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# Endocrine-immunological Interactions in Autoimmune Diseases

Aghayeva Asiya Haji[1], Valiyeva Gulnara Jafar[1], Mashadiyeva-Bayramova Sabina Anvar[2], Kazimova Mehriban Mamoy[1], Bayramov Adil Allahyar[1]
[1]Department of Normal Physiology, Azerbaijan Medical University, Baku, Azerbaijan
[2]IIDepartment of Internal Diseases, Azerbaijan Medical University, Baku, Azerbaijan

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**Abstract**

Autoimmune diseases result from complex interactions between the immune and endocrine systems. Hormonal imbalances not only reflect immune dysfunction but also modulate immune responses, influencing susceptibility, progression, and severity of autoimmune disorders. A deeper understanding of this bidirectional crosstalk is clinically relevant for improving diagnostic and therapeutic approaches. This review aims to address gaps in the literature regarding the molecular mechanisms linking hormonal regulation with immune modulation. This article explores the bidirectional crosstalk between the endocrine and immune systems, highlighting key hormones involved in immune modulation and their roles in the pathogenesis of autoimmune diseases such as type 1 diabetes, Hashimoto's thyroiditis, Graves' disease, Addison's disease, and systemic lupus erythematosus.

**Keywords:** Autoimmune diseases, endocrine system, immune stsyems.

## Introduction

The complex interplay between the endocrine and immune systems is increasingly recognized as a critical determinant in the development and progression of autoimmune diseases. Understanding this interaction is clinically important as it can reveal novel therapeutic targets and help predict disease onset and progression. Despite extensive research, significant gaps remain in delineating the molecular mechanisms through which hormones influence immune tolerance and autoimmunity. This review seeks to address these gaps by focusing on the endocrine-immune axis and its relevance in common autoimmune disorders.

The endocrine and immune systems are intricately interwoven through complex biochemical signaling networks that maintain homeostasis and protect the body from internal and external threats. The immune systems defends against pathogens and abnormal cells, while the endocrine system regulates metabolism, growth, reproduction, and stress responses through the secretion of hormones. These two systems engage in continuous bidirectional communication that significantly influences physiological and pathological outcomes [1].

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Hormones such as glucocorticoids, sex steroids, thyroid hormones, and vitamin D metabolites have well-documented immunomodulatory properties. These hormones influence immune cell development, differentiation, cytokine production, and apoptosis. Conversely, immune mediators such as cytokines and prostaglandins can modulate endocrine function, including the hypothalamic-pituitary-adrenal (HPA) axis, thereby affecting hormonal synthesis and release. This dynamic crosstalk enables the body to coordinate responses to infection, injury, and stress, ensuring survival and functional integrity [2].

Autoimmune diseases arise when immune tolerance mechanisms fail, allowing self-reactive lymphocytes to attack the body's own tissues. This loss of self-tolerance can result from genetic predisposition, environmental triggers, and crucially, endocrine imbalances. Hormonal fluctuations, particularly in glucocorticoids and sex hormones, have been shown to alter the threshold for immune activation and tolerance, thus contributing to the initiation and perpetuation of autoimmunity [3]. The higher prevalence of autoimmune diseases in females has been partially attributed to the immune-enhancing effects of estrogens and the relative immunosuppressive properties of androgens.

Certain autoimmune diseases target endocrine glands themselves, such as the pancreatic islets in type 1 diabetes, the thyroid gland in Hashimoto's thyroiditis and Graves' disease, or the adrenal cortex in Addison's disease. These conditions exemplify how immune dysregulation and endocrine dysfunction are closely linked, with each exacerbating the other. In addition, systemic autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis often present with alterations in hormonal profiles, including cortisol and prolactin, indicating a broader systemic disruption of neuroendocrine-immune interactions [4].

The Endocrine System and Immune Regulation

The endocrine system plays a central role in shaping and modulating immune responses through the systemic actions of hormones on immune cells. Hormones function as critical regulators of the immune systems by influencing the development, differentiation, activation, and suppression of immune cells.

At the molecular level, hormones modulate gene transcription by binding to nuclear receptors in immune cells. For instance, glucocorticoids enter the cell and bind to glucocorticoid receptors, altering transcription of proinflammatory genes such as TNF-α, IL-1β, and IL-6. Glucocorticoids, secreted by the adrenal cortex under the regulation of the HPA axis, are potent anti-inflammatory and immunosuppressive agents. They inhibit proinflammatory cytokine production, impair antigen presentation, and regulate immune cell trafficking and apoptosis. Chronic dysregulation of the HPA axis can disturb immune tolerance and promote the development of autoimmune diseases [4].

Sex hormones exert significant effects on immune function. Estrogens promote the survival of autoreactive B cells by upregulating anti-apoptotic genes and increasing expression of co-

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stimulatory molecules, thereby facilitating autoantibody production. Estrogens enhance B cell survival, antibody production, and favor Th2-type responses, which may predispose females to higher autoimmunity rates. In contrast, androgens and progesterone support immune tolerance by promoting regulatory T cell activity and suppressing inflammatory cytokines [5].

Vitamin D, through its active form calcitriol, modulates both innate and adaptive immunity. It inhibits Th1 and Th17 responses, promotes regulatory T cells, and limits dendritic cell maturation and B cell antibody production. It also reduces expression of costimulatory molecules like CD80/86 on antigen-presenting cells, limiting T cell activation. Vitamin D deficiency has been linked to a higher risk of autoimmune diseases such as multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus [6].

Autoimmune Endocrine Diseases

Autoimmune endocrine diseases exemplify the convergence of immune dysregulation and endocrine dysfunction. These include:

**Type 1 Diabetes Mellitus (T1DM):** This condition results from autoreactive T-cell-mediated destruction of pancreatic β-cells. Proinflammatory cytokines like IL-1β, IFN-γ, and TNF-α contribute to β-cell apoptosis. HPA axis alterations and vitamin D deficiency have also been implicated in disease progression [7]. Reduced Treg activity and aberrant antigen presentation contribute to immune-mediated destruction of islet cells.

**Autoimmune Thyroid Diseases (AITDs):** These include Hashimoto's thyroiditis and Graves' disease. The former involves destructive cell-mediated responses, while the latter is driven by stimulating autoantibodies. Enhanced B cell activation and autoantibody production are modulated by estrogens and thyroid-stimulating immunoglobulins. Estrogens enhance B cell activity in AITDs, and altered cortisol dynamics may weaken immunoregulation [8].

Addison's Disease: This arises from autoimmune adrenalitis, leading to cortisol and aldosterone deficiency. The loss of endogenous glucocorticoids removes a vital check on immune activation, thereby facilitating systemic inflammation [9].

Systemic Lupus Erythematosus (SLE): A systemic autoimmune disease characterized by autoantibody production and immune complex deposition. Estrogens exacerbate SLE activity, while androgens are protective. Impaired Treg function, hyperactive B cells, and increased expression of type I interferons are central to disease pathogenesis. Vitamin D deficiency and HPA axis dysfunction further impair immune regulation [10].

Mechanistic Insights into Crosstalk

Hormones regulate gene expression in immune cells via receptor-mediated transcriptional mechanisms. For instance, estrogens bind estrogen receptors on T and B cells, enhancing

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expression of genes involved in proliferation and antibody production. Glucocorticoids inhibit NF-κB signaling, reducing expression of inflammatory genes. Meanwhile, inflammatory cytokines (e.g., IL-6, TNF-α) damage endocrine tissues by activating stress pathways, leading to hormonal insufficiency and glandular apoptosis. This bidirectional dysfunction creates a vicious cycle that sustains autoimmunity [1, 2, 4].

**Therapeutic Implications**

Recent advances in immunoendocrinology have emphasized the therapeutic potential of targeting both hormonal and immune pathways in autoimmune diseases. Glucocorticoids remain a mainstay in clinical management due to their immunosuppressive properties, particularly in conditions such as Addison's disease, where physiological replacement with hydrocortisone or fludrocortisone is essential. However, long-term use is complicated by the emergence of glucocorticoid resistance, often driven by chronic exposure to inflammatory cytokines such as TNF-α and IL-1β. This resistance is mediated through alterations in glucocorticoid receptor expression and function, leading to diminished therapeutic response. In this context, selective glucocorticoid receptor agonists (SEGRAs) are being investigated as novel agents with the potential to retain anti-inflammatory efficacy while minimizing systemic side effects.

In parallel, vitamin D has emerged as a key immunomodulator, with accumulating evidence supporting its role in restoring immune tolerance. The active form, calcitriol, suppresses pro-inflammatory cytokine expression (e.g., IL-17, IFN-γ) and promotes the differentiation of regulatory T cells. Meta-analyses and clinical trials have shown that high-dose vitamin D supplementation may reduce disease activity in autoimmune disorders such as multiple sclerosis and systemic lupus erythematosus. For instance, the ongoing VIDAMS trial (NCT01440062) is evaluating whether high-dose vitamin D can reduce relapse rates in relapsing-remitting multiple sclerosis.

The use of biologic therapies has revolutionized the treatment landscape by targeting specific cytokine-mediated pathways. Tocilizumab, an IL-6 receptor antagonist, has demonstrated significant efficacy in rheumatoid arthritis and giant cell arteritis, as evidenced by the randomized controlled trial conducted by Stone et al. (2017), which showed reduced relapse rates and steroid-sparing effects. Similarly, TNF-α inhibitors such as infliximab and adalimumab remain central to the treatment of rheumatoid arthritis and inflammatory bowel disease. Another promising approach involves abatacept, a fusion protein that inhibits CD80/86-mediated T-cell co-stimulation, which has shown notable disease activity reduction in rheumatoid arthritis patients, especially in biologic-naïve populations.

Sex hormones also exert considerable influence over immune regulation, contributing to sex-based disparities in autoimmune disease prevalence and treatment outcomes. Estrogens tend to enhance B-cell activation and autoantibody production, a mechanism implicated in the female predominance of systemic lupus erythematosus. Clinical research is underway to evaluate the safety and efficacy of hormonal modulators such as gonadotropin-releasing hormone (GnRH)

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analogs and selective estrogen receptor modulators (SERMs) in modulating autoimmune activity (e.g., NCT03839593). Conversely, androgen supplementation has shown limited but suggestive benefit in conditions like Sjögren's syndrome, although concerns remain regarding metabolic side effects.

Given the complex interplay between hormones and immune function, precision medicine approaches are essential for optimizing therapeutic efficacy. Integration of endocrine profiling—including estradiol, testosterone, and cortisol levels—into treatment algorithms may enable more accurate prediction of treatment response. A recent study published in The Lancet Rheumatology (2022) highlighted that female rheumatoid arthritis patients with elevated estradiol levels had attenuated response to methotrexate, suggesting a potential role for hormonal modulation in refining standard therapies. Moreover, the development of machine learning tools that incorporate hormonal status, cytokine patterns, and genetic variants represents a promising frontier in individualized autoimmune disease management. Precision medicine approaches that consider sex, age, and endocrine profile are essential for effective autoimmune management [5, 10]. Emerging treatments targeting Treg enhancement, antigen-specific immunotherapy, and personalized hormonal modulation are promising approaches.
Table 1 summarizes the hormonal effects on immune function and their associated autoimmune diseases.

Table 1. Summary of Hormones, Immune Effects, and Associated Autoimmune Diseases

| **Hormone** | **Immune Effect** | **Associated Autoimmune Diseases** |
|---|---|---|
| Glucocorticoids | Immunosuppressive, in hibit cytokines & T cells | Addison's Disease, SLE |
| Estrogens | Enhance B cells, autoantibodies, Th2 responses | SLE, Hashimoto's, Graves' |
| Androgens | Promote Treg cells, suppress inflammation | Protective in SLE, RA |
| Vitamin D | Promotes Tregs, inhibits Th1/Th17 | MS, T1DM, SLE |
| Thyroid Hormones | Modulate APCs, cytokines | AITDs (Graves', Hashimoto's) |

## Conclusion

The endocrine and immune systems are interdependent, with hormonal imbalances contributing to immune dysfunction and autoimmunity. Further elucidation of this bidirectional relationship is vital for developing integrated diagnostic and therapeutic strategies. Gender-specific and hormone-targeted interventions may enhance autoimmune disease management and patient outcomes.

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