Mathematical model of evaluation of Insulin Resistance using Homeostasis Model Assessment – Insulin Resistance Index in patients with Hyperthyroidism

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Abstract

Aim: To evaluate insulin resistance using HOMA-IR index in patients with overt and subclinical hyperthyroidism.

Materials and Method: A randomized case control study on female population was conducted. For which 30 overt hyperthyroid, 30 subclinical hyperthyroid and 30 age and sex matched Euthyroid controls were selected. Biochemical parameters like Total triiodothyronine (T3), Total Thyroxine (T4), Thyroid Stimulating Hormone (TSH), Fasting Insulin, Fasting Blood glucose were estimated from serum samples in auto analyzers. HOMA-IR Index was calculated using formula [Fasting insulin in uIU/ml × Fasting blood glucose in mg/DL / 405]. Statistical analysis was done using Graph pad prism software, parameters expressed in Mean ± SD, individual changes was assessed by students "t" test and Pearson's coefficient of correlation was used.

Results: HOMA-IR was significantly high in cases than control group ($p<0.0001$), Insulin levels were also high in cases compared to controls ($p<0.0001$). HOMA-IR index and Insulin levels were negatively correlated with TSH, in both overt and subclinical hyperthyroid cases than controls ($r=0.97$, $p=0.0001$ and $r=0.45$, $p=0.001$ respectively).

Conclusion: Insulin resistance which was calculated by HOMA-IR index indicates the presence of insulin resistance in both overt and subclinical hyperthyroidism.

Keywords: Homeostasis Model Assessment - Insulin Resistance (HOMA-IR), Fasting Insulin, Fasting blood glucose, Overt Hyperthyroidism, Subclinical Hyperthyroidism, Insulin Resistance.

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Introduction

Hyperthyroidism is a hyper metabolic condition caused by excessive production of thyroid hormones. The prevalence of hyperthyroidism is quite low in general population (0.3% - 0.6%) and women are more prone to develop hyperthyroidism compared to men.[(1)]

Overt Hyperthyroidism biochemically shows an increase in T3 and T4 with suppressed TSH values. It is associated with increased metabolic rate. As a result body adapt to higher energy loss, both baseline and insulin-stimulated rate of cellular glucose depletes, glucose oxidation increases and hence lactic acid formation also increases. The availability of excess lactic acid triggers the liver to accelerate gluconeogenesis and hence the production of endogenous glucose.[(2-3)] In previous studies, it was documented that thyrotoxicosis increases the synthesis of hepatic endogenous glucose in fasting state and also it will decrease the hepatic sensitivity to insulin.[(4)]

Normal glucose metabolism may be altered by either a deficit or an excess of thyroid hormones, which can lead to disorders of carbohydrate metabolism as illustrated in Fig. 1.

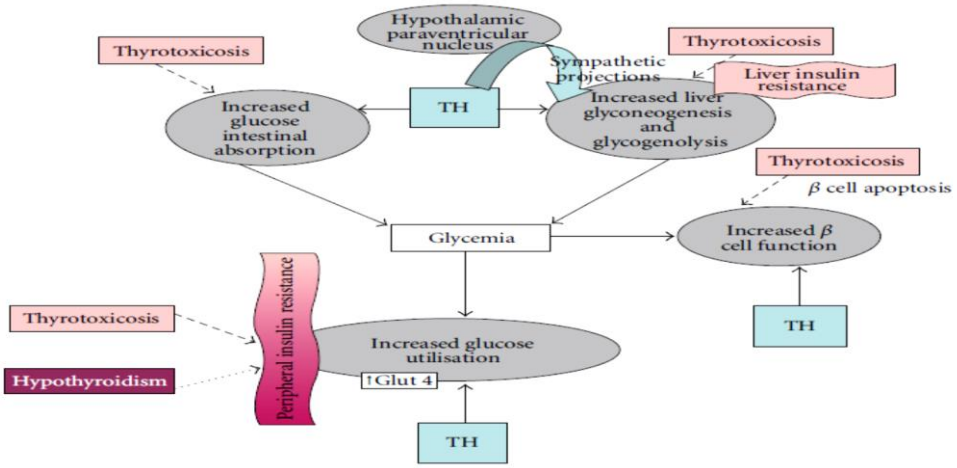

Fig. 1: Illustrates influence of thyroid hormones on carbohydrate metabolism in Euthyroids, hyperthyroids and hypothyroids

The prevalence of thyroid disorder in diabetic patients is higher than in general population.[5] In about 50% of hyperthyroids, glucose tolerance disorders are seen, and 2-3% of them had diabetes. Many studies suggests that Hyperthyroidism is often associated with both abnormal glucose tolerance and insulin resistance.[2,6-9] However in non-diabetic hyperthyroids, altered levels of fasting insulin, C-peptide and pro-insulin concentrations are observed.

Subclinical Hyperthyroidism (SHR) is a condition biochemically characterized by decreased serum TSH levels with normal levels of Total T3 and Total T4. Many exogenous or endogenous factors can cause subclinical hyperthyroidism and the condition can be either transient or persistent.[10] The studies on abnormal glucose tolerance and insulin resistance in subclinical hyperthyroid cases are sparse. The previous reports on insulin resistance in SHR showed that, it can be either reduced or unaltered.[11-13]

Homeostasis Model Assessment (HOMA) of Insulin Resistance (IR) is a mathematical formula used to assess Insulin Resistance using fasting glucose and insulin or c-peptide concentration. It is one of the indirect, easy methods of assessing insulin resistance widely used nowadays. This HOMA-IR index gives an idea of beta cell function as it estimates insulin sensitivity from basal insulin and glucose concentrations.[14]

Thus study was undertaken to know the possible linkage between Thyroid hormones, Insulin and Insulin resistance, which will be calculated using HOMA-IR index in overt and subclinical hyperthyroid cases.

Materials and Method

The study was conducted in tertiary care ESIC Hospital, Bangalore. The patients for the study were selected from Endocrinology outpatient department.

A total of 90 subjects participated in this study. Hyperthyroidism being commoner in female, we preferred to select only female subjects for our study. 30 Overt Hyperthyroid [HR] females, 30 Subclinical Hyperthyroid [SHR] females were considered as Cases group and 30 age matched Euthyroid [EU] females were selected as controls.

Inclusion criteria adopted for selection of cases were; age 18-45 years, newly diagnosed, untreated cases of overt and subclinical hyperthyroidism. Patients suffering from Diabetes mellitus, Hypertension and other endocrine disorders, those with previous history of thyroid disorder on treatment, patients on medications like Androgens, Estrogens, Oral contraceptive pills, Phenytoin that alter T3 and T4 values and those on L-dopa, Glucocorticoids, Iodine, Lithium, Amiadarone that alters TSH values, pregnant and lactating women were accounted for exclusion from the study.

After overnight fasting, using standard aseptic precautions, 5 ml venous blood samples were collected in plain vacutainers. Followed by biochemical analysis, this was done in fully automated analyzers. Total T3, Total T4, TSH and Fasting Insulin were analyzed by the method of Chemiluminescence immunoassay in Beckman Coulter Access 2 (USA). Fasting blood sugar was estimated using Hexokinase method in Cobas Integra 400 plus (Switzerland). HOMA-IR index was calculated using mathematical formula.

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

Normal reference ranges as per our methodology for Total T3 = 0.67-1.98 ng/ml, Total T4 = 6.09- 12.23 µg/dl, TSH = 0.34 –5.6 µIU/ml, Fasting Insulin = 1.93 – 23 µIU/ml, Fasting glucose <110 mg/dl and HOMA-IR index normal physiological value is < 3, with moderate insulin resistance 3 – 5 index value is seen and with severe insulin resistance shows value > 5.

Patients with decreased TSH and increased T3 and T4 were considered Overt hyperthyroids, those with decreased TSH, normal T3 and T4 values were Subclinical hyperthyroids and one who had normal T3, T4 and TSH values were Euthyroids.

Data collected was subjected to standard statistical analysis. Data was expressed as Mean ± SD. Students t - test and ANOVA was employed to compare parameters of controls and cases. Pearson's correlation was used to find relationships between parameters. A p value < 0.05 will be considered as statistically significant. All statistical analysis were done using Graph Pad Prism version 5.00 for windows, Graph Pad software, San Diego California USA, www.graphpad.com.

Results

30 Euthyroids (EU), 30 Hyperthyroids (HR) and 30 Subclinical hyperthyroid (SHR) females were included in this study. Baseline characteristics of study participants were expressed in Mean ± SD, which are shown in Table 1.

Table 1: Baseline characteristics and biochemical parameters of different study groups

Parameters	EU (n = 30)	HR (n = 30)	SHR (n = 30)
Age (years)	36.40±1.54	29.40±1.53	31.97±1.43
T3 (ng/ml)	1.18±0.26	1.42±0.43	1.21±0.27
T4 (µg/dl)	10.39±1.14	15.45±2.80	10.89±1.73
TSH (µIU/ml)	2.39±0.95	0.08±0.07	0.25±0.42
FBS (mg/dl)	92.23±9.9	121.1±10.95	117.3±14.85
Insulin (µIU/ml)	10.01±3.96	20.81±10.95	15.95±9.60

HOMA-IR	2.24±0.72	5.77±2.32	4.86±3.05

Age was comparable in all three groups. Euthyroid control group had lower level of T3 and T4 (T3-1.18±0.26 ng/ml, T4-10.39±1.14 µg/dl) as compared to Hyperthyroid group (T3-1.42±0.43 ng/ml, T4-15.45±2.80 µg/dl) is shown in Fig. 2.

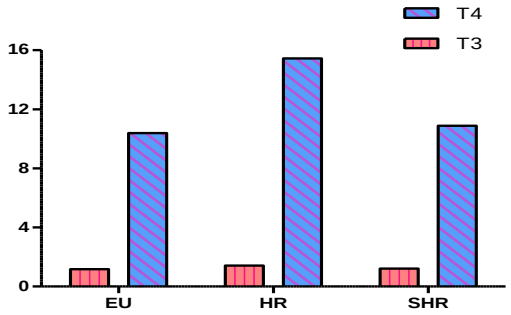

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Fig. 2: Mean T3 & T4 values of 3 study groups

Whereas TSH was higher in Euthyroids compared to Overt and Subclinical Hyperthyroid group (TSH-EU: 2.39±0.95 µIU/ml, TSH-HR: 0.08±0.07 µIU/ml, TSH-SHR: 0.25±0.42 µIU/ml) as shown in Fig. 3. The above mentioned data is in accordance with the conventional knowledge of Hyperthyroidism.

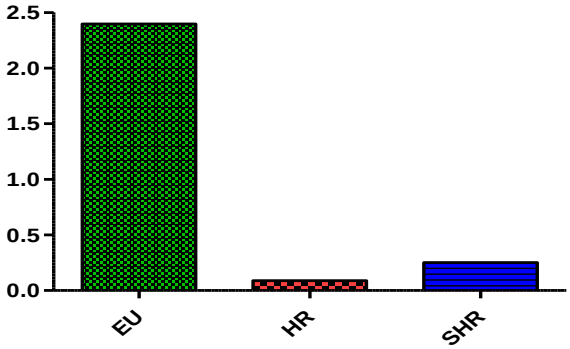

Fig. 3: Mean TSH values of study groups

Mean FBS in control group is 92 mg/dl but mean FBS was more than upper limit of normal reference (i.e., FBS < 110 mg/dl) in both HR – 121 mg/dl and SHR – 117 mg/dl groups respectively.

Insulin levels were significantly high in HR group (20.81±10.95 µIU/ml) as compared to SHR group (15.95±9.60 µIU/ml) and EU group (10.01±3.96 µIU/ml).

Mean HOMA-IR index values in HR group (5.77±2.32) and SHR group (4.86±3.05) was significantly ($p < 0.0001$) higher than EU group (2.24±0.72) as shown in Fig. 4. Difference of HOMA-IR values between HR and SHR group was statistically insignificant (p – 0.19).

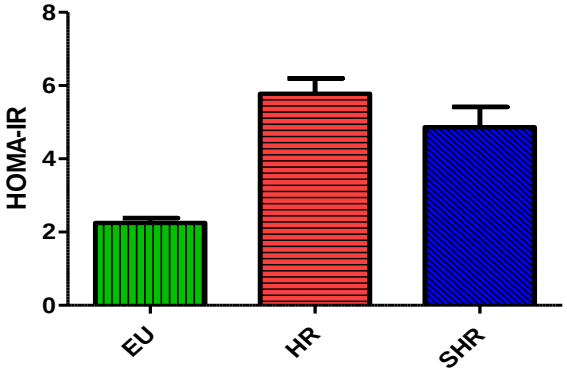

Fig. 4: Mean ± SD HOMA-IR index values of three study groups

Pearson's correlation coefficient for the relationships between serum TSH versus (vs) Insulin as well as TSH versus HOMA-IR and Insulin versus HOMA-IR were calculated in HR and SHR groups. r - values and p- values of which are shown in Table 2.

Table 2: Correlation of TSH, Insulin and HOMA-IR in cases groups

Parameters	Correlation coefficient (r) in HR	P-value	Correlation coefficient (r) in SHR	P-value
TSH vs				
Insulin	-0.6	0.1	-0.2	0.09
HOMA-IR	-0.5	0.15	-0.2	0.16
Insulin vs				
HOMA - IR	0.97	0.0001	0.45	0.001

In our study TSH levels were negatively correlated with insulin (r = -0.6, p-0.1 and r= -0.2, p-0.09) and HOMA-IR (r= -0.5, p-0.15 and r=-0.2, p-0.16) in patients of HR and SHR group respectively. Serum Insulin was positively correlated with HOMA-IR in HR group (r=0.97, p-0.0001) and SHR group (r=0.45, p-0.001) which was statistically significant. Correlation of thyroid hormones T3 and T4 with FBS, Insulin and HOMA was analyzed in EU, HR and SHR groups, values are shown in Table 3, which were statistically non-significant.

Table 3: Correlation coefficients of thyroid hormones and fasting sugar in three study groups

	EU	HR	SHR
T3 vs			
FBS	r = 0.08, p-0.65 ns	r = 0.06, p-0.75 ns	r = - 0.01, p-0.96 ns
Insulin	r = 0.02, p-0.87 ns	r = 0.07, p-0.68 ns	r = 0.16, p-0.39 ns
HOMA-IR	r = 0.06, p-0.71 ns	r= -0.08, p-0.96 ns	r = 0.09, p-0.61 ns
T4 vs			
FBS	r = 0.01, p-0.93 ns	r = 0.17, p-0.35 ns	r = 0.06, p-0.97 ns
Insulin	r = -0.18, p-0.33 ns	r = 0.07, p-0.70 ns	r = -0.15, p-0.40 ns
HOMA-IR	r = -0.08, p-0.66 ns	r = -0.24, p-0.19 ns	r = -0.04, p-0.80 ns
FBS vs			
HOMA-IR	r = 0.90, p-0.12 ns	r = 0.53, p-0.002	r = 0.4, p – 0.01

Discussion

In recent times tremendous interest has been raised in the influence of thyroid hormone action on insulin levels.

Thyroid disease is much more prevalent in women than in men.[15] Women are five to ten times more likely to develop thyroid disorder, which can increase the risk of cardiovascular disease, infertility, dyslipidemia, osteoporosis, insulin resistance and diabetes as well.

Our study illustrates the association between thyroid hormonal status and insulin levels in the development of Insulin resistance, which is seen even with slight alterations in thyroid hormones levels, which may lead to type 2 diabetes.

Method used for assessing insulin resistance is based on measurement of fasting blood glucose and fasting insulin levels in serum and then a mathematical formula HOMA-IR index was used. This index helps to assess beta cell function and insulin resistance from basal glucose and insulin or C-peptide levels.[16] The relationship between fasting glucose and fasting insulin reveals the equilibrium associated with hepatic glucose output and insulin secretion, and this is maintained by a feedback loop between hepatic and beta cells. Thus HOMA-IR index aids to estimate and compare insulin sensitivity and beta cell function in subjects with abnormal glucose tolerance.[17]

Mean FBS value was higher in HR and SHR groups compared to EU controls in the conducted study. This gives a clue that, in hyperthyroidism glucose production increases in fasting state.

Mild to moderate hyperinsulinemia was observed in subclinical and overt hyperthyroidism in this study. Which is in consistent with findings of other researchers.[18-20] Also hyperthyroid patients had a non-significant negative correlation between serum insulin and thyroid hormones, thus persistent hyperinsulinemia in such patients will lead to development of insulin resistance.

In our study HOMA-IR was significantly higher in cases than control group. This finding shows the presence of severe to moderate insulin resistance in both HR and SHR in fasting state.

Previous studies by Maratou et al., also demonstrated the presence of insulin resistance in both overt and subclinical types of hyperthyroidism. In his study increased HOMA index and decreased Matsuda and Balfiore indices was found in patients with HR and SHR than euthyroids, which suggested that insulin resistance was present in either postprandial or fasting state.[3] Yavuz et al, in his study reported significantly low insulin sensitivity in SHR group.[11]

HOMA-IR index as well as Insulin shows a negative correlation with TSH in both overt and subclinical hyperthyroidism in this study. Roos et al., found that even slightly lower levels of thyroid hormones within the physiological range showed a negative correlation with HOMA-IR index.[21] However correlations of thyroid hormones with insulin, FBS and HOMA were insignificant in our study.

Further studies can be undertaken in larger population with more sample size, including males. Estimation of BMI and Lipid profile can be added for further evaluation of metabolic syndrome and cardiovascular risks in such patients. Free T3 and Free T4 were not measured due to logistic problem, which would have given more precise results.

Conclusion

HOMA-IR Index indicates insulin resistance in both overt and subclinical hyperthyroid cases. One of the underlying mechanisms of insulin resistance could be due to altered insulin secretion caused by beta cell dysfunction in hyperthyroidism, as assessed by HOMA-IR index. Thus care must be given in evaluating such hyperthyroid cases who may develop glucose related disorder such as diabetes, due to insulin resistance.

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