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Serum insulin and glucose tolerance in hypo & hyperthyroid states

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Abstract

Impaired glucose tolerance, an index of altered glucose metabolism has long been recognised as a frequent complication of hyperthyroidism involving changes in both insulin secretion and its degradation. Hence the study aims on effect of hyperthyroid and hypothyroid status on glucose

tolerance and insulin secretion in comparison with euthyroid status. Among 60 subjects, the modified Oral Glucose Tolerance Test (OGTT) and Insulin levels were estimated. Analysis of variance (ANOVA) and post-hoc Tukey test was used to analyse the data. A statistically significant ($p < 0.001$) rise in mean glucose levels was observed in hyperthyroid and hypothyroid subjects compared to euthyroid subjects both at 0 hours and 2 hrs. In hypothyroid subjects 85% of the patients had glucose intolerance, where as in hyperthyroid only 35% had impaired GTT and no patient reported frank diabetes. The higher values were observed for fasting plasma insulin and glucose levels in the hypo and hyperthyroid subjects on comparison with euthyroid subjects, on diagnosis thyroid status strict follow up should be done for fasting glucose and insulin levels, so that the comparison can be detected early. This would be a milestone in management of thyroid status and its associated complications especially hyperthyroid and hypothyroid status.

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1. Introduction

The principal effect of thyroid hormone is to increase the metabolic effects of most tissues in the body (with few exceptions such as brain, retina, spleen, testes and lungs). Thyroid hormone plays an important role on growth and development and acts on peripheral tissues of the adult to regulate their level of metabolism (Ganang et al., 2010). Thyroid hormones increase the uptake of glucose by all cells, glycolysis, and gluconeogenesis and glucose absorption from gastro-intestinal tract. In practice, thyrotoxicosis will "unmask" diabetes mellitus or may make the control of diabetes more difficult. Thyroid hormone status is important for glucose homeostasis. The direct effect of thyroid hormones on glucose metabolism is well documented (Guyton et al., 2006). Impaired glucose

tolerance, an index of altered glucose metabolism has long been recognised as a frequent complication of hyperthyroidism. According to previous studies, this may involve changes in both insulin secretion and its degradation. Most studies have been performed in patients with clinical thyrotoxicosis, but studies available on hypothyroid patient are very minimal. This study aims at including hypothyroid patients in addition to hyperthyroid patients for understanding the effects of thyroid hormones on insulin action and glucose tolerance (Leslie et al., 1989; Boron et al., 2009).

1.1 The objectives of the study

1. To study the effects of hyperthyroid on glucose tolerance and insulin secretion in

comparison with euthyroid subjects.

2. To study the effects of hypothyroid on glucose tolerance and insulin secretion in comparison with euthyroid subjects.

2. Materials and Methods

A Comparative controlled study was conducted at R.L. Jalappa Hospital and Research Centre, Kolar during the period of July 2008 to June 2010. Ethical clearance was obtained from Institutional Ethical Clearance Committee. Study group consisted of 60 subjects aged between 20-60 years. Twenty newly diagnosed patients in each hyperthyroidism; hypothyroidism and twenty euthyroid healthy volunteers were included in the study. The study subjects were selected based on inclusion/ exclusion criteria laid down for the purpose of the study. Patients with conditions known to affect glucose metabolism were excluded. The Informed consent was obtained from selected subjects, the data regarding history and clinical examination was collected by using semi-structured proforma. The modified Oral Glucose Tolerance Test (OGTT) was done in the study subjects. OGTT involves the administration of 75 gram of anhydrous glucose to a person who has been fasted overnight prior to the test. Plasma glucose is measured before and 2 hours after the consumption of glucose drink. On the basis of OGTT subjects are classified into Normal, impaired glucose tolerance and those with diabetics (World Health Org., 1999).

The fasting Insulin level was estimated by Radioimmuno assay by Bio-Line INSELISA a solid phase Enzyme Amplified Sensitivity Immunoassay performed on micro-titter-plates.

2.1 Statistical methods

Descriptive statistical tools like mean standard deviation and proportions were used for analysis. Analysis of variance (ANOVA) has been used to find the significance of difference

of mean values. Post-hoc Tukey test has been used to compare between the groups.

3. Results

A total of 60 subjects were examined. The mean age group in euthyroid subjects was 37.40 years, hypothyroid was 41.90 years and hyperthyroid was 33.25 years. 35% of the subjects in euthyroid belonged to 20-29 years, 45% in hypothyroid belonged to 40-49 years age group and in hyperthyroid 40% of the subjects belonged to 30-39 years age group. Majority of the subjects were females in all three groups, in euthyroid it is 90%; in hypothyroid and hyperthyroid it is 85%.

A statistically significant rise in mean glucose levels was observed in hyperthyroid and hypothyroid subjects compared to euthyroid subjects both at 0 hours and 2 hrs. But

There was no significant rise in the fasting insulin levels in hypo and hyperthyroid patients ($p=0.489$). In post-hoc between euthyroid vs hypothyroid, euthyroid vs hyperthyroid and Hypothyroidvs hyperthyroid in GTT highly significant, but when the fasting Insulin levels were compared it was not statistically significant. ($p=0.659, 0.485, 0.957$ respectively).

There is an impaired GTT in majority of subjects at both 0 hours 11 (55%) and after 2 hours 12 (60%) in Hypothyroid subjects, Where as in hyperthyroid subjects, there is normal glucose levels in majority of subjects at 0 hours 12 (60%) and after 2 hours that is 13 (65%) and 40% and 35% of the hyperthyroid patients had impaired glucose tolerance at 0 and 2 hours respectively. The prevalence of glucose intolerance in hyperthyroid state was 35% and no diabetes mellitus. The plasma insulin levels were within the normal range in majority of the subjects of hypothyroid 18(90%) and hyperthyroid status 16 (80%).

Table 1: Mean value of Thyroid hormones of study subjects

Variables	Euthyroid	Hypothyroid	Hyperthyroid
T3 ng/dl	1.08±0.33	0.89±0.25	2.81±1.83
T4 µg/dl	7.29±2.01	5.29±2.34	16.83±4.75
TSH µIU/ml	2.71±1.38	37.06±27.57	1.17±1.80

Table 2: Comparison of mean values of glucose and insulin in study subjects

Variables	Euthyroid	Hypothyroid	Hyperthyroid	p Value
OGTTO Hours (mg %)	88.35±4.67	114.05±9.06	100.75±14.86	<0.001**
OGTT 2Hours (mg %)	114.05±5.74	151.25±21.59	132.25±15.79	<0.001**
INSULIN(Fasting)(µu/ml)	3.37±1.47	4.19±2.44	4.46±4.31	0.489

Table 3: post -hoc comparison

Variables	Euthyroid Vs Hypothyroid	Euthyroid Vs Hyperthyroid	Hypothyroid Vs Hyperthyroid
OGTT 0Hours (mg %)	<0.001**	0.001**	<0.001**
OGTT 2Hours (mg %)	<0.001**	0.002**	0.001**
Insulin (fasting)(μ u/ml)	0.659	0.485	0.957

Table 4: Comparison of OGTT and insulin values in study subjects

Variables	Euthyroid(n=20)	Hypothyroid(n=20)	Hyperthyroid (n=20)	p value
OGTT 0 Hours (mg/dl)				
75-110	20(100.0%)	6(30.0%)	12(60.0%)	<0.001**
110-126	0	11(55.0%)	8(40.0%)	
>126	0	3(15.0%)	0	
OGTT after 2 Hours (mg/dl)				
90-140	20(100.0%)	7(35.0%)	13(65.0%)	0.150
140-200	0	12(60.0%)	7(35.0%)	
>200	0	1(5.0%)	0	
Plasma Insulin (μ u/ml)				
<0.3	0	0	0	0.150
0.3-8.0	20(100.0%)	18(90.0%)	16(80.0%)	
>8.0	0	2(10.0%)	4(20.0%)	

4. Discussion

Carbohydrate metabolism is altered in hyperthyroidism. The mechanism seems to be different in animals and humans. In animals, depressed insulin secretion is primarily responsible, while in human insulin secretion is not impaired (Kuo et al., 1996). Hyperinsulinaemia in addition to hyperglycaemia in hyperthyroidism suggests that insulin resistance is the underlying factor (Pandolfi et al., 1996). Insulin resistance in hyperthyroidism has been explained by the hyper secretion of glucagon, increased number of glucagon receptors, and reduced glucose uptake in the muscle. Impairment of carbohydrate metabolism in hyperthyroid subjects has been well established by various studies (Kuo et al., 1996; Pandolfi et al., 1996; Kawakubo et al., 1994; Ikeda et al., 1990). In the present study the prevalence of glucose intolerance in hyperthyroid state was 35% and no diabetes mellitus, which is similar to study by Roubanthisuk et al., 2006. While Ohguni et al., 1995 observed normal glucose and increased plasma insulin in patients with hyperthyroid Graves' disease, where as in our study normal fasting insulin levels observed in 80% of the hyperthyroidism patients. Owecki et al., 2008 observed inverse correlation between insulin and FT4 only but not with FT3 or TSH in profound hypothyroidism (Owecki et al. 2008). while in the present study there is inverse correlation between insulin and T4 and positive correlation between insulin and TSH but not statistically significant. (p=0.404, p=0.996 respectively) Fasting glucose level was 24% lower and the blood lactate levels was 35% lower in the untreated hypothyroid

myopathy patients than the euthyroid (Huey et al., 2004). While in the present study, the blood glucose was significantly increased at zero and two hours in hypothyroid patients as compared to the euthyroid patients. Hypothyroidism is associated with a reduction in glucose disposal to skeletal muscle and adipose tissue. Thyroid hormone has been shown to stimulate expression of the insulin sensitive glucose transporter (GLUT-4) and the levels of this transporter are reduced in hypothyroidism. Hypothyroidism is also, however, associated with reduced gluconeogenesis. The net effect of these influences is usually a minimal effect on serum glucose levels. Thyroid hormone down-regulates expression of prohormone processing enzymes, which, therefore, have increased activity in hypothyroidism. Degradation of insulin, therefore, is slowed and the sensitivity to exogenous insulin may be increased (Ganang et al., 2010).

Our results demonstrated that fasting blood glucose and postprandial blood sugar level increase in both hyperthyroid and hypothyroid groups as compared to euthyroid groups and an increase in the fasting insulin levels in hyperthyroid and hypothyroid patients was noted as compared to the euthyroid patients. In euthyroid state all patients had normal blood glucose levels at both 0 and 2 hours, where as in hypothyroid state 55% and 60% of the patients had impaired glucose tolerance at 0 and 2 hours, and in hyperthyroid state 60% of patients had normal blood glucose levels on fasting as well as on postprandial. Only 40% and 35% of patients had impaired glucose at 0 and 2 hours. All euthyroid patients had normal

insulin levels. While only 10% of the hypothyroid and 20% of the hyperthyroid patients had insulin levels more than 8 μ U/ml. The role of insulin in glucose intolerance of hyperthyroidism has been studied by several workers with conflicting results. However, Mano T and others observed glucose and insulin values in the Graves' disease were twice as high as in the normal. The present study showed increased glucose and insulin levels in hyperthyroid patients. Mean fasting plasma glucose and insulin levels were significantly higher in the hyper thyroid patients (Jap et al., 1989). Present study shows the postprandial mean plasma glucose level was significantly higher in hyperthyroidism ($p < 0.001$), insulin levels increased but was not significant. Hypothyroidism patients also showed increased insulin levels and raised serum glucose levels at both zero and two hours. It is concluded, that insulin sensitivity is decreased and the metabolic clearance rate with the secretion of insulin is accelerated with a correlation with plasma free T4 levels in hyperthyroidism (Ohguni et al., 1995). As per Roubansathisuk study hyperthyroid patients 39.4% had glucose intolerance. This was significantly higher than that of 30.7% in healthy subjects.

Conclusion

The higher values were observed for fasting plasma insulin and glucose levels in the hypo and hyperthyroid subjects on comparison with euthyroid subjects, on diagnosis thyroid status strict follow up should be done for fasting glucose and insulin levels, so that the comparison can be detected early. This would be a milestone in management of thyroid status and its associated complications especially hyperthyroid and hypothyroid status

Limitations

This is a hypothesis generating study and further work needs to be done in a large scale population.

Recommendation

This study has done on rural population, to predict better results; urban population also should be included.

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Author's contribution and competing interests

Dr. Raja Reddy P.: Concept and Design of the study, analysis and interpretation, manuscript preparation, critical revision of the manuscript, and literature search.

Dr. Vinutha Shankar M.S.: Concept and Design of the study, clinical studies, manuscript preparation, and critical revision of the manuscript, data collection, statistical analysis, and literature search. Clinical studies, manuscript preparation, critical revision of the manuscript, data collection, statistical analysis, and literature search.

Nachal Annamalai: Concept and Design of the study, Clinical studies manuscript preparation, critical revision of the manuscript, statistical analysis, and literature search.

Anil N.S.: Data collection and analysis and data acquisition.

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