Chronic Stress: Its Impact on Exacerbation and Progression of Endocrine Autoimmune Diseases.

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Abstract. Prolonged exposure to stress results in sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to persistent elevation of cortisol levels. Although the role of stress in the etiology of endocrine autoimmune diseases has been extensively investigated, its impact on the exacerbation and progression of already established conditions remains less understood. This review examines recent evidence (2000-2024) linking chronic stress to the worsening of symptoms, disease progression, and treatment resistance in autoimmune endocrine disorders, with a particular focus on type 1 diabetes, Hashimoto's thyroiditis, Graves' disease, and Addison's disease. The dysregulation of cortisol secretion patterns under chronic stress appears to interfere with metabolic control, immune function, and hormonal signaling pathways, potentially accelerating disease progression and contributing to unfavorable clinical outcomes. The evidence suggests that chronic stress represents a significant modifiable factor in disease management, with implications for both clinical care and public health strategies. This review highlights the urgent need for longitudinal studies specifically designed to assess stress as a variable in disease progression and for health policies that recognize and address stress-related factors in patients with autoimmune endocrine conditions.

Keywords. Chronic stress, cortisol, endocrine autoimmune diseases, disease progression, type 1 diabetes, Hashimoto's thyroiditis, Graves' disease, Addison's disease.

1. Introduction

Endocrine autoimmune diseases comprise a group of complex conditions in which the immune system, through mechanisms not yet fully elucidated, begins to attack components of the endocrine glands, culminating in progressive hormonal dysfunction [1]. Among these conditions, type 1 diabetes mellitus (T1DM), Hashimoto's thyroiditis, Graves' disease, and Addison's disease stand out, affecting millions of people worldwide, causing significant morbidity, and compromising the quality of life of patients [2].

Chronic stress, characterized by prolonged and repeated exposure to stressors of a physical or psychological nature, triggers a series of complex and interconnected physiological responses. Among them, the sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis and the consequent persistent elevation of cortisol levels stand out [3]. The medical and scientific literature has extensively explored the role of stress as a possible triggering factor for these diseases; however, less attention has been given to the influence of chronic stress on the course, progression, and control of pre-existing endocrine autoimmune diseases [4].

This review aims to analyze recent scientific evidence (2000-2024) regarding the impact of chronic stress on the exacerbation of symptoms and the progression of already diagnosed endocrine autoimmune diseases, with an emphasis on cortisol-mediated mechanisms. We aim, therefore, to shed light on how the physiological changes resulting from prolonged stress can interfere with metabolic control, the function of the affected endocrine glands, and the response to treatment, potentially contributing to unfavorable clinical outcomes and

the early onset of complications.

2. Methodology

A narrative review of the scientific literature published between January 2000 and December 2024 was conducted. The searches were conducted in the PubMed, MEDLINE, Scopus, and SciELO databases, using the following combinations of terms: "chronic stress" AND ("autoimmune endocrine disease" OR "type 1 diabetes" OR "Hashimoto's thyroiditis" OR "Graves' disease" OR "Addison's disease") AND ("progression" OR "exacerbation" OR "symptoms" OR "cortisol"). Original articles, systematic reviews, and meta-analyses in English, Spanish, and Portuguese were included.

The studies were selected based on their relevance to understanding the effects of chronic stress on already established endocrine autoimmune diseases, with an emphasis on cortisol-mediated mechanisms and effects on disease progression. Studies that focused exclusively on the role of stress as an etiological factor in autoimmune diseases, as well as those that concentrated solely on psychological aspects or stress management techniques, were excluded.

3. Results and Discussion

3.1 Pathophysiology of Chronic Stress and Changes in the HPA Axis

Acute stress, under normal conditions, triggers a coordinated adaptive response, with activation of the sympathetic nervous system and the HPA axis. This activation results in the release of substances such as catecholamines and cortisol, which prepare the body to deal with the stressful situation [5]. However, when stress becomes chronic, the regulation of the HPA axis is affected, leading to desensitization of glucocorticoid receptors, alteration of circadian patterns of cortisol secretion, and dysregulation of the stress response [6]. As elucidated by Guyton and Hall [7], cortisol performs a variety of metabolic functions, including the stimulation of gluconeogenesis, the mobilization of fatty acids, the increase of proteolysis, and the modulation of the immune response. All these functions can have a significant impact on the course of endocrine autoimmune diseases.

A prospective study conducted by Hackett et al. (2020) revealed that individuals with established autoimmune endocrine diseases exhibit abnormal patterns of cortisol secretion in response to stress, when compared to healthy individuals. These abnormal patterns include greater diurnal variability and an exaggerated response to acute stressors [8]. Such alterations in cortisol homeostasis appear to be associated with poorer metabolic control and a higher frequency of exacerbations in patients with T1DM and Hashimoto's thyroiditis.

3.2 Impact of Chronic Stress on Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized by the autoimmune destruction of pancreatic β cells, leading to an absolute deficiency of insulin [9]. Recent studies have shown that chronic stress can significantly influence glycemic control in patients with established type 1 diabetes.

Falco et al. (2021) observed that patients with type 1 diabetes (T1D) exposed to high levels of chronic stress, assessed through validated scales and salivary cortisol levels, had significantly higher glycated hemoglobin (HbA1c) levels than those with low stress levels, even after adjusting for confounding factors such as treatment adherence and physical activity [10]. The authors also reported greater daily glycemic variability in individuals under chronic stress, a factor recognized as associated with the development of microvascular complications.

Dysfunction in the HPA axis, marked by, among other factors, elevated and prolonged secretion of cortisol, plays a significant role in insulin resistance, which is one of the main mechanisms associated with glycemic dysregulation [11]. Moreover, cortisol plays a role in stimulating glucose production by the liver, resulting in an increase in blood glucose levels, particularly in contexts of prolonged stress. On its own, this would be sufficient to compromise the therapy; however, it is further exacerbated by the immune system suppression induced by cortisol, making the patient susceptible to opportunistic infections, which in turn contribute to the dysregulation of the disease.

The underlying mechanism of these effects seems to be related to the metabolic actions of cortisol, which include [7,12]: (1) increased insulin resistance – cortisol induces insulin resistance in peripheral tissues, exacerbating hyperglycemia in patients with T1D, who already have an absolute insulin deficiency; (2) stimulation of hepatic gluconeogenesis – sustained activation of glucocorticoid receptors in the liver results in increased hepatic glucose production, contributing to hyperglycemia; (3) effects on glycemic counterregulation – cortisol amplifies the action of counterregulatory hormones, such as glucagon and adrenaline, complicating glycemic control and increasing the risk of severe hypoglycemic episodes, which are often followed by rebound hyperglycemia.

A noteworthy phenomenon, observed by Brosig et al. (2020), is the higher frequency of diabetic ketoacidosis episodes in patients with elevated levels of chronic stress [13]. In their study, 32% of diabetic ketoacidosis episodes in adults with previously well-controlled type 1 diabetes were temporally associated with periods of intense psychosocial stress, suggesting that stress can precipitate acute metabolic decompensations, even in patients with a history of stability.

3.3 Impact of Chronic Stress on

Autoimmune Thyroid Diseases

Hashimoto's thyroiditis and Graves' disease, the two main autoimmune thyroid diseases, also appear to be significantly influenced by chronic stress in their progression and clinical manifestation.

The course of Hashimoto's thyroiditis (HT), which is defined by the progressive autoimmune destruction of thyroid tissue and consequent hypothyroidism, can be accelerated by chronic stress. Agha-Hosseini et al. (2016) demonstrated that plasma cortisol levels in individuals with HT were considerably elevated compared to healthy controls. Statistical analysis revealed that each 1 ng increase in cortisol levels corresponded to a 19% increase in the likelihood of Hashimoto's thyroiditis [14]. Disruptions in the HPA axis, as demonstrated by this study, may exacerbate the clinical manifestations and progression of hypothyroidism in individuals with confirmed HT. This may result in a feedback loop related to stress that further compromises thyroid function. It indicates, irrespective of the mechanism, a potential role of stress in the exacerbation of the underlying autoimmune condition.

In Graves' disease, characterized by autoimmune hyperthyroidism, stress seems to play an important role in precipitating the condition. A research by Matos-Santos et al. (2001) has shown that numerous patients diagnosed with Graves' disease have reported encountering considerable stressful events in the months leading up to the appearance of symptoms. This observation supports the idea that stress may not only contribute to the initiation of the condition but also has a direct impact on its severity and overall outcome [15].

The proposed mechanisms to explain these effects include [16,17]: (1) Changes in sensitivity to thyroid hormones – Cortisol can modulate the expression of thyroid hormone receptors in target tissues, altering peripheral sensitivity to these hormones; (2) interference in the peripheral conversion of T4 to T3 – chronic elevation of cortisol can inhibit the peripheral conversion of thyroxine (T4) to triiodothyronine (T3), the biologically more active hormone, potentially masking or exacerbating clinical manifestations of hypothyroidism; (3) alteration in the regulation of the hypothalamic-pituitary-thyroid axis – chronic stress can interfere with the sensitivity of the negative feedback of the hypothalamic-pituitary-thyroid axis, leading to changes in TSH secretion and potentially complicating therapeutic management.

A relevant study conducted by Torres and collaborators (2021) observed that patients with hypothyroidism due to Hashimoto's thyroiditis, even when apparently well-controlled with levothyroxine, exhibit greater variability in TSH levels under conditions of chronic stress [18]. This hormonal fluctuation can lead to alternating periods of subclinical hypothyroidism and hyperthyroidism, resulting in symptomatic oscillations and, consequently, making the ideal adjustment of medication therapy difficult.

3.4 Impact of Chronic Stress on Addison's Disease

Addison's Disease, a condition characterized by primary adrenal insufficiency, usually of autoimmune origin, presents a unique scenario in the investigation of the relationship between chronic stress and endocrine autoimmune diseases. The dependence on exogenous glucocorticoid replacement in patients with this condition complicates the direct assessment of the effects of stress on disease progression.

However, recent evidence suggests that chronic stress can impact the effectiveness of hormone replacement therapy and trigger adrenal crises. Husebye and collaborators (2020) observed that, in patients with Addison's disease under prolonged psychosocial stress, higher doses of glucocorticoids are often necessary to achieve adequate symptomatic control. This may be attributed to changes in the pharmacokinetics or pharmacodynamics of the administered hormones [19].

In individuals with Addison's disease, the inability to mount an adequate cortisol response to stress can lead to adrenal crises, a life-threatening condition. Chronic stress may accelerate the progression of adrenal insufficiency by increasing the demand for cortisol, which the adrenal glands cannot meet. This creates a vicious cycle of HPA axis dysfunction and worsening disease severity [17,20].

3.5 Impact on Quality of Life and Development of Complications

Chronic stress is not limited to exacerbating symptoms and accelerating the progression of endocrine autoimmune diseases. It also significantly influences both the development of complications and the quality of life of patients.

Pouwer et al. (2020) conducted a study that corroborates the relationship between stress, increased cortisol levels, and the risk of cardiovascular and renal complications in individuals with diabetes. A meta-analysis of longitudinal studies indicated that people with diabetes who had elevated levels of stress and depression showed a significant increase in the risk of cardiovascular morbidity and mortality. This association was observed independently of microvascular complications, which also had an increased prevalence in individuals with diabetes and chronic stress [21].

In their 2023 study, Wang et al. performed a systematic review and meta-analysis aimed at investigating the influence of stress on Graves' disease, with a specific focus on its onset and the effectiveness of antithyroid treatment. It's been evidenced that chronic stress significantly

contributes to the worsening of the disease, affecting both its clinical presentations and the effectiveness of treatments. Their analysis indicated that individuals dealing with high levels of stress faced an increased likelihood of developing Graves' disease and exhibited a diminished response to standard antithyroid treatment [22]. Hence, one can infer that stress plays a role in the initiation of the disease and may also negatively influence its progression and the efficacy of treatment.

Regarding quality of life, Martino et al. (2021) revealed that, in patients with Hashimoto's thyroiditis, emotional distress, particularly alexithymia, has been shown to exacerbate thyroid dysfunction, worsen symptoms, and decrease quality of life for patients.

4. Conclusion

This review highlights the significant impact of chronic stress on the intensification of symptoms and the progression of pre-existing endocrine autoimmune diseases. The analysis of the data revealed multiple mechanisms by which stress, especially through changes in cortisol levels and secretion dynamics, interferes with the clinical course of these conditions, accelerating the deterioration of endocrine function, triggering acute crises, and contributing to the early development of complications.

The data analyzed in this review strongly suggest that chronic stress is a crucial factor that must be considered in the treatment of endocrine autoimmune diseases. Chronic stress can have a significant impact both on long-term outcomes and on the quality of life of patients. The incorporation of stress management as a component of the treatment of these conditions can be beneficial for the proper control of the diseases.

Additional prospective studies are necessary to evaluate the specific impact of stress on the progression of endocrine autoimmune diseases. Such studies could support the development of public policies aimed at reducing stress exposure in patients with these conditions, with the goal of improving disease control and preventing future complications.

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