ORIGINAL ARTICLE

Correlation Between Insulin Resistance and Homocysteine in Hypothyroid Patients

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Abstract:

Background: Hypothyroidism has been associated with disorders of glucose and insulin metabolism involving defective insulin secretion in response to glucose, hyperinsulinemia, altered peripheral glucose disposal and insulin resistance. Assessment of insulin resistance and homocysteine may help identifying subjects at high risk of Cardiovascular Disease (CVD). *Aim and Objectives:* The present study was designed to assess the susceptibility of hypothyroid patients to CVD by determining the relationship between Homocysteine (HCY) and Insulin Resistance (IR). *Material and Methods:* One hundred patients of hypothyroidism in the age group of 18-45 years was included in this cross sectional study. Homocysteine and insulin was estimated by ELISA method. Homeostasis Model of Assessment (HOMA) which is an index for IR was used to measure insulin resistance. *Results:* In the present study hypothyroid patients had several fold increase in insulin levels demonstrating IR by increased HOMA index and also increased homocysteine levels which may play an important role in pathogenesis of complications of thyroid hormone. In our study there was significant positive correlation between TSH and serum insulin values r = 0.447 and also homocysteine r = 0.302. We also found positive correlation between IR and homocysteine in hypothyroid patients with r = 0.295. *Conclusion*: Therefore to conclude our study emphasised the importance of TSH that is positively correlated with IR and homocysteine independent of thyroid hormones. Homocysteine and IR both are associated with endothelial dysfunction and are common mediators in the pathogenesis of accelerated atherosclerosis and cardiovascular complications.

Keywords: Cardiovascular diseases , Homocysteine, Insulin resistance

Introduction:

Thyroid hormone exert both insulin agonistic and antagonistic actions in different organs. T_4 and T_3 have a large impact on glucose homeostasis. Deficit or excess of thyroid hormones can break this equilibrium leading to alterations of metabolism in general specifically carbohydrate metabolism. Hyperthyroidism has been related to glucose intolerance and ketoacidosis. Hypothyroidism has been associated with disorders of glucose and insulin metabolism involving defective insulin secretion in response to glucose, hyperinsulinemia, altered peripheral glucose disposal and Insulin Resistance (IR) [1].

According to Maratou *et al*. [2] even subtle decrease in the levels of thyroid hormones within the physiological range have been shown to correlate inversely with the Homeostasis Model Of Assessment (HOMA) which is an index for IR.

IR and beta cell dysfunction involves the underlying pathophysiology of pre-diabetes and its subsequent progression to overt diabetes [3]. IR leads to an increased production of hepatic cholesterol and deleterious effect of hypothyroidism on the lipid profile are also suggested by Bakker *et al*. [4].

The extent to which various degrees of thyroid dysfunction affects cardiovascular events and lipid profile continues to be debated and increased

risk for cardiovascular disease cannot be fully explained by atherogenic lipid profile. Various cardiovascular risk factors are included in metabolic syndrome and IR is said to be one such important risk factor [5]. Furthermore, hyper-insulinemia has been identified as an independent predictor of ischemic heart disease in the general population [6]. Many pathways seem to link IR to cardiovascular disease, whether it involves classic risk factors (e.g., diabetes, dyslipidemia and hypertension) [7], or non-classic risk factors (e.g. coagulation and fibrinolytic abnormalities, interleukins and myeloperoxidase) [8]. Thus assessment of IR may help identifying subjects at high risk of cardiovascular disease.

Other pathogenic factors like Homocysteine (HCY) either by elicitation of oxidative stress, systemic inflammtion and or endothelial dysfunction is also known to promote IR and beta cell function [9] and is an independent risk factor for Cardiovascular Disease (CVD) and accelerated atherosclerosis.

Thus assessment of IR and homocysteine allows an assessment of cardiovascular disease and atherosclerosis. However as per our literature search very few studies have been done to show correlation between insulin resistance, HCY and hypothyroidisim [10]. Hence, with this in mind, the present study was designed to assess the susceptibility of hypothyroid patients to CVD by determining the relationship between HCY and insulin resistance. The prime objectives of the study were as follows: to compare and correlate IR levels with thyroid hormone levels in hypothyroid patients, to compare and correlate HCY with thyroid hormone in hypothyroid patients and association between IR and HCY in hypothyroid patients.

Material and Methods:

The cross sectional study was undertaken on 100 patients of hypothyroidism in the age group of 18-45 years in the department of biochemistry, NKP Salve Institute of Medical Sciences after taking informed consent. The subjects were included by purpose sampling technique.

Patients were diagnosed by increased TSH level >6 uIU/ml and decreased T_3, T_4 levels <0.5 ng/ml and <4.4 µg/ml respectively. Patients suffering from diabetes mellitus, hypertension, endocrine disorders, kidney diseases, cardiac diseases, antiepileptic drugs, pregnant or lactating females polycystic ovarian disease and on medication that alter lipid levels were excluded from the study. The research protocol was approved by Institutional Ethics Committee. Five ml of fasting venous blood sample was collected in plain bulb from hypothyroid patients. Blood was centrifuged for 5 minutes. Serum levels of fasting blood glucose, insulin, and HCY was estimated in collected samples. Blood glucose was estimated by Glucose Oxidase Peroxidase (GOD-POD) method using randox kit. The results were expressed in mg/dl. HCY and insulin was estimated by commercially available kits from Bio-Rad and AccuBind by ELISA method respectively. The results were expressed in µmol/l and µlU/ml. IR was calculated using HOMA-IR method.

HOMA 1-IR = fasting plasma glucose in mmol/l x fasting serum insulin in µIU/ml / 22.5

The mean and standard deviation were determined for each variable. All the results were expressed as Mean ± S.D. Comparison of data was done by applying student 't'-test. The correlation between insulin resistance, HCY and T3, T4 and TSH were determined by pearson's correlation co-

efficient. P-value <0.05 was considered significant.

Results:

The present study analysed the correlation between thyroid hormones, IR and HCY in hypothyroid patients. Descriptive statistics of parameters in hypothyroid patients are presented in Table 1.

HOMA-IR model has been used as a tool for assessment of IR but there is great variability in the threshold levels of HOMA-IR to define IR. Various studies had been conducted in different geographical areas to define cut-off values of HOMA-IR [11-12]. However the study by Gayoso-Diz *et al.* [13] evaluated cut-off values of HOMA-IR for diagnosis of IR by considering cardio metabolic risk factors to better understand the relationship between IR and cardio metabolic risk. According to this study the cut off values of HOMA-IR were between 1.85-2.05.

In our study, the mean ± SD of HOMA-IR values were 7.57±1.97 in hypothyroidisim patients. When Pearson's correlation was applied for Insulin, HOMA-IR and HCY versus thyroid hormone i.e. T_3,T_4 and TSH values, significant positive correlation of TSH was seen with insulin, HOMA-IR and HCY, r= 0.447, r = 0.488, r = 0.302 respectively and negative correlation between T_3, insulin and HOMA-IR (r = -0.307, r = -0.293) (Table 2 and 3). But there was no correlation of T3 with HCY. Insulin, HOMA-IR and HCY that was not at all corelated with T4.

Table 1: Laboratory Findings of Hypothyroid Patients

Parameters	Reference value (normal range)	Present study (n=100) Mean ± SD
T_3 (ng/ml)	0.5-2.0	0.59 ± 0.38
T_4 (µg/ml)	4.8-11.6	3.46 ± 1.606
TSH (uIU/ml)	0.39-6.16	28.22 ± 12.65
Insulin (µlU/ml)	0.7-9.0	31.53 ± 7.46
Fasting plasma glucose (mg/dl)	80-100	97.27 ± 9.42
Homocysteine (µmol/l)	5-15	70.84 ± 52.72

Table 2: Pearson's Correlation between Different Parameters in Hypothyroid Patients

Thyroid Hormones	Parameters	r- value	p-value
T_3	Insulin	-0.307	<0.001
	HOMA-IR	-0.293	<0.001
	Homocysteine	-0.132	<0.001
T_4	Insulin	-0.0827	<0.001
	HOMA-IR	-0.0827	0.0420
	Homocysteine	-0.0809	<0.001
TSH	Insulin	0.447	<0.001
	HOMA-IR	0.488	<0.001
	Homocysteine	0.302	<0.001

**p-value <0.05 is statistically significant, r=correlation coefficient*

Table 3: Pearson's Correlation between Insulin, HOMA-IR and Homocysteine

Parameters	r-value	p-value
Homocysteine Vs Insulin	0.29563	<0.001
Homocysteine Vs HOMA-IR	0.27972	<0.001
Insulin Vs HOMA-IR	0.9138	<0.001

**p-value <0.05 is statistically significant, r=correlation coefficient*

Discussion:

Tremendous interest has been raised on the influence of thyroid hormone action on insulin levels in recent times. Available results are conflicting regarding how insulin levels affect thyroid dysfunction. The development of IR leads to many metabolic abnormalities.

Although, hyperthyroidisim is associated with IR, there is little information on insulin action in hypothyroidisim. The main pathophysiological basis underlying glucose intolerance, dyslipidemia, abdominal obesity and hypertension has been attributed to IR [5,14].

In the present study, hypothyroid patients had several fold increase in insulin levels and fasting blood glucose demonstrating IR by increased HOMA index and also increased HCY levels which may play an important role in pathogenesis of complications of thyroid hormone. High HOMA values indicate state of IR and low HOMA values are associated with better insulin sensitivity. Our results were in agreement with those of Abdel-Gayoum [15] who observed several fold increase in fasting insulin and serum glucose concentrations in hypothyroid patients. In our study, there was significant positive correlation between TSH and serum insulin values r=0.447 and p=<0.0000001

Measurement of T_3, T_4 and TSH levels have been widely used to assess thyroid hormone status in patients but correlation between TSH, HOMA-IR and HCY is not assessed to greater extent and increase in the levels of TSH along with HOMA-IR and HCY increases the relative risk of cardiovascular events. IR if it is demonstrated in hypothyroid patients as revealed in our study because of positive correlation between HOMA-IR and TSH r=0.488 and p=<0.0000001 is the most prominent and earliest defect detected in prediabetic state and lead to subsequent evolution to overt diabetes. In diabetic patients, cardiovascular morbidity is a major burden with endothelial dysfunction. These findings are consistent with the studies reporting an increased cardiovascular risk in these patients [16-17].

Along with IR various other metabolic processes are regulated by thyroid hormones like regulation of HCY metabolism. Remethylation pathway of HCY, methionine synthase and methylene tetra hydrofolate reductase are affected by thyroid hormones by influencing the activity of hepatic enzymes [18-19]. Also low levels of thyroid hormone probably reduces glomerular filtration rate leading to increased HCY levels [20-21].

In this study we demonstrated an association between thyroid hormones and HCY, which is an independent risk factor of cardiovascular diseases. We found positive correlation between high TSH levels, indicative of low thyroid functions and HCY, r=0.302, p=<0.0000001. These observations were in line with previous studies done by Sengul *et al.* [22] and Bamashmoos *et al.* [23] in hypothyroid patients. They reported positive correlation of TSH with HCY. However, other studies contradictory to our study observed negative correlation of homoocysteine with T4 [24] and T3 [25].

In our study, we showed positive correlation between IR and HCY in hypothyroid patients with r = 0.295. Very little is known about the relationship between IR and HCY in hypothyroid patients but in our previous study on polycystic ovarian syndrome association of both the parameters was reported [26]. Also the association between both the parameters were reported in hypertension by Catena *et al.* [27]. Our results were consistent with the findings of Ning Yang [10] and who provided data regarding correlation between IR and HCY in hypothyroid patients for the first time. Previous studies also showed that coronary endothelial injury can be induced by HCY and also can promote chemokine expression and IR by inducing stress in endoplasmic reticulum of monocytes and adipose tissue in mice [28]. Also insulin affects the enzymes that are involved in HCY metabolism as reported by studies done on rats [29].

Therefore to conclude our study emphasised the importance of TSH that is positively correlated with IR and HCY independent of thyroid hormones. HCY and IR are both associated with

endothelial dysfunction and are common mediators in the pathogenesis of accelerated atherosclerosis and cardiovascular complications. In our study, both HCY and IR levels are raised along with TSH suggesting that in hypothyroidism increased HCY may increase the risk for atherogenesis and cardiovascular complications by affecting insulin levels which inturn increase IR.

Thus measuring the HCY and IR along with TSH can help in assessment of cardiovascular status and also maintaining appropriate TSH levels favours improvement of health status in hypothyroid patients.

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