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Review Article

Insulin Resistance as a consequence of Hypothyroidism. A review article on effect of thyroid hormones on glucose homeostasis.

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Abstract : Thyroid gland is the foremost endocrine gland of the body. It controls metabolism, development, growth and maintenance of the body. Imbalance in secretions of thyroid hormones affects almost every aspect of health and metabolism. Disturbances in glucose homeostasis is obivious. Thyroid hormones have effect on glucose metabolism and probably on the development of insulin resistance (IR). Recently hypothyroidism has been linked to increased insulin resistance or decreased insulin sensitivity. The aim of this article is to review the earlier research work showing the effect of thyroid hormone deficiency on glucose metabolism, insulin levels and insulin resistance in hypothyroidism, to get a better perspective on association between hypothyroidism and insulin resistance.

Key Words: Hypothyroidism, Thyroid hormones, Insulin resistance, Glucose homeostasis

Introduction

Approximately 300 million people, all around the world are suffering from thyroid abnormalities. About 42 million among them are present in India[1]. The prevalence of hypothyroidism is 4-15% in India and risk is three times more in females 15.8% as compared to the males 5% [2]. Thyroid gland produces two main hormones tri-iodothyronine (T3) and thyroxine (T4). These hormones are regulated by thyroid stimulating hormone (TSH), released by anterior lobe of the pituitary gland and TSH is under the control of thyrotropin releasing hormone (TRH) of hypothalamus. Hypothyroidism is a common disorder of thyroid hormone deficiency. It is further categorized on the basis of onset of the disease, level of endocrine dysfunction and severity of the disease. Hypothyroidism can be easily diagnosed by the measurement of thyroid hormones T3 and T4 along with TSH levels. Low levels of T3 hormones are especially responsible for the clinical and biochemical indications of the disease. Patients exhibit symptoms like tiredness, fatigue, cold, weight gain and dryness of skin which are helpful in the diagnosis of the condition [3]. Thyroid disorders and Diabetes Mellitus are interconnected. The prevalence rate of Diabetes mellitus is high in patient suffering from thyroid disorders [4-6]. Patients with hypothyroidism showed 40% higher prevalence of Diabetes Mellitus compared to control group [6].

Effect of Thyroid Hormones on Glucose Metabolism

In body, plasma glucose levels are regulated by entry and removal of glucose from the circulation. Glucose enters in the circulation from intestinal absorption during the well fed state, glycogen

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breakdown and gluconeogenesis. The rate of glucose entry in the circulation is mainly determined by the rate of gastric emptying while glycogenolysis and gluconeogenesis are other main sources of circulating glucose [7]. Glucose homeostasis is a well regulated process to maintain normal life in mammals. This is achieved by maintaining a balance of several hormones and neuropeptides which are synthesized or released from the brain, liver, intestine, pancreas, adipose and muscle tissue [8]. Thyroid hormones are well known to affect plasma glucose homeostasis. Thyroid hormones have been reported to have role in pancreatic β-cell development and influence metabolism of glucose involving several organs. (Fig-1).

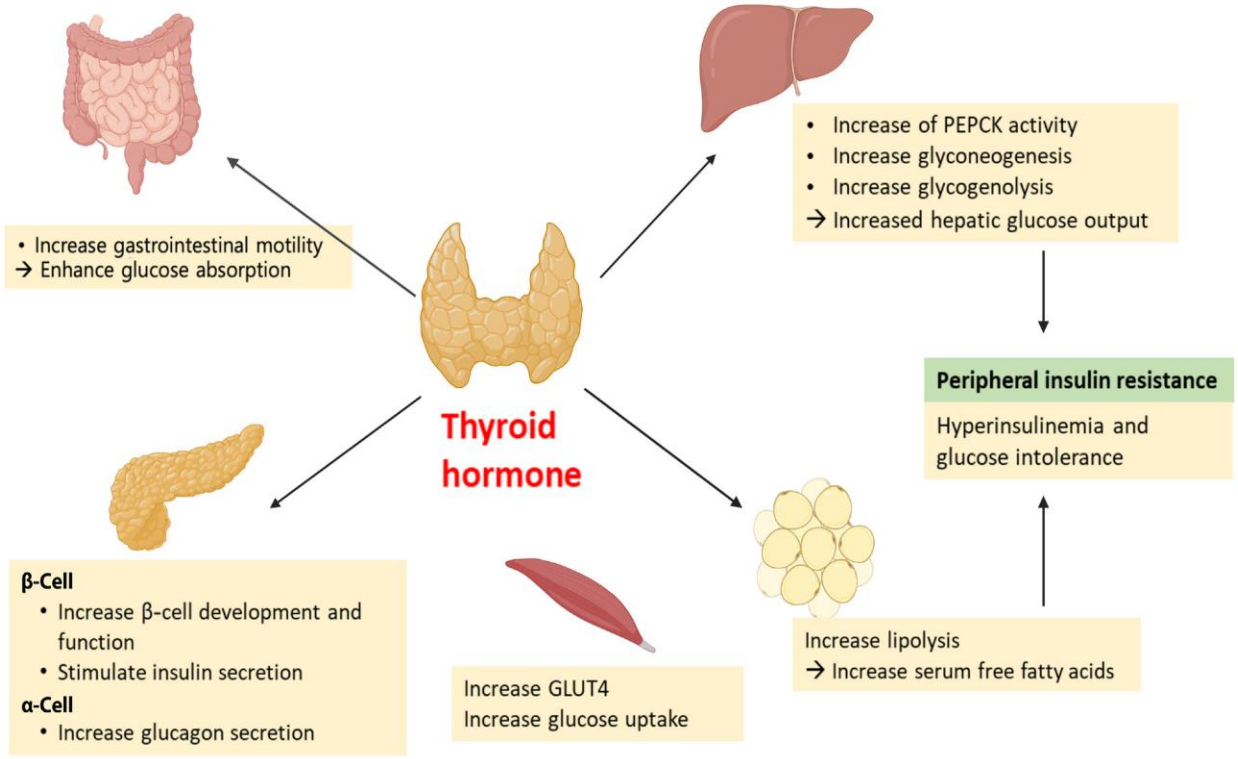

Fig.1 Effects of thyroid hormone on glucose homeostasis. PEPCK, phosphoenolpyruvate carboxykinase, GLUT4, glucose transporter type 4 [9]

Thyroid hormones have important role in metabolism of carbohydrates by stimulating hepatic gluconeogenesis, glycogenolysis and enhacing the expression of (GLUT-4) and phosphoglycerate kinase enzyme. Thus it facilitates the uptake and utilization of glucose in peripheral tissues, acting collectively with insulin [10-13]. Thyroid hormones and insulin show collaborative role in maintaining glucose homeostasis at cellular as well as molecular level [14]. Thyroid hormones act as Insulin agonist at Pheripheral tissue level and show antagonist action at the liver that lead to increased hepatic glucose output. In addition to already existing mechanisms some new pathways involved in the maintenance of glucose homeostasis regulated by thyroid hormones have also been discovered. New findings include the stimulation of hepatic glucose production in response to thyroid hormones acting via the sympathetic pathway from the hypothalamus [15] and the identification of transcriptional regulators of metabolic as well as mitochondrial genes that are under the influence of intracellular T3 levels [16]. T3 can regulate the production of glucose

through a sympathetic pathway from hypothalamus to liver. It is independent of glucoregulatory hormones. Several genes have been identified that are under the regulation of thyroid hormones and are involved in glycogen metabolism, gluconeogenesis and also insulin signaling.

Table 1: Effects of T3 hormone on different genes that regulate glucose homeostasis at different sites such as liver and peripheral tissues [17].

Gene	Expression	Site	Net effect
glucose-6-phosphatase	Increase	liver	Increase gluconeogenesis and glycogenolysis
protein kinase B (Akt2)	decrease	liver	Decrease glycogen synthesis
β2-adrenergic receptor	Increase	liver	Increase gluconeogenesis and glycogenolysis
inhibitory G protein (Gi)	decrease	liver	Increase gluconeogenesis and glycogenolysis
phosphoenolpyruvate carboxykinase	Increase	liver	Increase gluconeogenesis
pyruvate carboxylase (PC)	Increase	liver	Increase gluconeogenesis
GLUT2	Increase	liver	Increase glucose output
malic enzyme	Increase	liver	lipogenesis
Carbohydrate-response element-Binding protein (ChREBP)	Increase	liver	lipogenesis
		Fat tissues	
GLUT1	Increase	peripheral tissues	Increase glucose transport (basal)
GLUT4	Increase	peripheral tissues	Increase glucose transport (insulin-induced)
β2-adrenergic receptor	Increase	Peripheral tissues	Increase lipolysis
phosphoglycerate kinase (PGK)	Increase	peripheral tissues	Increase glycolysis
Hypoxia-inducible factor 1 (HIF-1α)	Increase	peripheral tissues	Increase glycolysis
PPAR gamma coactivator-1 alpha (PGC-1 alpha)	Increase	peripheral tissues	Increase mitochondrial biogenesis & function
uncoupling protein 3 (UCP3)	Increase	peripheral tissues	Increase mitochondrial energy expenditure

Effect on Insulin Secretion

Many studies supported that Insulin level is increased in Hypothyroidism [18-21]. Thyroid hormones influence the secretion of insulin and uptake of glucose via differing effects in the liver, gastrointestinal tract, skeletal muscles and adipose tissue. Thyroid Hormones enhances gastrointestinal motility leads to increased glucose absorption [22]. In pancreas thyroid hormones are responsible for increased beta cell development and function. It also stimulates insulin secretion [23]. Also stimulated glycogenolysis and gluconeogenesis leads to hyperinsulinemia and glucose intolerance, which results in peripheral insulin resistance [22]. In liver, it enhances glucose output by increased hepatic expression of (GLUT2) which stimulates the production of glucose in the body by increasing gluconeogenesis and glycogenolysis. T3 hormone also enhances hepatic gluconeogenesis by increasing phosphoenolpyruvate carboxykinase (PEPCK) enzyme activity [24,25]. In Adipose tissue, thyroid hormones increases lipolysis, hence increased free fatty acids. As a result of increased hepatic glucose output and Free Fatty Acids at tissue level, hyperinsulinemia is observed leads to Insulin resistance [26].

Insulin Resistance as a concequence of Hypothyroidism

A nice balance of glucose homeostasis is maintained by thyroid hormones, acting as both insulin agonistic and antagonistic. To maintain the state of glucose homeostasis in the body, pancreatic β-cells try to compensate by enhancing insulin secretion, leading chronic hyperinsulinemia.. Hypothyroidism break this equilibrium and alter the glucose metabolism, which can further lead to insulin resistance [17]. Insulin resistance is the main patho-physiological phenomenon responsible for metabolic syndrome, which is a cardiovascular risk factor [27]. Previous studies have reported overt hypothyroidism as one of the risk factor for insulin resistance [28,29]. Insulin resistance

plays a important key role in the pathogenesis of Type II Diabetes Mellitus. Thyroid function is related with insulin resistance in clinically diagnosed patients of Diabetes Mellitus as well as in individuals with a normal glucose tolerance [30,31]. There is no unanimous definition for the term Insulin Resistance, still this can described as decreased metabolic response of the liver and peripheral tissues such as muscular and adipose tissue for the present Insulin hormone as compared to the normal healthy individual [32,33].The decreased sensitivity to Insulin could be estimated by reduced insulin dependent uptake of glucose by all the tissues [34]. In vitro studies acknowledged that tri-iodothyronine (T3) rapidly increases the uptake of glucose in muscle cells without increasing the surface transporters such as GLUT4, GLUT1 and GLUT3, they supposed that rapid uptake of glucose is due to activation of GLUT4 transporters at the cell surface. A positive correlation was observed for TSH with Homeostatic Model of Assessment of Insulin Resistance (HOMA IR) [35]. As earlier reported by some researchers that thyroid hormones and insulin have collaborative role in maintenance of glucose homeostasis at both cellular and molecular level. They hypothesised that decreased level of thyroid hormones, impairs glucose uptake which is stimulated by insulin [14]. It is also observed that in hypothyroidism, flow mediated endothelial vasodilation in impaired which is responsible for insulin resistance [36]. According to the evidences reported in the literature, hypothyroidism is correlated with fasting Insulin levels, HOMA IR and Diabetes [37].

Several studies were performed to establish a correlation between subclinical hypothyroidism and effects of insulin on glucose regulation [18-21]. Available literature, supported that Subclinical Hypothyroidism is associated with increased Insulin Resistance [38]. Some studies on subclinical hypothyroidism found only significant increase in insulin levels, but no significant change was found in insulin resistance [21]. Intracellular T3 influences some transcriptional regulators of mitochondrial genes, and are also responsible for the development of insulin resistance [16].
Appropriate functioning of thyroid gland is important to prevent many diseases, especially cardio metabolic diseases. Insulin resistance indicates a main key pathogenic mechanism of cardio-metabolic diseases, and its prevention is necessary in the current dominance of cardio-metabolic diseases in overall rate of mortality [39,40].

Measurement of Insulin Resistance

A most common method used for measurement of Insulin Resistance in clinical practice is Homeostatic Model of IR (HOMA-IR), using fasting plasma glucose and fasting Insulin concentration. Homeostatic model index (HOMA IR=fasting insulin (µIU/ml) x fasting glucose (mmol/L) / 22.5 [41]. Even fasting insulin levels itself can reflect insulin resistance to some extent [42].

Contrast Findings

The available data related to insulin sensitivity and resistance in the condition of thyroid hormone deficiency is controversial [43-45]. Thyroid Hormones stimulates the secretion of insulin and causes hyperinsulinemia, although in thyrotoxicosis insulin degradation is rapid due to decreased half-life of insulin [46]. The study including i.v. insulin tolerance test was done to determine insulin sensitivity in patients suffering from acute overt hypothyroidism. In Comparison to euthyroid controls, hypothyroid patients showed a significantly lower glucose disposal [18]. In contrary there are findings supporting no significant difference of Insulin resistance in Euthyroid and Hypothyroid [47] Few negative results, have also been reported. A preceding study in overt hypothyroid patients formulated on the homeostasis model assessment (HOMA-IR) [48] not

showed any association between insulin sensitivity and hypothyroidism. Furthermore, some researchers reported that after treatment of hypothyroid patients with levothyroxine, unimpaired insulin-stimulated glucose disposal is observed in the forearm of patients [49]. In subclinical hypothyroidism, insulin resistance has been reported [50] but not in all studies, where HOMA levels were found comparable to Euthyroids [47,51,52]. It is important to mention that hyperinsulinemia that was reported in subclinical hypothyroidism was represented as an early sign of impairment normal metabolism of glucose.

Conclusions

Glucose homeostasis and insulin level is undoubtedly affected by the thyroid hormones. Many studies favours that insulin resistance, specially in peripheral tissues is observed in Hypothyroidism. Contrasting, many studies observed increased insulin secretion in Hypothyroidism with no change in Insulin resistance. Results are diferrent and contrast, this may be due to short sample size, difference in the average TSH level and neglecting the other confounding factors. Somewhere insulin resistance is mentioned same in subclinical and overt hypothyroidism. This indicates thyroid hormone may not be only responsible factor for the manifestations. Although majority agree that either insulin level or its signaling pathway is disturbed. Therefore, further research is needed to confirm the level of Insulin, and insulin resistance which may shed light on the association between insulin resistance and hypothyroidism. Still, screening of hypothyroid patients for insulin resistance may be helpful in early detection of comorbidities associated with the disease.

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