Thyroid Dysfunction in Patients with Prediabetes and its Correlation to Cardiovascular Risk

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Abstract:

Prediabetes, diabetes mellitus and thyroid dysfunction are the most common endocrine disorders in clinical practice. The unrecognized thyroid dysfunction may adversely affect the metabolic control and add more risk to an already predisposing scenario for cardiovascular diseases.

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Introduction:

Diabetes mellitus is a metabolic syndrome characterized by impaired carbohydrate, lipid and protein and metabolism as a result of insufficient insulin secretion or decreased insulin sensitivity in the tissues. Prediabetes is a perilous health problem addressed globally, that affects both industrialized and developing countries. DM and thyroid problems are both endocrine illnesses that are linked. Thyroid diseases and diabetes mellitus have a complicated inter-dependence. prediabetes was correlated with a higher prevalence of retinopathy, nephropathy, cardio-vascular disease [CVD], and subclinical hypo-thyroidism (**1).**

Thyroid Stimulating Hormone [TSH] is a hormone released by the anterior pituitary gland that regulates the secretion of total thyroxine [TT4] and total triiodothyronine [TT3]. As a result, diabetes patients should have their thyroid function checked. The American Diabetes Association [ADA] has long presumed that DM should be tested for thyroid disorders(**2).**

Because diabetes is the most prevalent endocrine metabolic disorder, more research into its relationship to another important endocrine gland function, the thyroid gland, was required. However, the prevalence of thyroid dysfunction in diabetics differs greatly between studies; the

link between these two disorders has long been acknowledged. Long-term prediabetes complications can considerably contribute to developing CVD and cancer, amid other diseases, along with the risk of death (**3).**

Diabetes mellitus is becoming more common around the world as an outcome of an aging population and lifestyle changes as a result of urbanization. According to statistics, 382 million people globally had DM in 2013, with 90 to 95 percent of them having prediabetes, and this figure by 2035 is expected to rise to 592 million [8.8 percent of adults aged 20 to 79 years] (**2).**

According to the most recent national survey, China has emerged as the global epicenter of the prediabetes epidemic, with diabetes mellitus afflicting more than 11.6 percent of the adult population [aged 18 and above. The thyroid gland is primarily in charge of regulating metabolism and energy balance. Thyroid dysfunction results in increased insulin resistance in adipose and muscle tissue and also lowers glucose transport in myocytes. In addition, recent research has shown that free triiodothyronine [FT3] regulates insulin secretion (**2).**

Thyroid hormone [TH] is thought to be an essential prognostic factor for developing prediabetes as insulin secretion and glucose metabolism are most strongly associated with the prediabetes pathogenesis. TSH binds to receptors on thyroid epithelial cells and stimulates TH production and secretion by inhibiting negative feedback. However, few studies in the general population with euthyroid status have looked at the relationship between TH, TSH, and prediabetes (**1).**

The thyroid function of 40% PREDIABETES patients was found to be abnormal with 35% of hypothyroidism and 5% hyperthyroidism. In the current study, 42 patients with prediabetes out of a total of 100 were male. In another study, Palit et al. observed that thyroid diseases were seen in 9.7% of prediabetes patients [n=306] and during their follow-up, 5.2% developed sustained thyroid dysfunction with subclinical hypothyroidism [3.9%] being the most prevalent (**2).**

According to previous findings, thyroid dysfunction is more often found in females than in males. The range of thyroid disorders was different by gender. Furthermore, in the current study, females [37.93%] have more sub-clinical hypothyroidism than males [7.14%]. Females [5.17 percent] had more hyperthyroidism than males [4.76 percent], but there was no statistical difference.

Thyroid hormones possess pleiotropic influence on body composition metrics in euthyroid prediabetes patients, according to retrospective cross-sectional research by Chen et al., and sex variations may impact the connection. Furthermore, ale patient's muscle and fat distribution is more prone to be impacted by thyroid function than females', and greater T3 levels are linked to a better body composition [less fat and more muscle mass] in female prediabetes patients (**1).**

Hypothyroidism was found in all age group of people with type 2 diabetes,

whereas hyper-thyroidism was found in people aged 46 to 60. In the light of clinical and laboratory evidence, 43 patients with prediabetes had diabetes complications in the form of retinopathy, nephropathy, and neuropathy in this study. Thyroid problems were found in 23 of the 43 patients. In a cross-sectional study, **Mehalingam, et al.** observed no association between thyroid disease and prediabetes complications (**1)**.

Cardiovascular Risk in Thyroid Dysfunction

The thyroid gland secretes thyroid hormones (THs), triiodothyronine (T3) and thyroxine (T4), which are formed from iodine, and influence metabolic rate and protein synthesis. Regulation of these hormones is driven by the anterior pituitary gland via the secretion of thyroid stimulating hormone (TSH), which itself is regulated by the hypothalamus via thyrotropin releasing hormone (TRH). THs incite multiple effects on the heart and peripheral vasculature. Notably, the intracellular cardiac effects of THs occur via two mechanisms: genomic or non-genomic, with most effects exerted via the genomic pathway (**4).**

In the genomic pathway, T3 binds to thyroid responsive elements in the promoter segment of target genes. This activates gene expression, specifically via messenger RNA that encodes for proteins with variable tissue-specific responses. Via this mechanism, synthesis of cardiac protein is stimulated, leading to myocardial hypertrophy and dysfunction (**5).**

In contrast, the non-genomic pathway affects changes in the cardiac myocyte plasma membrane and cytoplasmic organelles, which may result in alterations within the intracellular signaling pathways in cardiac and smooth muscle cells. The effects of these two pathways working in tandem have been postulated as the mechanism driving cardiac dysfunction in a hyperthyroid state; this has been shown to be present in 5-10% of the population, with a higher prevalence in the elderly (**6).**

Heart failure has been diagnosed in about 5.8 million patients in the USA. Several studies have analyzed the association between heart failure and hypothyroidism, but few studies have assessed the correlation between hyperthyroidism and cardiac pathologies, with exception of atrial fibrillation and tachyarrhythmias. This review presents an analysis of various studies addressing the correlation between these medical conditions (**7).**

T3 and T4 have been shown to exert physiological effects on multiple organ systems, including the vascular system. T3 directly affects vascular smooth muscle cells and promotes relaxation. It has been postulated that T3 reduces expression of angiotensin II type 1 receptors, and thereby reduces the contractile response to angiotensin II. T3 also activates the phosphoinositol 3-kinase (PI3-K)/Ak-mediated endothelial nitric oxide synthase signaling pathway, which stimulates the production of nitric oxide (NO). NO is vital for vascular homeostasis and affects dilator tone. The consequence of these effects is reduced vascular constriction (**8).**

Additional reports have shown that T3 promotes angiogenesis, and may increase the density of coronary arterioles, thus impacting the process of myocardial ischemic reconditioning. Patients with hypothyroidism may develop increased diastolic blood pressure, via decreased endothelium-mediated relaxation and vascular compliance. Conversely in hyperthyroidism, there is a decrease in peripheral vascular resistance, increased blood volume, and increased venous return. These changes may lead to development of heart failure secondary to a high level of output (**9).**

TH Effects on Cardiovascular Physiology:

THs affect myocardial contractility, total peripheral resistance and heart rate. They enhance myocardial contractility by upregulating calcium handling and myosin heavy chain isoforms, and stimulating the beta adrenergic system. Hyperthyroidism has been shown to incite arrhythmias, vascular changes, and myocardial remodeling. These changes can decrease cardiac output and promote the development of heart failure.

Notwithstanding, current literature analyzing the relationships between myocyte function and global cardiac function in the setting of hyperthyroidism is limited. It has been demonstrated that excess TH may result in tachycardia, widened pulse pressure, increased cardiac output, and decreased total peripheral resistance. Although these effects have been well analyzed, there is no established consensus regarding mechanism of action **(10).**

The mechanism of action of THs is prominently a result of their action on nuclear thyroid hormone receptors (TR). TR-alpha, the main TR isoform receptor of the cardiovascular system, is activated by T3. TR cardiomyocyte growth is due to phosphorylation of PI3-K, protein kinase B, and mammalian target of rapamycin (mTOR), which enhance developmental processes, such as sarcomere protein translation. The activation of these signaling pathways leads to changes in gene expression, which is comparable to physiologic mechanism of cardiac hypertrophy (**11).**

There is evidence that serum levels of T4 and T3 are frequently decreased in heart failure patients, and decreased thyroid function may contribute to systolic and diastolic dysfunction. The data relating to a prolonged hyperthyroid state and heart failure are less consistent. Numerous other conditions have also been correlated with thyroid function, including pericarditis, cardiac tamponade, tachycardia, atrioventricular block, pericardial effusion, sinus bradycardia, torsade de pointes, cardiomyopathy, endothelial dysfunction, hypertension, and dyslipidemia (**10).**

A Brief Look at Hypothyroidism and Cardiology:

Hypothyroidism, a condition with low levels of T4 and T3 and compensatory high levels of TSH, can result in diastolic hypertension, sinus bradycardia, and heart failure. A brief overview of the causal

relationship between hypothyroidism and cardiovascular disease will be reviewed prior to addressing the lesser-studied association seen with hyperthyroidism. Chronic hypothyroidism has been shown to increase the risk of atherosclerosis owing to its association with hyperlipidemia (**9).**

Secondly, electrocardiogram (ECG) changes typically found in hypothyroid states include sinus bradycardia, prolonged QTc and atrioventricular block. A combination of these findings has been demonstrated an increased risk of coronary artery disease (CAD). Other factors associated with hypothyroidism include endothelial dysfunction, decreased nitric oxide, and subsequently decreased vascular relaxation. These factors have similarly been seen in cases of subclinical hypothyroidism, where TSH levels are high with normal T4 and T3 levels. This condition has been correlated with left and right ventricular systolic and diastolic dysfunction and will be reviewed later (**10).**

For hypothyroid patients with CAD, lower doses of levothyroxine should initially be utilized, with a gradual increase in dose. Physicians may consider starting treatment with levothyroxine 12.5 µg orally daily and increasing the dose after 6 weeks, to lower the peripheral vascular resistance and thus ameliorate the myocardial ischemia to achieve a euthyroid state. Many articles have analyzed the association with low or subclinical thyroid states and cardiac conditions, but few have looked into the effects of hyperthyroidism, along with prognosis and therapy. This article will further focus on hyperthyroidism and the associated cardiovascular conditions (**11).**

Subclinical Thyroid Dysfunction and Cardiovascular System:

Overt hyperthyroidism has been linked to cardiac conditions, and similarly, subclinical thyroid states have shown their own association. Subclinical thyroid abnormalities are characterized as having an abnormal TSH level and normal FT4 level. This is more common in older patients, with an overall prevalence of 10% for subclinical hypothyroidism and 0.7-3.2% for subclinical hyperthyroidism (**9).**

It has been shown that even subclinical thyroid conditions can be linked to cardiac dysfunction, and some studies have demonstrated that T4 replacement can improve cardiac function, even in patients with subclinical hypothyroidism. There are a limited number of known studies, however, discussing the association between subclinical thyroid dysfunction and heart failure in particular (**10).**

One population-based analysis of adults (ages 70 - 79) illustrated an association between subclinical thyroid dysfunction and heart failure episodes. In this study, patients with TSH levels > 7 mU/L had greater than a 2-fold risk of heart failure episodes, compared to that of euthyroid subjects. A second study supported these findings, with the addition of echocardiographic findings. This trial consisted of 3,044 adults, age greater than 65 years, initially free of heart failure, who were followed over a mean of 12 years.

Changes in cardiac function were analyzed both in the patients with subclinical hypothyroidism and subclinical hyperthyroidism. Over the 12 years, 736 patients out of 3,044 were found to develop heart failure symptoms. Patients with TSH levels greater than 10 mU/L were found to have a greater incidence of heart failure versus euthyroid participants (P value = 0.01, and 95% confidence interval of 1.05 - 3.34) (**10).**

These findings were more prominent and statistically significant in patients with subclinical hypothyroidism rather than subclinical hyperthyroidism. The baseline peak E velocity to measure diastolic dysfunction was higher in those with TSH > 10 compared to euthyroid participants (P value = 0.002). These patients were also found to have an increase in left ventricular mass, while other echocardiographic measurements remained unchanged. The patients with subclinical hyperthyroidism and thus TSH levels of 4.5 - 9.9 did not demonstrate a statistically significant increase in heart failure (**11).**

Most recently, a pooled analysis of six prospective studies examining data from 25,390 participants was conducted to determine the effects of subclinical thyroid dysfunction (with euthyroid defined as TSH 0.45 - 4.49 mIU/L, subclinical hypothyroid as TSH 4.5 - 19.9 mIU/L and subclinical hyperthyroidism as TSH < 0.45 mIU/L; both with normal FT4 levels). In this study, the risk of heart failure events was found to be increased with both higher and lower TSH levels, particularly when TSH > 10 mIU/L and for TSH < 0.10 mIU/L (P value for quadratic pattern < 0.01). The results of this study are notably in contrast to the results of the aforementioned study (**10).**

The Famingham Heart study, which included 4,331 patients, did not show a link between subclinical hypothyroidism and increased risk for cardiovascular disease or mortality. In contrast, a study by Tseng et al found that subclinical hypothyroid was associated with increased risk for all-cause and cardiovascular mortality. This study included 115,746 adult patients in Taiwan from 1998 to 1999 (**9).**

Physicians should be aware of the potential cardiac complications associated with subclinical thyroid dysfunction, mainly hypothyroidism. Subclinical thyroid dysfunction has been well associated in several studies with systolic and diastolic cardiac dysfunction. Importantly, T4 replacement has shown improved measurements of cardiac function in subjects with subclinical hypothyroidism. Elevated TSH levels, even in patients with subclinical hypothyroidism, has been correlated with a decrease in stroke volume, a decrease in cardiac index, and an increase in systemic vascular resistance (**10).**

Nevertheless, no large-scale studies have been conducted to further support these findings. In terms of subclinical hyperthyroidism, several studies have demonstrated an increased average heart rate, left ventricular mass, and impaired diastolic function compared to overt hyperthyroidism. Subclinical hyperthyroidism has also been correlated with higher rates of atrial fibrillation. This

correlation may explain why cardiac dysfunction has been found in patients with subclinical rather than overt hyperthyroidism (**11).**

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