Indian J.Sci.Res. 7(1) : 155-158, 2016 ISSN : 0976-2876 (Print)
ISSN : 2250-0138 (Online)

STUDY OF INSULIN RESISTANCE IN SUBCLINICAL HYPOTHYROIDISM PATIENTS

RAHIMTAJ BASARIKATTI[a1] AND FARHEEN FATIMA[b]

[a]Department of Biochemistry, BMCH Chitragurga, Karnataka, India
[b]Department of Medical Microbiology, Tabuk University, KSA

ABSTRACT

To study the levels of fasting plasma glucose, fasting serum insulin values and presence of insulin resistance (HOMA) in subclinical hypothyroidism patients compared to healthy controls. There was significant increase in fasting serum insulin (p=< 0.001), HOMA 1 (p=< 0.001) and HOMA 2 (p=< 0.001) values between subclinical hypothyroidism patients and controls. This study suggests that subclinical hypothyroid patients have significant alterations in carbohydrate metabolism. Insulin resistance which is known risk factor for development of diabetes and cardiovascular consequences is observed in subclinical hypothyroid patients too.

KEYWORDS : HOMA, FPG, GLUT, Hypothyroidism

Primary hypothyroidism is a graded phenomenon with different levels of severity showing wide inter individual range of clinical and biochemical presentation. The earliest form of hypothyroidism called as subclinical hypothyroidism or mild thyroid failure is defined by an increased serum TSH level in the presence of normal concentrations of circulating thyroid hormones (Meier et al., 2001).

In some this represents an early stage of a progressive decline towards clinical (overt) hypothyroidism, in others, thyroid function test remains unchanged during follow up, or they might actually normalize. Appropriate recognition of patients at risk for progression allows early interventions and prevention of symptomatic disease (Chiu and Sherman,1997).

The most common etiology for subclinical hypothyroidism that can progress to clinical disease is autoimmune thyroiditis (Chiu AC 1997). Patients with a serum titer of antimicrosomal antibodies greater than 1:1600 and an elevated TSH have a 5% to 7% annual risk of developing clinical (overt) hypothyroidism, and higher incidences have been reported in patients with higher ranges of TSH levels. SCH has been linked with abnormalities of lipid metabolism (increased serum cholesterol and LDL-C) associated with increased risk of coronary heart disease (Meier et al., 2001).

Insulin resistance has traditionally been defined with a glucocentric view i.e., when a defect in insulin action results in fasting hyperinsulinemia to maintain euglycemia. Insulin resistance is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal circulating concentrations of insulin. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, followed by fasting hyperinsulinemia and ultimately, hyperglycemia (Eckel, 2008).

The major mechanism by which insulin activates glucose transport activity is by recruiting intracellular glucose transport proteins to the plasma membrane. Increased numbers of cell surface transporters augment facilitative diffusion of glucose into the cell, where glucose is rapidly phosphorylated by hexokinase and metabolized. Importantly, the glucose transport step is rate-limiting for insulin-stimulated glucose uptake and metabolism in peripheral target tissues under physiological conditions. Upon dissipation of the insulin signal, deactivation of glucose transport activity is the result of a reverse translocation of transporters back into the cell interior. The major insulin-responsive glucose transporter isoform is GLUT4, which is predominantly expressed in such target tissues as skeletal and cardiac muscle and adipose tissue. Given the rate-limiting role of plasma membrane transport in cellular glucose metabolism, GLUT4 defects could readily result in insulin resistance at the level of the glucose transport effecter system. These defects could involve either a decrease in cellular expression, diminished functional activity, or impaired translocation of GLUT4 to the cell surface.

Diminished expression of GLUT4 transporters constitutes an obvious mechanism of insulin resistance, since there will be fewer intracellular transporters available for recruitment to the plasma membrane. This in fact is an important abnormality in adipocytes. Reduced basal and

[1]**Corresponding author**

insulin-stimulated glucose transport rates in isolated adipocytes are accompanied by reduced expression of both GLUT4 proteins and the encoding mRNA in obesity, Type 2 diabetes (Hunter and Garvey,1998).

Whole-body sensitivity of glucose disposal to insulin in hypothyroid patients has been examined by euglycemic-hyperinsulinemic clamps and intra venous or oral administration of glucose and found to be normal, increased, or decreased . In the forearm muscles of hypothyroid patients, the sensitivity of glucose disposal to insulin was found to be normal, whereas in adipocytes isolated from hypothyroid patients and examined in vitro, the sensitivity of glucose oxidation to insulin was normal and that of glucose transport was decreased. In rats made hypothyroid, the responsiveness of glucose disposal to insulin was decreased in muscle but increased in adipocytes(Dimitriadis et al., 2006).

It is known that T_3 and insulin have a synergistic role in glucose homeostasis, since these hormones possess similar action sites in the regulation of glucose metabolism, at both cellular and molecular levels. It could therefore be hypothesized that a reduced intracellular content of T_3 could lead to an impaired insulin stimulated glucose disposal. Even subtle decreases in the levels of thyroid hormones within the physiological range have been shown to correlate inversely with the HOMA index (Maratou et al., 2009).

MATERIALS AND METHODS

A cross sectional study was conducted taking hypothyroid patients as cases and healthy subjects as controls from May 2011 to April 2012. The study cases and controls were selected from Bapuji Hospital and Chigateri Hospital, Davangere. Each participant gave an informed consent and this study was approved by the ethical and research committee of J.J.M. Medical College, Davangere to use human subjects in the research study.

A. Subjects

Based on inclusion and exclusion criteria a total number of 60 subjects (30 cases and 30 controls) were selected.

Inclusion Criteria

Clinically newly diagnosed, biochemically proved cases of hypothyroidism in the age group of 18-70 years, patients with signs and symptoms of goiter and myxedema.

Subclinical hypothyroidism patients with ((increased serum TSH and normal T_3 and T4 levels).

Normal values of thyroid profile considered for the study7. (T_3:70-204 ng/dl), (T_4:5.5-11.0 µg/dl), (TSH:0.4-4.2 µIU/ml)

Controls

Healthy euthyroid age and sex matched individuals without any major illness and not on any medications.

Exclusion Criteria

Patients with Diabetes, hypertension.Patients on thyroxine treatment, hypolipidemics, antiepileptic drugs, women on oral contraceptives.Pregnant women, previous thyroid surgeries, and other systemic illness like liver disorders and kidney disorders.

Under aseptic conditions blood was collected serum was seperated and T_3, T_4, TSH, insulin was estimated(chemiluminescent immunoassay)., fasting plasma glucose (Glucose oxidase (GOD-POD) method by semi-autoanaylzer).. HOMA 1(HOMA 1-IR = (fasting plasma glucose in mg/dl x fasting serum insulin in µIU/ml) / 405) was calculated with respective formulas. HOMA2-IR (updated homeostasis model assessment) was calculated using Microsoft Excel based HOMA-2 calculator.

Data Analysis

Statistical analysis was done with t-test and ANOVA test. For all the tests, a p-value of 0.05 or less was considered for statistical significance.

RESULTS

Mean concentration of TSH is increased in subclinical hypothyroidism patients as compared to controls and is highly significant ($p< 0.001$). There is no statistically significant correlation between T_3 and T_4 concentration in subclinical hypothyroidism patients as compared to controls.

There is significant increase in serum insulin concentrations, HOMA 1 and HOMA 2 values in subclinical hypothyroidism patients as compared to controls which is statistically significant ($p< 0.001$). FPG is not significantly altered (Table 1).

Comparison of Serum T_3, T_4, and TSH Between Controls and Subclinical Hypothyroidism Subjects

		T_3 ng/dl	T_4 µg/dl	TSH µIU/ml
Controls	Mean ±SD	112.2±19	8.11±1.71	2.04±0.817
Subclinical hypothyroidism	Mean ±SD	120.07±23.35	7.29±2.28	11.80±10.74
t test between Subclinical Hypothyroid & Controls	t value	1.429	-1.573	4.962
	p value	.159	.122	< 0.001
ANOVA TEST	F value	68.381	43.221	114.245
	p value	< 0.001	< 0.001	< 0.001

One way ANOVA p< 0.001 Highly significant p< 0.05- Not significant

Comparison of FPG, Insulin, Homa 1 and Homa 2 Between Controls and Subclinical Hypothyroidism Patients.

		FPG (mg/dl)	Insulin (µIU/ml)	HOMA 1	HOMA 2
Controls	Mean±SD	81.34±5.31	6.016±1.95	1.21±0.41	0.817±0.327
Subclinical hypothyroidism	Mean±SD	83.387±4.95	16.74±2.285	3.44±0.484	2.080±0.268
t test between Subclinical Hypothyroid & Controls	t value	1.537	19.544	19.155	16.357
	p value	.130	< 0.001	< 0.001	< 0.001
ANOVA TEST	F value	300.614	218.927	234.609	166.173
	p value	< 0.001	< 0.001	< 0.001	< 0.001

One way ANOVA showed that there is significant increase in of FPG, serum insulin, HOMA 1 and HOMA 2 between, subclinical hypothyroidism patients (p< 0.001) compared to healthy controls (Table 2).

DISCUSSION

Hypothyroidism affects 0.52.4% of the population. In the first stages it may go unnoticed as the symptoms may proceed insidiously. Before overt hypothyroidism is established, the only abnormality which may be detected is elevated serum thyrotropin (TSH). At this stage, when thyroid hormones are still in the normal range, the diagnosis of subclinical hypothyroidism is made. Several studies have shown that this disorder is quite common (10% in an elderly population) Michalopoulou et al., 1998.

Thyroid disease is associated with atherosclerotic cardiovascular disease This is undoubted for overt hypothyroidism, but there is controversy as to whether this association is also present in subclinical hypothyroidism The association of thyroid disease with atherosclerotic cardiovascular disease may in part be explained by thyroid hormone's regulation of lipid metabolism. Several cardiovascular risk factors cluster within the metabolic syndrome. Insulin resistance is supposed to be the central pathophysiological phenomenon underlying this clustering (Roos et al., 2007).

The HOMA model is used to yield an estimate of insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells. HOMA 2 updated version of the HOMA model accounts for variations in hepatic and peripheral glucose resistance (i.e, the reduction in the suppression of hepatic glucose output [by hyperglycemia] and the reduction of peripheral glucose estimated glucose uptake).

High risk individuals have demonstrated that the insulin resistance is the most prominent and earliest defect that can be detected in pre diabetic state confers high risk for subsequent evolution to overt diabetes (Iervasi et al., 2007).

Whole-body sensitivity of glucose disposal to insulin in hypothyroid patients has been examined by euglycemic-hyperinsulinemic clamps and intra venous or

oral administration of glucose and found to be normal, increased, or decreased. In the forearm muscles of hypothyroid patients, the sensitivity of glucose disposal to insulin was found to be normal, whereas in adipocytes isolated from hypothyroid patients and examined in vitro, the sensitivity of glucose oxidation to insulin was normal and that of glucose transport was decreased. In rats made hypothyroid, the responsiveness of glucose disposal to insulin was decreased in muscle but increased in adipocytes David and Sacks, 2006; Demers and Spencer, 2006.

CONCLUSION

Insulin resistance is considered to be most important risk factor for development of diabetes mellitus and future cardiovascular complications. Since thyroid hormones are major thermogenic hormones, a disturbance in their activity leads to major alteration in carbohydrate metabolism.

In our study there is marked increase in serum insulin levels in subclinical hypothyroidism patients. We observed presence of insulin resistance in subclinical hypothyroidism patients compared to controls. This signifies that thyroid hormones deficiency leads to major alterations in carbohydrate metabolism. We conclude that even subclinical hypothyroidism patients need continues monitoring of fasting glucose level and fasting serum insulin levels.

REFERENCES

Chiu A. C. and Sherman S. I., 1997. Clinical manifestations and differential diagnosis of hypothyroidism. In: Stephan A Falk editor. Thyroid disease, endocrinology, surgery, nuclear medicine and radiotheraphy. Second edition. Philadelphia. New York.Lippincot-Revan : 379-391.

David B Sacks, 2006. Carbohydrates. In:Burtis CA, Ashwood ER and Bruns DE,eds.Tietz textbook of clinical chemistry and molecular diagnostics,4th edn.New Delhi:Elsiever Co., : 837-901.

Demers L. M, and Spencer C., 2006. The Thyroid, pathophysiology and thyroid function testing. In: Burtis CA, Ashwood ER and Bruns DE,eds.Tietz textbook of clinical chemistry and molecular diagnostics,4th edition. New Delhi:Elsiever Co., 2053-2095.

Dimitriadis G., Mitrou P., Lambadiari V., Boutati E., Maratou E. and Panagiotakos D. B., 2006. Insulin action in adipose tissue and muscle in hypothyroidism.J Clinical Endocrinol metab 2006;92:4930-493.

Eckel R. H., 2008. The metabolic syndrome. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL Jameson J. L. et al., editors. Harrison's Principles of Internal Medicine vol 1, 17th edition. New York: McGraw Hill Co; 2008: 1509-13.

Hunter S. J. and Garvey W. T., 1998. Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction, and the glucose transport effector system. Am J Med **105**:331-345.

Iervasi G., Molinaro S., Landi P., Taddei M. C., Galli E., Mariani F., L'Abbate A. and Pingitore A., 2007. Association between increased mortality and mild thyroid dysfunction in cardiac patients. Arch Intern Med., **167**(14):1526-1532.

Maratou E., Hadjidakis D. J., Kollias A., Tsegka K., Peppa M. and Alevizaki M., 2009. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. European Journal of Endocrinology, **160**: 785-790.

Meier C., Staub J., Roth C., Gudlielmetti M., Kunz Maya, Miserez A. R., Drewe J., 2001. TSH-controlled L-Thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind, placebo-controlled trail (basel thyroid study). J of Clin Endocrinol Metab 2001;**86**:4860-4866.

Michalopoulou G., Alevizaki M., Piperingos G., Mitsibounas D., Mantzos E., Adamopoulos P. and Koutras D. A., 1998. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? European Journal of Endocrinology :138;141-145.

Roos A., Bakker SJL, Links T. P., Gans ROB and Wolffenbuttel BHR, 2007. Thyroid function is associated with components of metabolic syndrome in euthyroid subjects .J Clin Endocrinol Metab **92** : 491-496.