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Review

Biochemical isthmus [nexus] between type 2 diabetes mellitus and thyroid status—an update

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ABSTRACT

Both Type 1 [T1DM] and Type 2 diabetes mellitus [T2DM] share a nexus with altered thyroid status. In recent times, evidences point to the link between thyroid hormones andT2DM in particular. Several lines of evidences suggest an array of biochemical and molecular events. Gene polymorphism, disturbances in gene expression and regulation, enhanced and bizarre absorption of dietary glucose from intestine, decreased utilization of glucose by tissues and aberrations in hepatic handling of glucose with the onus on Gluconeogenesis are some of the projected mechanisms. Insulin resistance, a progressive condition is the hallmark in T2DM. Hypothyroidism as well as hyperthyroidism have been associated with insulin resistance which are synonymous with impaired glucose metabolism in T2DM. A multitude of basic, clinical and molecular studies provide an insight into thyroid comorbidity in T2DM, though there are a few instances to suggest equivocal link denoting cause-effect relationship. In biochemical pharmacology, as fortified by pharmacogenomics, modalities have now been proposed, through drug trials, to underline the utility of specifically designed thyroid hormone analogues in addressing metabolic syndrome, DM and associated cardiovascular pathology. A thorough understanding of the physiological, biochemical and molecular mechanisms would certainly open newer vistas in the perspectives of T2DM with special reference to alterations in thyroid status.

1. Introduction

The credit accrues to Coller and Huggins for citing the association between hyperthyroidism and aggravating diabetes mellitus. They demonstrated elegantly that the surgical resection of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients suffering from diabetes mellitus [1]. Studies have revealed that autoimmunity is a major cause of alterations in thyroid function associated with diabetes mellitus [2,3].

There is a deep nexus between diabetes mellitus and thyroid dysfunction [4]. There seems to be complex mechanisms that account for the comorbidity [4,5]. Mention must be made of adenosine monophosphate activated protein kinase [AMPK] that is regarded as a pivotal target for insulin sensitivity and also feedback mechanism of thyroid hormones associated with appetite, satiety and energy [5]. Hashimoto's thyroiditis and Graves' disease have also been linked with diabetes mellitus.

Inappropriate secretion of insulin attributed to defective islet cell function or beta cell mass is the key to DM. Various factors aggravate this endocrine condition that include binge eating, consumption of empty calories and sedentary lifestyle that eventually culminate into diabetes. A projected 300 million people would suffer from DM by the year 2020 unless aggressive measures to curb this metabolic and endocrine disorder are initiated globally [6].

Defective insulin secretion exacerbated by insulin resistance is the cause for a plethora of metabolic aberrations observed in T2DM. Insulin mediated glucose transport in adipose tissue, skeletal muscle and cardiac muscle is the major biochemical worry that culminates in hyperglycemia. Enhanced hepatic output of glucose with associated dyslipidemia adds to the misery [7].

Epidemiologic data also is in support of the pronounced thyroid comorbidity observed in DM. The Wickham survey conducted in England denotes a significant prevalence of thyroid dysfunction in adult males [8]. According to another prevalence study, 9.5% of participants were found to have enhanced tropic hormone levels [TSH], while 2.2% had a low TSH. NHANES III study signified hypothyroidism and hyperthyroidism, as exemplified by 4.6% and 1.3%

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of the total participants respectively [9]. The prevalence of thyroid dysfunction advances with age globally and frequency of prevalence was higher in women than men. Subclinical hypothyroidism also has also been reported. The prevalence of subclinical hypothyroidism is reported and has been observed to be high in elderly women [> 60 years]. The prevalence of subclinical hyperthyroidism is reported to be approximately 2%.The prevalence of altered thyroid function in DM was reported to be 13.4% with higher prevalence in females [10]. Considerably, T2DM patients are more prone to developing thyroid disorders.

1.1. Metabolic effects of thyroid hormones and their implications in insulin sensitivity and insulin resistance

Thyroid hormones regulate carbohydrate metabolism as well as processes related to insulin secretion. Thyroid hormones directly control insulin secretion. In hypothyroidism, there is a decline in glucose-induced insulin secretion by pancreatic beta cells. On the contrary, the response of pancreatic beta cells to glucose or catecholamine is increased in hyperthyroidism that is attributed to increased beta cell mass. Insulin clearance is enhanced in the hyperthyroid state [11,12]. Increased glucose output from liver is regarded as the cardinal reason for hyperinsulinemia, induction of glucose intolerance, and development of peripheral insulin resistance [13]. Alterations in glucose tolerance in thyrotoxicosis [hyperthyroid] state is caused by elevated hepatic glucose output in association with up regulated glycogenolysis [4]. This phenomenon is implicated in the worsening of subclinical diabetes and exaggerated hyperglycaemia in T2DM. It is quite possible that thyrotoxicosis may culminate in ketoacidosis due to elevated lipolytic action and enhanced hepatic beta oxidation of free fatty acids [14,15]. Elevated hepatic glucose output and increased hepatic beta oxidation denote the important biochemical events in the hyperthyroid state. The biochemical events in hyperthyroid state and hypothyroid state are depicted in Figs. 1 and 2 respectively. The pictorial representation of Thyroid storm is indicated in Fig. 3. The implications as indicated in these figures are self explanatory.

Studies have demonstrated that reduced glucose absorption from the gastrointestinal tract, in combination with prolonged peripheral glucose accumulation, alterations in gluconeogenesis mechanism, diminished hepatic glucose output and a marked decline in disposal of glucose account for hypothyroidism [16].

2. Insulin resistance and thyroid status

Surprisingly insulin resistance has been directly and indirectly linked to hypo- and hyperthyroidism [17]. A conglomerate of

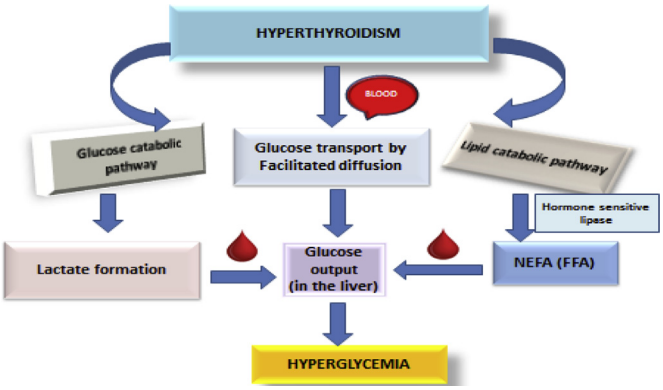

Fig. 1. Proposed mechanism for depicting the nexus between hyperthyroidism and hyperglycemia.

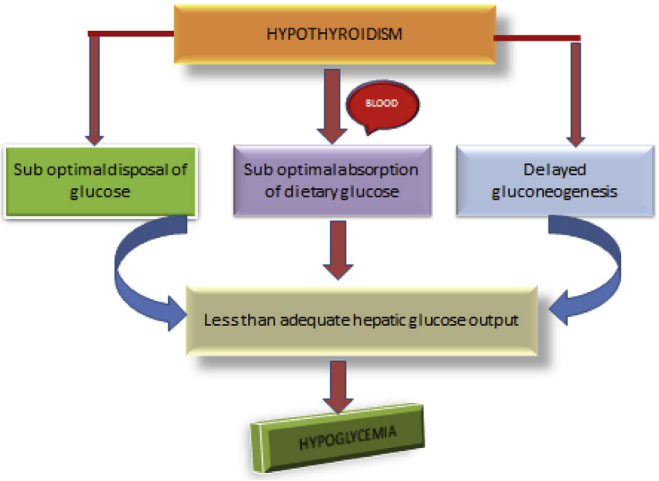

Fig. 2. Proposed mechanism for depicting the nexus between hypothyroidism and hypoglycemia.

pathological features assign significance to the events related to thyroid as observed with reference to insulin resistance. These include a variety of alterations in glucose absorption, insulin secretion, β-cell mass, insulin degradation, hepatic glucose production, catecholamines [through the second messenger cyclic Adenosine monophosphate] and other counter regulatory hormones of insulin and insulin resistance itself. Of all these biochemical events, insulin resistance has been unequivocally regarded as the single most important facet connecting thyroid dysfunction and T2DM [18–21].

2.1. Insulin resistance and role of organs

Insulin resistance in the muscles and liver is a typical feature of T2DM, especially in the light of the fact that an optimal glucose homeostasis mechanism and intact insulin secretory modality combined with sensitivity of the tissues to insulin are regarded as absolutely mandatory for the maintenance of normal blood glucose levels [22–25].

Disposal of glucose is an emphatic, major important biochemical event that needs to be taken due cognizance of. Hyperglycemia and hyperglycemia mediated insulin release are important preceding factors.

Three significant avenues take us through with respect to glucose disposal.

1] Hepatic output of glucose
2] Uptake of glucose (hepatic and splanchnic)
3] Upregulation of glucose by peripheral tissues, namely skeletal muscle.

Glucose uptake into muscles is mediated by glycolysis and glycogenesis. A typical aberration lies in the hepatic insulin resistance that is characterized by glucose overproduction, inspite of fasting hyperinsulinemia, and enhanced rate of hepatic glucose output that is the central modulator of increased fasting [post absorptive] plasma glucose concentration in type 2 diabetics [19]. In insulin resistance in the post absorptive state, muscle glucose is up regulated, but the efficiency of uptake is reduced. Hence, reduced glucose uptake into the insulin sensitive muscles and enhanced hepatic glucose output exacerbate glucose metabolism. These events need to be brought to the fore when Thyroid Storm is discussed [Fig. 3].

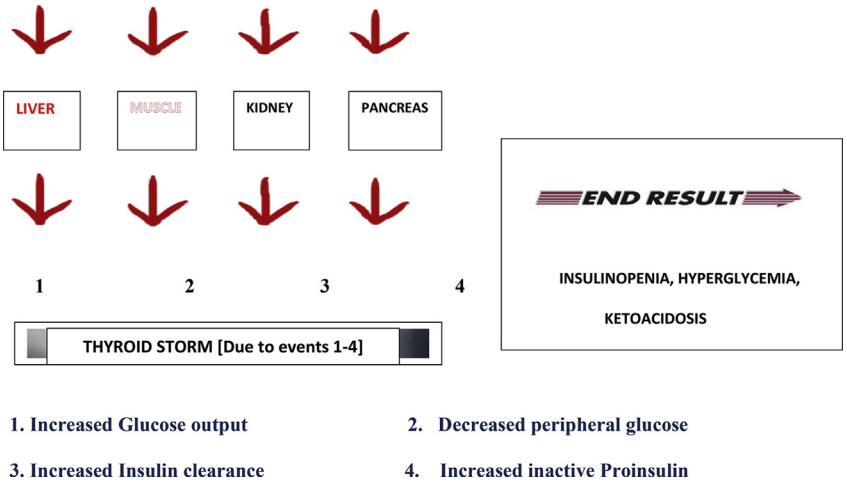

Fig. 3. Thyroid storm.

2.2. Glucolipotoxicity and thyroid status

Bizarre events in glucose disposal and metabolism of glucose in adipocytes and muscle [insulin sensitive tissues that take up glucose through GLUT 4], and liver in association with impaired insulin secretion by the pancreatic beta cells denote organ pathology with reference to T2DM [19,26]. Insulin resistance also leads to impaired lipid metabolism according to recent findings. This is the concept of glucolipotoxicity [27]. All these features point to insulin resistance which could be the possible link between T2DM and thyroid dysfunction.

It is documented that Insulin resistance and β cell function are inversely associated with thyroid stimulating hormone [TSH], which is the tropic hormone elaborated by anterior pituitary. This may be explained by the insulin-antagonistic effects of thyroid hormones along with an increase in TSH. The higher serum TSH usually goes with lower thyroid hormones through negative feedback mechanism. As TSH is increased, thyroid hormones decrease and thus insulin antagonistic effects are weakened. These attributes convincingly tell us that insulin imbalance has a nexus with thyroid dysfunction and this is mediated through pancreatic β cell dysfunction [28].

Hyperthyroidism as related to insulin resistance has been linked to an increased glucose turnover, enhanced intestinal glucose absorption, elevated hepatic glucose output, increased free fatty acid concentrations, increased fasting and or postprandial insulin and proinsulin levels. Increased peripheral glucose transport accompanied by glucose utilization is yet another feature that is synonymous with hyperthyroidism [29,30]. The susceptibility to glucolipotoxicity is recognised as a major biochemical entity in thyroid dysfunction in T2DM [31–35]. In hyperthyroidism, several alterations in mechanisms including gluconeogenesis, glycogenesis, glycogenolysis and GLUT 2 have been proposed [36–39].

Glucose utilization by skeletal muscle is enhanced in hyperthyroid state [40–43]. In this scenario, reduced glycogenesis has been attributed to insulin mediated non oxidative glucose disposal, a sequelae which is accompanied by diversion of intracellular glucose towards lactate formation The transport of lactate from periphery to liver leads to enhanced production of glucose through Cori's lactic acid cycle [29]. Hyperthyroidism is also linked to enhanced insulin sensitivity. Increased insulin resistance is linked to inflammatory mediators [44].

Lipolysis in the subcutaneous fat depot is linked to catecholamine release [counter regulatory hormone of Insulin] and adrenergic post receptor signaling facilitated by thyroid hormones. Other studies point to the fact that thyroid hormones are necessary for the mobilization of brown adipose tissues [45–47], a factor that assumes relevance in thermogenesis.

3. Insulin resistance and thyroid STATUS—STUDIES on Puducherry [Pondicherry] population: summary of research carried out at our laboratory and observations based on our publications

The Union territory of Pondicherry has a unique population type, since it is a mix of urban, semi urban and rural. Hence, we were curious to find out the nexus involving type 2 diabetes mellitus and thyroid status in a mixed population, but as a unique function of obesity. Later we realized that caution and restraint have to be exercised in choosing the correct anthropometric measure to study the biochemical implications of thyroid status, as perceived in insulin resistance. Accordingly, we found out to our surprise that the status of thyroid, as exemplified by hormonal status varied differentially with insulin resistance, when considered in non -obese, overweight and obese type 2 diabetics. Moreover, the revelations were different when body mass index and waist circumference were used as anthropometric indices. These findings from our lab have already been published which are enumerated in the subsequent paragraph that denote some interesting and unique findings.

We found out relationship with insulin resistance, in the light of thyroid status, with Low density Lipoprotein particle size, T3, T4, TSH, Insulin, divalent cations and Adiponectin gene polymorphism. An earlier paper published from our laboratory had implicated Triacylglycerol: High Density Lipoprotein ratio [a surrogate marker of small dense LDL] and thyroid hormone levels in IR as observed in T2DM. We had concluded from that study that small dense LDL could be used as a reliable marker for IR, with accompanying alterations in thyroid status in overweight type 2 diabetics [48]. Data from our lab as per another report on divalent cations had cited only waist circumference as an anthropometric measure which was able to segregate the study group [Type 2 diabetics] only into two, namely obese and non -obese [49]. However, as per one of our publications, BMI has been used as the anthropometric index that has unfurled an additional group, namely overweight. This further proves that strategy based on combinatorial drugs including oral hypoglycemic agents and divalent cations could be the panacea to regulate thyroid function.

Furthermore we suggest that the use of hypolipidemic drugs and thyroid receptor modulators/analogs could help in maintaining euthyroid status. Yet another report from our laboratory was based on a study done on the postmenopausal women, as observed in type 2 diabetics. In that research publication, we had evaluated thyroid status in type 2 diabetes mellitus among pre- and postmenopausal women using BMI as the anthropometric measure. We had suggested a few lines of thinking and action, wherein therapeutic modalities could be planned taking thyroid status, glycemic control, Insulin resistance into holistic consideration, without even having to resort to the assessment of the estrogen status [50]. Gene polymorphism of adiponectin has been studied by researchers using insulin resistance as the pivot. One such polymorphism is SNP+45 of Adiponectin. We extended the study on adiponectin gene polymorphism as linked to insulin resistance, but with reference to thyroid status. Our study showed that even the wild type SNP+45 in exon 2, namely TT could itself be used as a molecular indicator of altered thyroid status in Insulin resistant type 2 diabetics, as studied in overweight and obese. Our study further depicted differential effects of gene polymorphism with reference to SNP + 45 in obese, non-obese and overweight type 2 diabetics. The same study of ours indicated LDL to be statistically significant while comparing non-obese and overweight T2DM. An interesting observation that had emerged from our data is that there was a perfect association between Triacylglycerol: High Density Lipoprotein ratio (a surrogate marker of Low Density lipoprotein) and Low Density lipoprotein signifying that the Low Density Lipoprotein particle size is a crucial entity that needs due consideration, while evaluating thyroid status in typ2 diabetics T2DM, as observed in the non-obese, overweight and obese groups. Hence, we had pronounced that both wild and heterozygous SNP + 45 should necessarily be studied alongside the anthropometric parameter, namely BMI in order to delineate the thyroid status in insulin resistant overweight type 2 diabetics, in addition to the other two groups namely non-obese and obese that have been frequently reported in the literature [51]. This was a recent finding of ours that could attract attention from the perspective of weight management as well as planning therapeutic modalities for alleviating insulin resistance and restoring euthyroid status.

3.1. Thyroid hormone analogues-An elixir

Recent studies carried out on insulin resistance cite pronounced influence on a number of physiological and biochemical processes as diverse and ramified as metabolism of carbohydrates, lipids, amino acids and proteins. Thyroid hormone analogs have enabled innovative therapeutic modalities in the treatment of cardiovascular complications. Molecular cross talk between hyperglycemia and thyroid dysfunction have been recognised and render many a possibility in laboratory medicine and diagnostic biochemistry.

It is possible to carefully design thyroid hormone analogues which are devoid of the dangerous cardiac complications. Carbohydrate response element-binding protein [ChREBP] is one such important transcription factor regulating hepatic lipogenesis mediated by glucose. This is the principal target of thyroid hormones in liver and white adipose tissues. There are three forms of thyroid hormone receptors, namely alpha-1, beta-1 and beta-2 respectively. All these receptors are capable of binding to Thyroid hormones. ChREBP has been reported to be regulated by TR β only and not TR α in liver and white adipose tissue [29,52–57]. ChREBP gene polymorphism seems to be an interesting proposition that is worthy of studies in the near future. This could open up newer vistas that could be exploited in pharmacogenomics and personalized medicine.

4. Conclusion

The association between altered thyroid status and diabetes mellitus is obvious as per several published reports, though the exact molecular mechanisms remain to be clearly delineated. However, equivocal relationships in certain facets are still quite obvious. Thyroid dysfunction comprises essentially of hypothyroidism and hyperthyroidism and several factors including dyslipidemia, insulin resistance are inherent. A multitude of endocrine influences and molecular cross talk cannot be ruled out and this could assume distinguishing characteristics when considered in the light of anthropometric measures. It is cardinal to investigate for thyroid pathology in all type 2 diabetics. Novel biomolecules, receptor agonists, antagonists and ligand biochemistry have paved the way for the development of suitable thyroid hormone receptor analogues to treat metabolic diseases, including the insulin resistant type 2 DM. More evidence based research on these facets would provide greater insights into the future of biochemical pharmacology, pharmacogenomics and laboratory medicine in the management of thyroid diseases as related to metabolic syndrome, insulin resistance and type 2 Diabetes mellitus.

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