circumference (cm): was measured at the midpoint of the distance between the lowest rib and the iliac crest using a standard measuring tape. Blood Pressure (mmHg): was measured by using a standard sphygmomanometer on the left upper arm with the patient in a sitting position.

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 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, and the 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 (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 [22,23].

The cut-off value used for HOMA-IR is ≥ 2.5
HOMA-IR = Fasting glucose (mg/dl) × Fasting insulin (µIU/ml)/405

Statistical Analysis:
Data are expressed as mean ± SD and proportion (%) of patients. Comparison of parameters between cases and controls was done using an unpaired student t-test. The Chi-square test was used for the comparison of qualitative data between cases and controls. Pearson's correlation coefficient (r) was used to assess the relationship between different variables. Statistical analysis was performed using 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 summarizes the clinical, demographic, and biochemical characteristics of the study participants. There was no significant difference observed regarding the age between the study groups. In overt hypothyroid patients, FT3 and FT4 levels were significantly decreased (p<0.0001), and TSH was significantly increased (p<0.0001) than the control group.

Similarly, waist circumference, both systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, fasting glucose and insulin levels, as well as the mean value of HOMA-IR index, were significantly increased, however, HDL-C was decreased as compared to the control group, but it was not statistically significant. Table-2 shows a significantly higher prevalence of insulin resistance (54% Vs 16%), as well as metabolic syndrome (52% Vs 16%), was found in an overt hypothyroid group compared to the control group.

On examining individual components of metabolic syndrome, it was observed that a significantly higher proportion of overt hypothyroid patients are having increased waist circumference ≥ 80cm (62% Vs 36%), raised blood pressure ≥ 130/85mmHg (52% Vs 12%), hyperglycemia ≥100mg/dl (52% Vs 10%), and Hypertriglyceridemia TG ≥ 150mg/dl (48% Vs 14%). The proportion of patients having low HDL-C levels (<50mg/dl) was found to be more in an overt hypothyroid group compared to the control group (48% Vs 32%) but it was not statistically significant.

Table-3 shows that in overt hypothyroid patients, there was a significant positive correlation between TSH and HOMA-IR (P<0.001). TSH and HOMA-IR both were significantly positively correlated with components of metabolic syndrome namely waist circumference, systolic and diastolic blood pressure, fasting glucose, and triglycerides (TG) whereas negatively correlated with HDL-C.

Table -1:   Clinical and Biochemical Parameters of Study Groups.

Parameters	Control (n=50)	Overt hypothyroid (n=50)	p-value
Age (years)	36.66 ± 6.78	37.24 ± 5.23	NS
FT3 (pg/ml)	2.82 ± 0.30	1.87 ± 0.77	p< 0.0001
FT4 (ng/dl)	1.34 ± 0.15	0.68 ± 0.11	p< 0.0001
TSH (µIU/ml)	2.17 ± 0.71	41.96 ± 11.38	p< 0.0001
Waist circumference (cm)	80.4 ± 5.11	84.48 ± 6.31	p< 0.001
Systolic blood pressure(mmHg)	120.8 ± 5.88	124.76 ± 6.34	p< 0.01
Diastolic blood pressure (mmHg)	80.04 ± 6.12	85.12 ± 4.12	p< 0.0001
Total cholesterol (mg/dl)	175.6 ±19.13	216.43 ± 20.61	p< 0.0001
HDL-C (mg/dl)	47.35 ± 7.6	44.55 ± 10.20	NS
LDL-C (mg/dl)	106.4 ±21.76	141.44 ± 24.96	p< 0.0001
Triglyceride (mg/dl)	112.7 ± 21.39	152.15 ± 16.33	p< 0.0001
Fasting glucose (mg/dl)	82.64 ± 10.12	98.52 ± 13.52	p< 0.0001
Insulin (µIU/ml)	7.66 ± 2.32	12.63 ± 2.85	p< 0.0001
HOMA-IR	1.60 ± 0.71	3.12 ± 1.02	p< 0.0001

Values are expressed as mean ± SD NS: non-significant (P>0.05) p < 0.05: considered significant

Table 2:Bivariate analysis for insulin resistance, metabolic syndrome, and its components in overt hypothyroidism.

Variable	Control (n=50)	Overt hypothyroidism (n=50)	Statistical test p-value
Insulin resistance (HOMA-IR ≥ 2.5)	16 %	54 %	X^2=15.709 P < 0.001
Metabolic syndrome	16 %	52 %	X^2=14.294 P < 0.001
Waist circumference (≥ 80cm)	36 %	62 %	X^2=6.695 P< 0.01
Blood pressure (≥ 130/85mmHg)	12 %	52 %	X^2=18.199 P < 0.0001
Fasting glucose (≥ 100mg/dl)	10 %	52 %	X^2=20.411 P < 0.0001
Triglyceride (≥ 150mg/dl)	14 %	48 %	X^2=13.376 P < 0.001
HDL-C (< 50mg/dl)	32 %	48 %	X^2=2.64 NS

Values are expressed as percent (%) of subjects.

NS: non-significant   p < 0.05: considered significant

Table-3: Correlation between TSH, HOMA-IR, and Components of metabolic syndrome in overt hypothyroidism.

Parameter	TSH Correlation coefficient(r) r-value p-value	HOMA-IR Correlation coefficient(r) r-value p-value
TSH	-	0.5876 P < 0.001
Waist circumference	0.6272 P < 0.001	0.6486 P < 0.001
Systolic blood pressure	0.5073 P< 0.001	0.5109 P< 0.001
Diastolic blood pressure	0.5299 P < 0.001	0.6097 P < 0.001
Fasting glucose	0.6868 P < 0.001	0.7896 P < 0.001
HDL-C	-0.577 P < 0.001	-0.585 P < 0.001
TG	0.4623 P < 0.001	0.5816 P < 0.001

NS: non-significant (P>0.05)   p < 0.05: considered significant
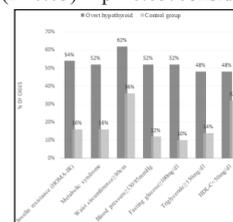

Figure: 1. Insulin resistance (HOMA-IR), Metabolic syndrome and its Components of metabolic Syndrome in Study Groups

DISCUSSION:

In recent times tremendous interest has been increased regarding the action of thyroid hormones on insulin levels. In the present study, we demonstrated (Table-2; Figure-1), a significantly higher prevalence of insulin resistance (HOMA-IR≥2.5) in the overt hypothyroid group (54% Vs 16%) compared to the control group. Similarly, the mean values of fasting glucose, insulin, and HOMA-IR were significantly increased in the overt hypothyroid group, as compared to the control group. We also observed that TSH was significantly positively correlated with fasting glucose, insulin as well as HOMA-IR in the overt hypothyroid group. These findings are in agreement with the previous studies[11-13] in which they stated that both subclinical and overt hypothyroidism 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. In contrast to the above findings, another study[14] observed that insulin and HOMA-IR were not different between hypothyroid and control groups.

There is increasing evidence that both hypothyroidism and metabolic syndrome are independent risk factors for atherosclerotic cardiovascular disease. In the present study (Table-2; Figure-1), we found a significantly higher prevalence of metabolic syndrome (52%Vs16%) and its components namely, raised waist circumference (62%Vs36%), high blood pressure (52%Vs12%), hyperglycemia (52%Vs10%), and hypertriglyceridemia (48%Vs14%) in women with overt hypothyroidism as compared to control group. The proportion of patients with low HDL-C (42%Vs32%) was also found to be more in the overt hypothyroid group as compared to the control group but it was not statistically significant. There are few studies [19,20] that demonstrated an association between hypothyroidism and metabolic syndrome.

One of the common features of hypothyroidism is weight gain or failure to lose weight, which may be due to water retention and accumulation of fat[1]. In the present study, waist circumference (Wc), the component of metabolic syndrome, was found to be significantly increased in the overt hypothyroid group than in the control group. We also observed that waist circumference was significantly positively correlated with TSH as well as HOMA-IR in these patients. Hypothyroidism has been recognized as a cause of secondary hypertension. Saito et al [8] found a strong association between elevated diastolic blood pressure and hypothyroidism. Diastolic hypertension in hypothyroid patients may be due to the increase in peripheral vascular resistance and arterial stiffness[1]. In the present study, we observed that both systolic and diastolic blood pressure were significantly increased in overt hypothyroid patients as compared to the control group. Similarly, both, systolic and diastolic blood pressure were significantly positively correlated with TSH and HOMA-IR in these patients.

Thyroid hormones influence nearly all major metabolic pathways and lipid metabolism is more influenced by thyroid hormones. Reduced activity of LDL receptors and lipoprotein lipase (LPL) are observed in hypothyroidism, which leads to increased levels of total-C, LDL-C, and TG. In our study, total cholesterol, LDL-C, and Triglyceride (TG) were found to be significantly elevated in overt hypothyroid patients, whereas HDL cholesterol level was found to be decreased in, but it was not statistically significant when compared with the control group. Similar findings were also reported by BM Singh, et al[12], and Nehad A. El-Nashar, etal [24]. We also observed that triglyceride (TG) was significantly positively correlated while HDL-C was significantly negatively correlated with TSH and HOMA-IR in overt hypothyroid patients.

CONCLUSION:

We have demonstrated that women with overt hypothyroidism are having a significantly higher prevalence of insulin resistance (HOMA-IR) as well as metabolic syndrome and its components, especially high waist circumference, hypertension, hyperglycemia, and hypertriglyceridemia. Therefore, early screening for insulin resistance and metabolic syndrome may help for proper treatment and reduce the risk of cardiovascular disease in these patients. Further larger studies are required to confirm the findings of our study.

Conflict of Interest: None

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