

Original Research Article

Assessment of insulin resistance in diabetic hypothyroidism patients – A clinical insight**Ravi Shankar Prasad¹, Manoj Kumar Nandkeoliar², Gladys Rai³, Saurabh Srivastava⁴, Rahul Saxena⁵**¹Post Graduate student, Final year, Department of Biochemistry, School of Medical Sciences & Research, Sharda University, Greater Noida, U.P., India²Assistant Professor, Department of Biochemistry, School of Medical Sciences and Research; Sharda University; Greater Noida, U.P., India³Professor, Department of Biochemistry, School of Medical Sciences and Research; Sharda University; Greater Noida, U.P., India⁴Professor, Department of Medicine, School of Medical Sciences and Research, Sharda University; Greater Noida, U.P., India⁵Assistant Professor, Department of Biochemistry, School of Allied Health Sciences, Sharda University, Greater Noida, U.P., India***Corresponding author**

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Abstract: Despite massive research, association of hypothyroidism(HT) with insulin sensitivity is poorly understood and still needs further clarification. In addition, thyroid dysfunction has been found to be associated with altered glucose and insulin metabolism. The objective of present study was to investigate the relationship between thyroid function, hyperglycemia and insulin resistance in hypothyroidism patients (without and with diabetes) and compared it with non diabetic euthyroid subjects. Fasting blood glucose levels, serum insulin and thyroid profile were estimated by using standard methods in 80 patients of HT divided into two groups of 40 HT nondiabetic patients and 40 HT diabetic patients as Group II and Group III respectively, and compared it with 40 age matched healthy controls (Group I). Homeostasis model of assessment (HOMA-IR) was employed to assess the level of insulin resistance. The values were expressed as Mean \pm SD and data from patients and controls were compared using students 't' test. Serum insulin, thyroid stimulating hormone(TSH) levels along with fasting blood sugar were significantly high ($p < 0.001$) whereas serum T3 and T4 levels were significantly low ($p < 0.001$) in patients group as compared to control. Nondiabetic and diabetic hypothyroidism patients demonstrated significantly increased insulin resistance as observed by the higher HOMA-IR as compared to the controls. Thus, hypothyroidism is associated with hyperglycemia and insulin sensitivity involving hyperinsulinemia, altered peripheral glucose disposal and insulin resistance. Therefore, maintenance of normal thyroid profile, regular monitoring of glucose levels along with control on insulin level in hypothyroidism patients will hopefully contribute to a more adequate management of diabetes.

Keywords: Thyroid stimulating hormone(TSH), insulin, Beta cell dysfunction, and hyperglycemia

INTRODUCTION

Diabetes and thyroid dysfunction, both are endocrine disorder and have found to be associated with each other [1]. Diabetes has evolved into an epidemic in India and it has been projected to rise to a staggering 101.2 million by 2030 [2]. Similarly, there is a significant burden of thyroid disease in India and it has also been estimated that about 42 million people in India suffer from thyroid disease. In general, the prevalence rate of thyroid dysfunction is higher in

females and in elderly as compare to males and young population [3,4].

Thyroid hormones directly control insulin secretion [5]. Insulin-antagonistic effects of thyroid hormones along with an increased thyroid stimulating hormone levels have been implicated in explaining the inverse correlation of TSH with insulin resistance and β cell function. The higher serum TSH usually corresponds to lower thyroid hormones via negative feedback mechanism. As TSH increased, thyroid

hormones decreased and insulin antagonistic effects are weakened. These observations demonstrate that insulin imbalance is closely associated with thyroid dysfunction and this phenomenon is mediated via β cell dysfunction [6]. In addition, previous studies have documented that the prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population which indicates a possible interplay between thyroid status and insulin sensitivity [7].

The extent to which various degrees of thyroid dysfunction affects diabetic complication followed by cardiovascular events continues to be debated. Although thyroid dysfunction, insulin resistance and altered glycemic profile commonly coexist in India, there is a lack of evidence on their association at a single platform. In addition, at present, there is lack of region wise data for meaningful analysis in India. Therefore, the overall aim and objectives of the present study was to investigate the relationship between thyroid function, hyperglycemia and insulin resistance in hypothyroidism patients (without and with diabetes) and compared it with non diabetic euthyroid subjects in order to suggest the possible strategies to reduce the risk of future complications.

MATERIALS & METHODS

In the present study, 40 healthy subjects, 40 hypothyroidism patients with diabetes and 40 hypothyroidism patients without diabetes were taken in study group as Group I, Group II and Group III respectively. A general information or pre-experimental questionnaire regarding demographic information, family history and limited physical examination including blood pressure measurement was completed from all the subjects after taking their informed consent and approval of protocol by ethics committee of college.

Inclusion criteria: The inclusion criteria adopted were: age 30 to 60 years, newly diagnosed and untreated cases for hypothyroidism with and without diabetes. Diabetes mellitus was diagnosed by following the American Diabetes Association criteria 2015.[8].

Exclusion criteria: Patients suffering from cardiovascular disease, hepatic disease, tuberculosis, renal disease and taking drugs like steroid, amiodarone, lithium, antioxidant vitamin supplement or non-steroidal anti-inflammatory drugs, antihypertensive drugs and other medications that alter thyroid functions and lipid levels led to exclusion from the study. Pregnancy and menopause also accounted for exclusion from the study.

Serum insulin was measured using commercially available enzyme-linked immunosorbent

assay (ELISA) kits (R&D Systems, USA), according to manufacturer's instructions. Insulin resistance was estimated using homeostasis model assessment (HOMA-IR) from fasting serum glucose and insulin using the Oxford HOMA calculator; or by using the following formula: [9, 10].

$$\text{HOMA-IR} = \frac{\text{Fasting plasma glucose (mmol/l)} \times \text{fasting insulin (}\mu\text{U/L)}}{22.5}$$

Estimation of serum thyroid profile (T3, T4 and TSH) was done in VITROS EciQ immunodiagnostic system using an immunometric assay technique. Fasting blood glucose was estimated by glucose oxidase method. Glucose oxidase converts glucose to gluconic acid. In addition, peroxidase (POD) produces hydrogen peroxide which oxidatively couples with 4-aminoantipyrine and phenol to produce red quinoneimine dye [11].

Statistical Analysis:

The data collected from study group subjects were entered separately in Microsoft Excel sheet of windows 2010 and values were expressed as Mean \pm SD. The significance of mean difference between study group subjects was compared by using Student's t test and distribution of probability (P).

RESULTS:

In the present study, more patients of hypothyroidism without and with diabetes belonged to age group 40- 50 years i.e. 45.9 ± 8.1 and 46.3 ± 6.5 years in Group II and Group III respectively as represented in Table 1. In addition to diabetes, Group III subjects were obese whereas Group II subjects were overweight with respect to Group I subjects, served as healthy controls. (Table 1.0) Marked alterations in glycemic profile, serum insulin and insulin resistance were observed in hypothyroidism patients without and with diabetes, as represented in Table 2. In the Group II subjects, fasting blood glucose level was increased insignificantly ($P < 0.1$; 8.93%) with respect to Group I whereas fasting blood glucose ($P < 0.001$; 86.38%) level was significantly increased in Group III subjects as compared to healthy controls. It was observed that abnormalities in serum insulin levels and insulin resistance were highly prevalent and significantly associated with hypothyroidism patients without and with diabetes. Alteration in serum insulin levels and HOMA (IR) index in hypothyroidism patients without and with diabetes mellitus were represented in Table 2 and Figure 1 respectively. Serum insulin levels were increasing continuously and significantly ($P < 0.001$) in both the patients group (Group II and Group III) as compared to healthy control group subjects (Table 2). Similarly, HOMA (IR) index were increasing significantly ($P < 0.001$) in both Group II and Group III subjects as compared to healthy controls (Fig. 1). The

observation made reveal significant changes in thyroid profile (including T3, T4 and TSH levels) in both the patients group as compared to healthy controls. Alteration in serum thyroid profile was represented in Table 2. Serum T3 level was significantly low (P< 0.05, 18% and P< 0.001, 26.36% low) in both Group II and Group III respectively as compared to control.

Similarly, serum T4 level was significantly low (P< 0.05, 20.47% and P< 0.001, 40.12% low) in both Group II and Group III respectively as compared to control. Serum TSH level was significantly high (P< 0.001, 439.3 % and P< 0.001, 1632.06% high) in both Group II and Group III respectively as compared to control.

Table-1: Demographic profile of the study group subjects (Mean ± SD)

S.No.	Parameters	Group I (n=40)	Group II (n=40)	Group III (n=40)
1	Age (years)	46.4 ± 7.4	45.9 ± 8.1	46.3 ± 6.5
2	M:F ratio	1:1	1:1	1:1
3	Height (meter)	1.60 ± 0.053	1.61 ± 0.047	1.60 ± 0.047
4	Weight (Kg)	59.3 ± 3.1	70.7 ± 5.0	80.7 ± 7.3
5	BMI (Kg/m ²)	22.8 ± 1.1	27.1 ± 1.7*	31.2 ± 3.2**

Where, p<0.1: Non-significant, p<0.05: Significant; p<0.001: Highly Significant;

Table-2: Serum insulin, glycemc and thyroid profile of the study group subjects (Mean ± SD).

S.No.	Parameters	Group I (n=40)	Group II (n=40)	Group III (n=40)
1	Serum insulin (mu/L)	4.51 ± 1.19	20.77 ± 5.20***	40.84 ± 5.10***
2	Fasting Blood Glucose (mg/dl)	88.08 ± 10.44	95.95 ± 8.48*	164.17 ± 12.95***
3	Tri-iodo thyronin (T3) (ng/dl)	109.5 ± 21.22	89.79 ± 16.36**	80.63 ± 15.70***
4	Thyroxin (T4) (µg/dl)	8.5 ± 1.22	6.76 ± 1.14**	5.09 ± 1.30***
5	Thyroid stimulating hormone (TSH) (uIU/ml)	2.62 ± 0.87	14.13 ± 3.22***	45.38 ± 9.94***

Where, . * P<0.1: Non-significant, ** P< 0.05: Significant, *** P< 0.001: Highly significant

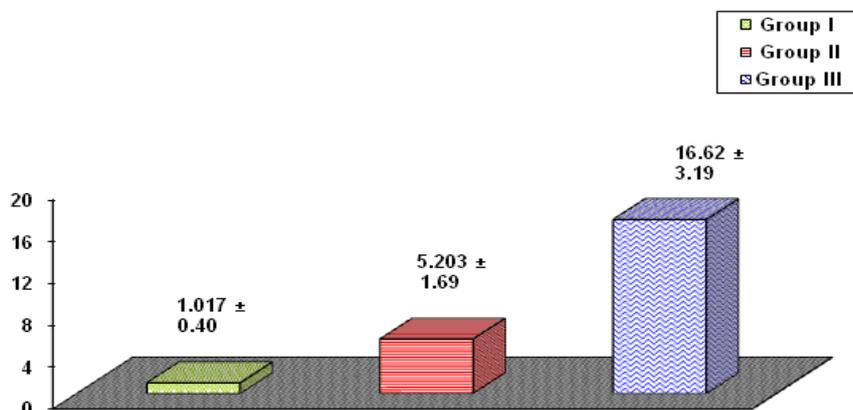


Fig-1: HOMA (IR) in index patients and control group

DISCUSSION:

It is noticeable that there is a deep underlying relation between diabetes mellitus and thyroid dysfunction [12] Previous studies have also found that thyroid dysfunction is much common in diabetic population as compared to nondiabetic population, and both the endocrine disorders i.e. diabetes and thyroid disorders are mutually influence each other [13,14].

Recently, tremendous interest has been raised in the alteration of thyroid hormone levels and insulin resistance. Our study illustrates the complex interplay between the depletion of thyroid hormone and elevation of serum insulin levels in the pathogenesis of insulin resistance. It is believed that a possible pathogenic mechanism involved in insulin resistance in

hypothyroidism is the decreased blood flow in the peripheral tissues [15].

An interesting feature of the present study was Homeostatic model assessment (HOMA) index in hypothyroidism patients without and with diabetes, which is a method for assessing β -cell function and insulin resistance (IR) from basal (fasting) glucose and insulin concentrations. The homeostasis model assessment (HOMA) for IR (HOMA-IR) derives estimates of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations [16]. Our findings suggested that the lower thyroid hormone levels in serum lowers the sensitivity of tissues to insulin. This could explain the insulin resistance found in hypothyroidism patients without and with diabetes in our study.

Interestingly, Ross *et al.* in their study reported that subtle decrease in the levels of thyroid hormones within the physiological range was inversely correlated with the HOMA index.[17] In our study, both the patient group subjects exhibited noticeable levels of insulin resistance which corresponds well with the studies showing that patients with high normal serum TSH values and mild thyroid failure have evidence of comparable atherogenic factors, such as endothelial dysfunction.[18] Conversely, Nada measured serum thyrotropin (TSH), free tetra iodo thyronine (FT4), free tri-iodothyronine (FT3), fasting insulin (FI) and fasting plasma glucose in hypothyroid patients and estimated insulin resistance (IR) by using homeostasis model assessment (HOMA-IR) to determine the impact of hypothyroidism and thyroxine therapy on insulin sensitivity in overt hypothyroidism female patients. According to his conclusion, hypothyroidism has no impact on insulin sensitivity and thyroxine replacement is not associated significantly with change of insulin sensitivity [19]. Moreover, the fact that significant incidence of insulin resistance in hypothyroidism patients without and with diabetes indicates that thyroid hormones levels per se may not be entirely responsible for the manifestation of this phenomenon and needs further investigation.

CONCLUSION:

Therefore, the present study authenticates that hypothyroidism is a common problem associated with Type 2 diabetes. Hyperglycemia is linked with hypothyroidism and the effects of this deficiency during Type 2 diabetes seem to have negative consequences on insulin resistance and glucose homeostasis. These findings could also justify the increased risk for insulin resistance-associated disorders, such as cardiovascular disease, observed in hypothyroidism patients without and with diabetes. However, there is a need for large studies designed to answer the question whether thyroid abnormalities are associated with diabetes and whether

restoration of euthyroidism might influence morbidity and mortality.

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