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HPAT Axis Dysfunction and Type II Diabetes Review

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Review Article

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Abstract

According to the CDC, 1 in 10 or more than 34 million Americans have diabetes, and approximately 90 to 95% have type II diabetes (T2D). Between 1990 and 2010, the number of new diagnoses doubled yearly, and the number of patients living with diabetes tripled. This review establishes a direct association between the hypothalamic-pituitary-adrenal and thyroid (HPAT) axis dysregulation and T2D. In this review, we will focus on the compelling evidence that shows the progressive dysregulation of the HPAT axis and the increased values of circulating cortisol which is involved in the formation of visceral obesity through thyroid hormones, which play a crucial role in regulating energy and metabolism by controlling insulin production and glucose homeostasis, and how the HPAT axis plays a significant role in preventing or causing the development of T2D.

Keywords: Type II Diabetes; Thyroid; Hyperglycemia

Abbreviations: T2D: Type II Diabetes; HPAT: Hypothalamic-Pituitary-Adrenal and Thyroid; IPF1: Insulin Promotor Factor 1.

Introduction

The condition of type 2 diabetes or T2D is a chronic metabolic disorder characterized by increased blood glucose or hyperglycemia. T2D is also known as adult-onset diabetes, indicating that T2D develops at middle- and late-adulthood. Nevertheless, more children and teens are diagnosed with this disease. T2D may be caused by insulin resistance, compromised insulin synthesis, or both [1]. Some T2D risk factor is being overweight, obesity, aging, genetics, being of a particular ethnic group like African American, American Indian, Alaska Native, hypertension, high triglycerides, history of gestational diabetes, and sedentary lifestyle [2].

According to the CDC, about 1 in 10 or more than 34 million Americans have diabetes, with the approximation that 90 to 95% of them have T2D. In 2018, 10% of the population was diagnosed with T2D, while in n 1958, only 1% of the population was diagnosed with T2D. Between 1990 and 2010, the number of new diagnoses doubled every year, and the number of patients living with diabetes tripled. People over the age of 45 are most vulnerable to developing this condition [3].

T2D starts when the body's response to insulin is impaired, leading to insulin resistance. At this stage, insulin becomes less effective, and the pancreas increases its production to maintain homeostasis. Most T2D patients are either overweight or obese and have a higher body fat concentration and excessive adipose tissue around the abdomen. This increased adipose tissue stimulates different inflammatory processes like increased FFA synthesis and adipokine dysfunction leading to insulin resistance [1]. Over time, the pancreas reaches a stage of burnout leading to beta-cell dysfunction and compromised insulin synthesis. Therefore, glucose levels rise in the blood unchecked, leading to hyperglycemia and T2D.

It has been established that the closer the genetic association between two people, the more they are inclined to have the same glucose tolerance status. A research study has demonstrated that identical twins show a higher concordance rate for T2D than non-identical twins [4]. Some of the genes involved in T2D are the glucokinase gene, in genes for various transcription factors HNF-1β, HNF-1α, HNF-4α, neurogenic differentiation 1 (NEUROD1), and insulin promotor factor 1 (IPF1) [5]. As with nearly any health condition, various environmental factors are involved in insulin resistance pathogenesis; genetic predisposition is only part of the condition. Nongenetic factors determine whether and how risk-associated genotypes lead to disease, including lack of physical activity, dyslipidemia, abnormal incretin biology with reduced incretins like glucagon-like peptide-1 or incretin resistance, excessive kidney glucose reabsorption, excess glucagon production, dense energy diet, dysbiosis, and pollution [1,5].

In this paper, we are going to focus on the compelling evidence that shows that progressive dysregulation of the hypothalamic-pituitary-adrenal axis, and the increased values of circulating cortisol, which is involved in the formation of visceral obesity lead to T2D. Through the thyroid hormone, which plays a crucial role in regulating energy and metabolism by controlling insulin production and glucose homeostasis, the HPAT axis plays a significant role in preventing or causing the development of T2D.

Discussion

HPAT axis is an extensive hormone system that reacts to stress. Stimulation of the HPAT axis leads to cortisol production. Since cortisol has receptors in all cell types, it regulates immunity, metabolism, and behavior to diffuse stress. Prolonged activation of the HPAT axis leads to its dysregulation leading to unwanted clinical consequences. Chronic stress increases the concentrations of the HPA axis hormones above the normal range. Simultaneously, cortisol levels' constant elevation redirects the body to increase adipose fat storage [6]. On the other hand, elevated cortisol levels prompt three feedback mechanisms to block the synthesis of CRH in the hippocampus and hypothalamus and to restrain the secretion of ACTH in the pituitary resulting in the clinical manifestations of the stress-associated disorder, like weight gain, fatigue, and depression [7]. Chronically increased cortisol levels are linked to T2D and depression [8].

A cross-sectional study assessed the association between serum cortisol and serum TSH levels in the 0.5-10 uIU/L range in a cohort of healthy young men and women. It concluded that there is a positive association between high cortisol and TSH levels from 0.2 to 10 uIU/L and that TSH levels > 2.0 uIU/L may be abnormal and correlate with subclinical hypothyroidism [9]. The study stated that even though T3 levels were still normal, it was just a matter of time before they started dropping. On the other hand, the mitochondrial gene expression and skeletal muscle function is regulated by the T3 hormone. A drop in T3-mediated transcription may also lead to T2D.

In another study, 16-week-old rodents chronically hyperglycemic were injected with T3 hormone, resulting in a swift attenuation in the rodents' hyperglycemia. The study demonstrated that a single injection of T3 swiftly reduced glucose level within two hours, suggesting that T3 effectiveness may be occurring at the functional level of the signaling pathway that regulates glucose homeostasis. The enzyme PI3-kinase, which is vital in the insulin signaling pathway, may be regulating T3 glucose-lowering effect in rodents because a PI3-kinase inhibitor blocks this effect. Daily injection of T3 attenuated hyperglycemia and improved insulin sensitivity in rodents [10]. Low circulating T3 caused by HPAT dysfunction results in elevated blood sugar and insulin resistance.

β-cell dysregulation, including reduced β-cell mass and insulin production, is essential to the pathogenesis of T2D [11]. It has been established that there is no hyperglycemia without β-cell dysfunction [12]. Research has shown that T3 enhanced the insulin storage in β cells, increased the β cells number in the pancreatic islet and plasma insulin levels. Recorded data shows that a reduction in T3 may promote the deterioration of β cells' function. On the other hand, T3 may restore β cells' capacity reducing hyperglycemia and insulin resistance.

The pathogenesis of HPAT axis dysfunction and T2D develops over multiple stages. Each stage has its signs and symptoms. Stage 1 is where early signs of this disease start to show. Chronic stress, either through physical exhaustion, emotional exhaustion, or chemical exhaustion, leads to the HPAT axis overstimulation, which may cause irritability, tiredness, weight gain, headaches, sleep apnea, appetite changes, digestive disturbances, low self-esteem, and frequent infections [13].

Stage 2 may be the phase in which excessive-high cortisol starts to impair thyroid function, and new symptoms start to develop consequently, including tiredness, cold limbs, constipation, increased weight gain, dry skin, muscle weakness, puffy face, hoarseness, high cholesterol, joint pain, thinning hair, depression, and compromised memory. Stage 3 is when insulin resistance develops and new symptoms start to evolve, like a waistline over 40" in men and 35" in women, fasting glucose at 100 mg/dL, blood pressure at 130/80 or higher, a fasting triglyceride over 150 mg/dL, HDL

cholesterol level under 40 mg/dL in men and 50 mg/dL in women, patches of dark skin, and skin tags, belly fat, and obesity, and hypertension.

Stage 4 is the phase in which T2D is fully developed. T2D signs and symptoms are often slow to develop. Many people are living with the disease without being aware of it. Signs and symptoms at this stage may include frequent urination, increased thirst, increased appetite, blurry vision, fatigue, sudden weight loss, frequent infections, tingling and numbness in the feet and hands, slow healing sores, and darkened skin in the neck and armpit [14].

Physicians usually use glycated hemoglobin (A1C) test to diagnose T2D. This test can only be done once every three months to be effective. The test shows the average blood glucose level for the past two to three months. Results are interpreted as follows: Below 5.7% is normal, 5.7% to 6.4% is diagnosed as prediabetes, 6.5% or higher on two separate tests confirms diabetes. A morning fasting glucose test of 126 mg/dL (7 mmol/L) or higher on two separate tests confirms diabetes. Also, a level of 200 mg/dL (11.1 mmol/L) or higher independent of when the last meal was consumed confirms diabetes, with signs and symptoms of diabetes included [15].

There is nothing as persistent, as constant, and as detrimental to the HPAT axis as dietary stimulants. Refined sugar, caffeine, nicotine, and alcohol are all stimulants that activate the HPAT axis and individually increase cortisol and blood glucose in the blood. They should be considered essential stressors that cause HPAT axis hyperactivity leading to chronic stress and HPAT dysfunction, and T2D. Eliminating these stimulants from the diet improves many symptoms, including reduced fatigue, feeling lighter, increased energy, reduced anxiety and depression, improved sleep, appetite, and blood glucose.

One example of these dietary stimulants is caffeine. Many studies show that acute high and moderate caffeine doses consistently activate the HPA axis, and even a low dose of 2 mg/kg activates the HPA axis 30 minutes after consumption [16]. Caffeine is found in coffee, tea, chocolate, soda, energy drink, and OTC pain killers. People may be consuming caffeine multiple times throughout the day unknowingly, overstimulating the HPAT axis and causing its dysfunction.

Magnesium regulates many neurobiological mechanisms, including the HPA axis [17]. A study shows that magnesium deficiency is associated with HPA axis upregulation, leading to increased cortisol in circulation and anxiety symptoms, and depression [18].

Magnesium deficiency is linked with an elevated risk of multiple preclinical and clinical issues, including insulin resistance, pancreatic beta-cell dysfunction, elevated risk of MetS, and T2D, as T2D is often associated with alteration of magnesium [19]. Many studies have confirmed that diabetics and nondiabetics with insulin resistance supplemented with magnesium showed significant improvement in their insulin resistance [20].

Walking is recommended for improving underactive thyroid; it is one of the easiest exercises to do. The only equipment needed is a pair of comfortable walking shoes. It gets the heart working and burns about 280 calories per hour [21]. Brisk walking for a minimum of 30 minutes activates underactive thyroid, alleviates fatigue, anxiety, and depression, and improves energy. Walking straight without interruption for a minimum of 30 minutes per day reduces the risk of T2D by 50%. It also reduces mortality. In contrast, housework and gardening do not [22]. Studies in both men and women with T2D have shown that eight weeks of aerobic walking (30 min/day, three days/week) reduced HbA1c levels by 18% [22-25].

Conclusion

This review establishes a direct association between HPAT axis dysregulation and type II diabetes. Further studies may be needed to confirm these results.

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