International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (966-971), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Association between Thyroid Hormones Changes and Development of Type 2 Diabetes: (Systematic Review)

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Abstract: **The aim of this review was to evaluate the Association between thyroid hormones changes and development of diabetes mellitus, through review the literatures concerning this matter. We intended to investigate whether diabetic complications were more prevalent in thyroid disease or dysfunction. We conducted comprehensive review among PubMed, EMBASE, and Web of Science, databases for literature search. We obtained studies published between up to December, 2016. The studies were selected to evaluate relation and impact of thyroid disease or hormonal changes on development of Diabetes, only studies with human subjects, and published in English language were included to our review other than that were excluded immediately. Evidence recommend that low and low-normal thyroid function belong to an increased risk of diabetes. In individuals with prediabetes and low-normal and low thyroid function, the risk of development to diabetes seems more popular. Our review included routes that insights into the magnitude of the risk of diabetes and prediabetes associated with variations of thyroid function within the regular range. Subsequent research studies might deal with possible screening and treatment methods for both diabetes and thyroid dysfunction.**

Keywords: **Diabetes, prediabetes, treatment methods.**

1. INTRODUCTION: (LITERATURE)

Diabetes is the most common chronic endocrine disease defined by hyperglycemia resulted from impaired insulin secretion and/or insulin action [(1)]. Chronic diabetic hyperglycemia is connected with long-term organ dysfunction, damage and failure. Issues, such as vision loss, renal failure and heart diseases, are frequently outcomes of diabetes [(2,3)]. As the population ages and weight problems increases, diabetes will increase too. The international prevalence is anticipated to be 11.1% in 2033, impacting 600 million people [(4)]. Many epidemiological studies show the greater occurrence of obvious hypothyroidism in type 2 diabetes mellitus (T2DM) population than in the basic population [(5,6)]. The relationship between hypothyroidism and T2DM is questionable. Hypothyroidism, the small hypothyroidism state, is mild but asymptomatic elevations in thyroid-stimulating hormonal agent (TSH) with regular circulating complimentary thyroid hormonal agent concentrations are observed [(7)].

Hypothyroidism is a scientific syndrome caused by decreased thyroid hormone secretion from the thyroid gland. Subclinical hypothyroidism is identified when thyroid hormone levels are within the typical recommendation variety (0.45 - 4.5 mIU/L), but thyroid stimulating hormone (TSH) is elevated and overt thyroid disease is diagnosed when the serum thyroid hormone levels (free T4, with or without T3) are unusual. Subclinical hypothyroidism is categorized as slightly elevated TSH (4.5 - 10 mIU/L) or noticeably raised TSH (≥ 10 mIU/L) with normal fT4 levels in both classifications [(4)].

Hyporthyroidism is more typical in females than males and its occurrence increases with age [(8)]. Subclinical hypothyroidism (SHT) is the most typical thyroid dysfunction and is generally asymptomatic; nevertheless, findings suggestive of hypothyroidism might be seen in 30% of patients (9). Some studies suggested that the upper typical TSH limitation can be lowered which level about 2.0-2.5 mU/L [(10,11)].

The role of hyperthyroidism in diabetes was investigated in 1927, by Coller and Huggins proving the association of hyperthyroidism and worsening of diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients experiencing coexisting diabetes [(12)]. There is a deep underlying relation between diabetes mellitus and thyroid dysfunction [(13)]. A myriad of research studies has actually evidenced a range of intricate linking biochemical, genetic, and hormone malfunctions mirroring this pathophysiological association [(13,14)]. 5 ′ adenosine monophosphate-activated protein kinase (AMPK) is a main target for modulation of insulin level of sensitivity and feedback of thyroid hormonal agents related to hunger and energy expense [(14)]. Hypothyroidism (Hashimoto's thyroiditis) or thyroid over activity (Graves' disease) has been examined to be related to diabetes mellitus. A meta-analysis reported a frequency of 11% in thyroid dysfunction in the patients of diabetes mellitus [(15)]. Autoimmunity has actually been implicated to be the significant reason for thyroid-dysfunction associated diabetes mellitus [(16)].

The aim of this review was to evaluate the Association between thyroid hormones changes and development of diabetes mellitus, through review the literatures concerning this matter. We intended to investigate whether diabetic complications were more prevalent in thyroid disease or dysfunction.

2. METHODOLOGY

We conducted comprehensive review among PubMed, EMBASE, and Web of Science, databases for literature search. We obtained studies published between up to December, 2016. The studies were selected to evaluate relation and impact of thyroid disease or hormonal changes on development of Diabetes, only studies with human subjects, and published in English language were included to our review other than that were excluded immediately.

3. RESULTS

➢ **Peripheral Effects of Thyroid Hormones on Insulin Secretion and Sensitivity and therefore diabetes development:**

Thyroid hormones directly control insulin secretion. In hypothyroidism, there is a decrease in glucose-induced insulin secretion by beta cells, and the reaction of beta cells to glucose or catecholamine is increased in hyperthyroidism due to increased beta cell mass. Insulin clearance is increased in thyrotoxicosis [(17,18)].

Increased glucose output from liver is the critical reason for the induction of hyperinsulinaemia, induction of glucose intolerance, and development of peripheral insulin resistance [(19)]. Glucose tolerance in thyrotoxicosis is caused by raised hepatic glucose output along with upregulated glycogenolysis [(18)]. This phenomenon is responsible for worsening of subclinical diabetes and exaggeration of hyperglycaemia in T2DM. Thyrotoxicosis may lead to ketoacidosis likewise due to raised lipolytic actions and increased hepatic β oxidation (**Figure 1**) [(20,21)].

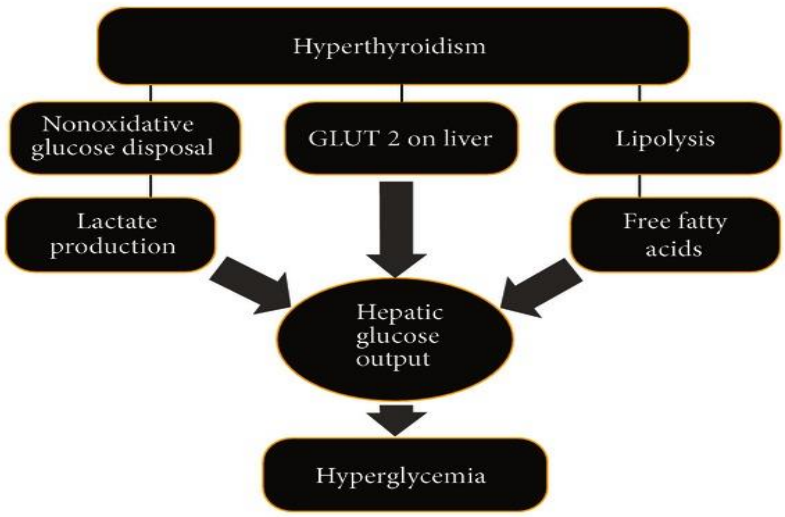

Figure1: The relation between hyperthyroidism and hyperglycemia via lipid metabolism oxidative stress and hepatic dysfunction. [(21)]

Reduced glucose absorption from intestinal system accompanied by extended peripheral glucose build-up, gluconeogenesis, decreased hepatic glucose output and decreased disposal of glucose are trademarks of hypothyroidism [22]. In obvious or subclinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion [23]. In subclinical hypothyroidism, decreased rate of insulin stimulated glucose transport rate caused by annoyed expression of glucose transporter type 2 gene (GLUT 2) translocation might lead to insulin resistance. Furthermore, due to lowered kidney clearance of insulin in hypothyroid conditions, physiological requirements of insulin were lessened. Anorectic conditions in hypothyroidism might likewise contribute to decreased insulin in this state. An improved dosage of insulin is needed to ameliorate hypothyroidism, but the therapy warrants caution for pituitary or adrenal failure (**Figure 2**) [21,24].

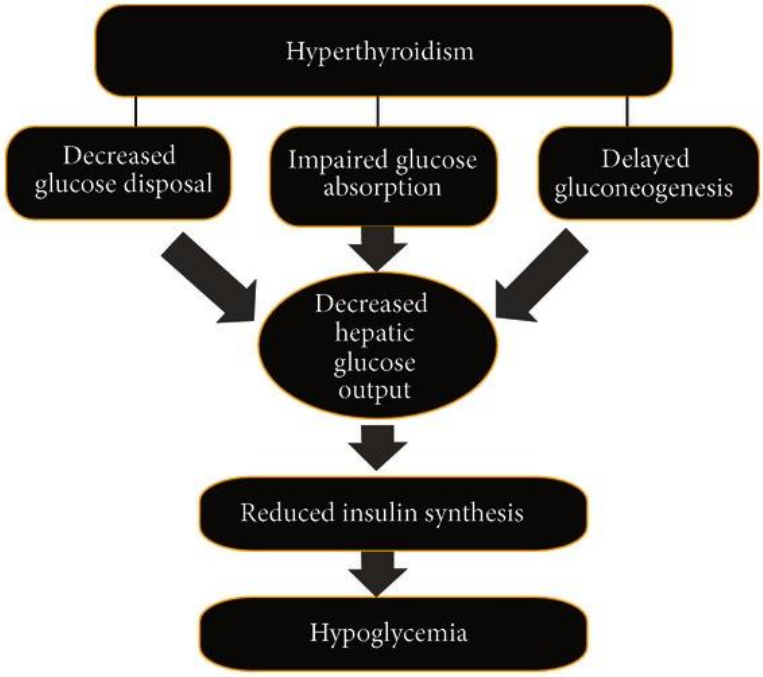

Figure 2: The relation between hypothyroidism and hypoglycemia mediated by reduced insulin synthesis and impaired hepatic glucose output.

- ***Relation between the Hyperthyroidism and T2DM:***

Insulin secretion, and change in the β-cell mass [25]. Even more, signs likewise include increased insulin deterioration [26], increased glucagon secretion [27], increased hepatic glucose production, boosted catecholamines, and insulin resistance [28]. These factors have actually been investigated to be an integral part of hyperthyroidism too [29]. An intersection of pathological basis occurs which gives us hint to an array of physiological aberrations which are typical in hyperthyroidism and T2DM. Amongst the above-mentioned symptomatology, insulin resistance has actually been the most important facet linking thyroid dysfunction and T2DM. Insulin resistance is a condition which happens in both hypothyroidism and hyperthyroidism [30].

Insulin resistance in the muscles and liver is a particular feature of T2DM. An undisturbed glucose homeostasis and undamaged insulin secretary response and undisturbed level of sensitivity of the tissues to insulin are essential to keep regular blood sugar levels [31].

Glucose disposal is moderated by the conjoint impact of insulin and hyperglycemia to modulate three fundamental phenomenon. Diminution of endogeneous (hepatic) glucose production. Secondarily, boosted uptake of glucose (hepatic and splanchnic). Finally, upregulation of glucose by peripheral tissues (skeletal muscles). Glucose uptake into muscles is modulated by glycolysis and glycogen synthesis. Hepatic insulin resistance is defined by glucose overproduction inspite of fasting hyperinsulinemia, and enhanced rate of hepatic glucose output was the essential modulator of increased fasting plasma glucose (FPG) concentration in T2DM topics [27]. In insulin resistance in the postabsorptive state, muscle glucose is upregulated but the performance of uptake is lowered. In the wake of such conditions, minimized glucose uptake into the muscles and enhanced hepatic glucose output cause worsening of glucose metabolism.

The term unified quartet is utilized to address the core pathology of insulin resistance [27]. Deregulated glucose disposal and metabolism in adipocytes, muscles, and liver, in addition to impaired insulin secretion by the pancreatic beta cells, constitute the four major organ system irregularities which play a definitive function in the pathogenesis of T2DM. It is worth thinking about that insulin resistance has actually been a proven condition in hyperthyroidism in addition to hypothyroidism. Insulin resistance also results in impaired lipid metabolic process according to current findings [32]. Thus, it appears that insulin resistance is the possible link in between T2DM and thyroid dysfunction.

Insulin resistance and β cell function are inversely associated with thyroid stimulating hormone which might be discussed by insulin-antagonistic impacts of thyroid hormonal agents together with an increase in TSH. The greater serum TSH normally corresponds to decrease thyroid hormonal agents by means of negative feedback mechanism. As TSH increased, thyroid hormones reduced and insulin antagonistic results are damaged. These observations show that insulin imbalance is closely connected with thyroid dysfunction and the phenomenon id mediated via β cell dysfunction [33].

- **Roles of Hyperthyroidism and Subclinical Hyperthyroidism in insulin resistant:**

Hyperthyroidism has been related to insulin resistance which has actually been linked with raised glucose turnover, increased intestinal glucose absorption, raised hepatic glucose output, increased complimentary fatty acid concentrations, increased fasting and or postprandial insulin a proinsulin levels, and increased peripheral glucose transportation accompanied by glucose usage [34]. T2DM patients with thyroid dysfunction have been proven to be more susceptible to ketosis [35] and ketogenesis [36]. Insulin resistance has been revealed to be related to subclinical hypothyroidism, which is in turn linked to impaired lipid balance and risk of advancement of metabolic syndrome [37,38]. Despite the fact that there are lots of cross-sectional reports studying the occurrence of diabetes and thyroid dysfunction, only couple of have investigated the association of thyroid function with the occurrence of diabetes and all were register-based research studies. Our outcomes remain in contrast to a Danish across the country registry research study by Brandt et al [39] that reported an increased risk of diabetes in hyperthyroid people, whereas we did not discover an increased risk of diabetes with higher thyroid function. However, there are several factors that could describe these distinctions, consisting of difference in the mean age and possible iodine status of the studied population. Two other register-based studies report an increased risk of diabetes in hypothyroid people [40,41]. There are a number of paths that may describe the observed relation in between low and low-normal thyroid function and the risk of diabetes. Subclinical and obvious hypothyroidism are related to a reduced insulin sensitivity and glucose tolerance, partially due to a decreased capability of insulin to increase glucose usage primarily in muscle [42]. Other mechanisms, such as downregulation of plasma membrane glucose transporters and direct impacts on insulin deterioration, have actually also been described [43,44].

4. CONCLUSION

Evidence recommend that low and low-normal thyroid function belong to an increased risk of diabetes. In individuals with prediabetes and low-normal and low thyroid function, the risk of development to diabetes seems more popular. Our review included routes that insights into the magnitude of the risk of diabetes and prediabetes associated with variations of thyroid function within the regular range. Subsequent research studies might deal with possible screening and treatment methods for both diabetes and thyroid dysfunction.

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