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Review Article

AUTOIMMUNE DISORDERS IN HUMANS: AN OVERVIEW OF CONCEPTS, CLASSIFICATION, AND VARIANTS - A REVIEW ARTICLE

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ABSTRACT
The phrase "autoimmune disease" refers to a broad range of body. An innate immunological reaction to pathogenic incursion encompasses transient inflammatory processes orchestrated by the immune system during the eradication of invading entities. In autoimmune illnesses, this persistent inflammation results in discomfort, long-term alterations to the tissues involved, or tissue destruction. Autoimmune illnesses have no known etiology; they exhibit remission and recurrence patterns; and they are challenging to identify since each individual symptom varies and depends on the particular disorder. Numerous autoimmune conditions and inflammatory myopathies are introduced in this article. A brief explanation of immunity is given along with a definition of autoimmune disorders.

Keywords: Autoimmune disease, Classification, Types, Causative factors

INTRODUCTION
The immune system particularly identifies and destroys foreign substances, defending the host against illness. During immunological maturation, autoreactive lymphocytes are eliminated, fostering self-tolerance. Recent findings indicate that individuals ubiquitously have self-reactive antibodies and autoreactive cells, suggesting that autoimmunity is an inherent phenomenon. Autoimmune illness is a result of a complex interaction between genetic predisposition and environmental variables. Since most autoimmune illnesses are chronic and need lifelong treatment, they have a disproportionately negative impact on public health since they frequently develop in childhood and persist throughout life. To create better therapeutics to treat and perhaps even prevent the autoimmune diseases, it is essential to percept the mechanisms underpinning immune system dysregulation that culminate in the onset of autoimmune diseases [1].

Historically, autoimmune illnesses were thought to afflict just a small percentage of the population, However, intense epidemiologists notes have now shown that they actually about 3-5% of the population influenced with type I diabetes (T1D) and autoimmune thyroid disease being the most common. Furthermore, there are about a hundred distinct types of autoimmune diseases. Some are multi-organ disorders, such as systemic lupus erythematosus, which is a spectrum of immunological dysfunction, while other diseases are organ specific

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disorders, such as cirrhosis. Over the past decade, substantial progress in the diagnosis, classification, and prognosis of diseases has been achieved through the evolution of advanced molecular immunology techniques and the implementation of refined evidence-based clinical laboratory assessments. A historical foundation for the breach of tolerance theory is presented in this review, together with discussions of autoimmune pathobiology and etiology, and a comprehensive overview of emerging therapeutic alternatives [2].

The Concept of Immune System

In order to protect the body against outside substances like viruses and tumor cells without harming self-molecules, the immune system is described as a complex network of cellular, chemical, and soluble protein systems. T and B lymphocytes in particular, which have special recognition molecules on their surface, play a crucial role in the complex systems that distinguish between self-molecules and foreign compounds. A small but representative fraction of the immune cell pool consists of T and B lymphocytes. Tolerance is maintained by the controlled interaction of soluble mediators and different cell types, but in certain circumstances, tolerance can be lost, leading to the emergence of an autoimmune pathogen [3].

- "Autoimmunity" refers to the phenomena of immunological reactivity, which is defined by T-cell responses against self-antigens and the production of autoantibodies. The spectrum of autoimmune diseases includes both systemic and organ-specific illnesses.
- The phrase "autoimmune disease" describes a wide range of disorders marked by immune system dysfunction that results in the body producing antibodies that attack its own tissues.
- Immune tolerance is the immunological system's specific non-reactivity to an antigen that, under different conditions, may trigger an immune response. The predominant constituents of the immune system are leukocytes, among which lymphocytes represent a key category. Each kind of lymphocyte in the adaptive immune system is responsible for a certain function. T-cells aid in the recognition and eradication of antigens, and B-cells create antibodies that bind to specific antigens and mark them for engulfment by other immune system cells [4] . T-cells constitute a pivotal component of the immune system, instrumental in the eradication of infected cells and the orchestration of the immune response. Three distinct subsets of T-cells include:

- Helper T cell: B-cells are informed by helper T-cells to make greater antibodies.
- Cytotoxic T cell (Cell-killing): T-cells that generate chemicals that kill antigen-carrying cells.
- Regulatory Tcell: T-cell suppressors that temper other immunological reactions.

The T-cell receptor is a surface molecule expressed on T lymphocytes. MHC and this receptor communicate (major histocompatibility complex). Most other bodily cells have MHC molecules on their surfaces, which aid T cells in recognizing antigen pieces. Antigen-presenting cells are the cells that alert the T-cells (APCs) [5].

The tolerance of immune system

In 1948, Macfarlane Burnet, from the Walter and Eliza Hall Institute for Medical Research in Melbourne, Australia, postulated that immunological tolerance is an acquired characteristic developed during ontogeny rather than an innate attribute. Peter Medawar and his associates experimentally proved that inbred mice could be trained to develop immunological tolerance a few years later, in 1953. The capacity of the immune system to stop itself from attacking self-molecules, cells, or tissues was the final definition of immunological tolerance [6] . Numerous researchers rejected the idea of autoimmunity, however it's intriguing to note that Paul Ehrlich's early 20th-century pioneering work had previously popularized the idea of "horror autotoxicus" [7] . The New Zealand black (NZB) mouse, the initial murine model of autoimmunity, was introduced in 1959. As a result of the discovery of thyroid autoantibodies, autoimmune thyroiditis was designated as the archetypal autoimmune illness. NZB mice and autoimmune thyroiditis were two contributions that sparked a surge in autoimmune disease research [8] .

Several fundamental concepts, including central tolerance, peripheral anergy, T regulatory cells (Tregs), and the homeostasis induced by cytokines and chemokines and their related receptors, should be considered while understanding immune tolerance. Central tolerance, which takes place in the thymus and bone marrow, significantly influences immune system homeostasis. Positive selection is applied to developing lymphocytes in the cortex before their growth and exit from the thymus. Notably, the thymic medulla negatively selects and removes lymphocytes that may be reactive to self-peptides in a healthy host otherwise. Notably, mature T cells go through secondary selection (peripheral tolerance) after emerging from the thymus, in which most self-reactive T cells are destroyed or turn anergic[9] .Figure 1 provides illustrations of these ideas.

One of the mechanisms of auto-tolerance is peripheral tolerance and central tolerance, which is characterized by a lack of response to personal antigens. In the stages of development of lymphocytes in the thymus gland, immature cells with a high affinity for binding that have recognized the personal antigen are killed, as these cells are killed through several regulatory mechanisms during Peripheral tolerance stage. A defect or failure in one or more of the immune tolerance mechanisms leads to the emergence of autoimmune diseases [10].

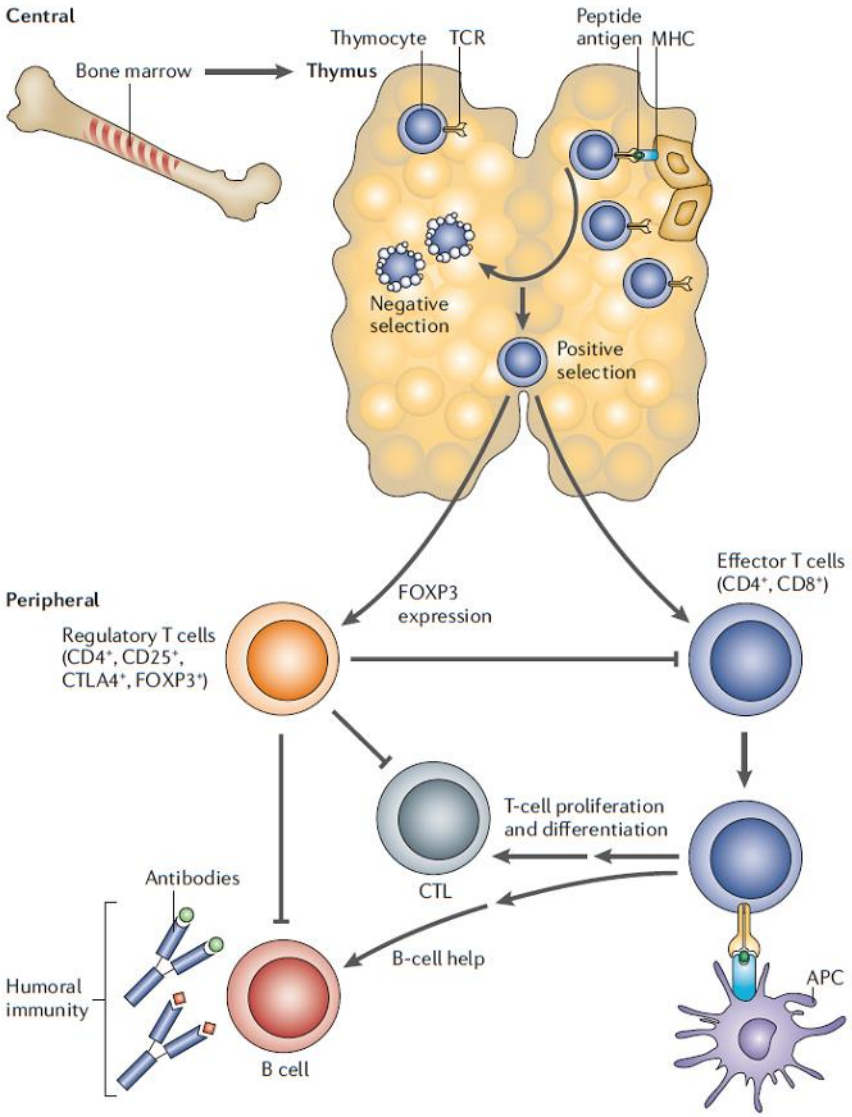

Figure1: Central and Peripheral tolerance [10]

Medical experts categorize autoimmune diseases as either systemic, ex: SLE, or ospecific, ex: diabetes mellitus(Type 1) While clinically relevant, this kind of classification doesn't always align with differences in the cause. A pragmatic classification differentiates disorders into those entailing a systemic alteration in T cell or B cell selection, regulation, or apoptosis, and those wherein an abnormal reaction to a specific antigen, whether self or exogenous, precipitates autoimmunity. A typical antigen-specific condition is the demyelination syndrome that accompanies enteric infection with Campylobacter jejuni. Losing the Fas protein or its receptor, which are proteins involved in cell death, is a common issue. This categorization is helpful in selecting a course of treatment since the pathogenic process may need a different approach. Changes that lower the threshold for autoreactive B cell activation and survival frequently result in the generation of numerous autoantibodies, exemplified by systemic lupus erythematosus with its characteristic antinuclear and anti-DNA antibodies [11,13] . Usually, individuals possess low levels of these autoantibodies. Inflammatory bowel illness is frequently brought on by genetic changes that have a significant impact on the generation of cytokines or the ability of regulatory T cells to function [14,15] . This process might be the result of T cells being more highly activated and responding enthusiastically to gut flora.

Genetic Risk Factors

A mix of hereditary and environmental variables affect how autoimmune disorders develop. It is believed that several genes have a role in the majority of autoimmune illnesses, which are polygenic. There is family clustering, and monozygotic twins are more likely than dizygotic twins to share an autoimmune illness [16,17] .A limited subset of autoimmune conditions, such as autoimmune poly-endocrinopathy-candidiasis-ectodermal dystrophy (APECED) and autoimmune lymphoproliferative syndrome, are induced by genetic mutations

.Although there are many genes that are responsible for the severity of the disease , there are cases in which symptoms do not appear even though they carry the gene [18] .

A number of susceptibility genes collaborate to create the aberrant phenotype in the majority of autoimmune disorders. Generally speaking, the polymorphisms are consistent with typical immunological function and also exist in healthy individuals. They only result in autoimmunity when paired with additional susceptibility genes [19] . The major histocompatibility complex, for example, significantly increases disease vulnerability. A few like these genes a higher risk than other genes. The preponderance of autoimmune diseases exhibits an association with specific class I or class II HLA molecules, although this correlation frequently requires a concurrent genetic association, such as with genes encoding tumor necrosis factor (TNF) or complement proteins [20] .

The greatest available indicator of developing an autoimmune illness is the HLA haplotype, or human lymphocyte antigen. Sharing HLA haplotypes with family members directly affects the risk of having comparable autoantibodies, and two shared haplotypes increase the likelihood of developing similar autoantibodies even more. Thus, around one-third of the chance of getting an autoimmune illness is determined by genetics, with the other 70% of the risk determined by non-inherited, environmental variables [21] as in Figure 2.

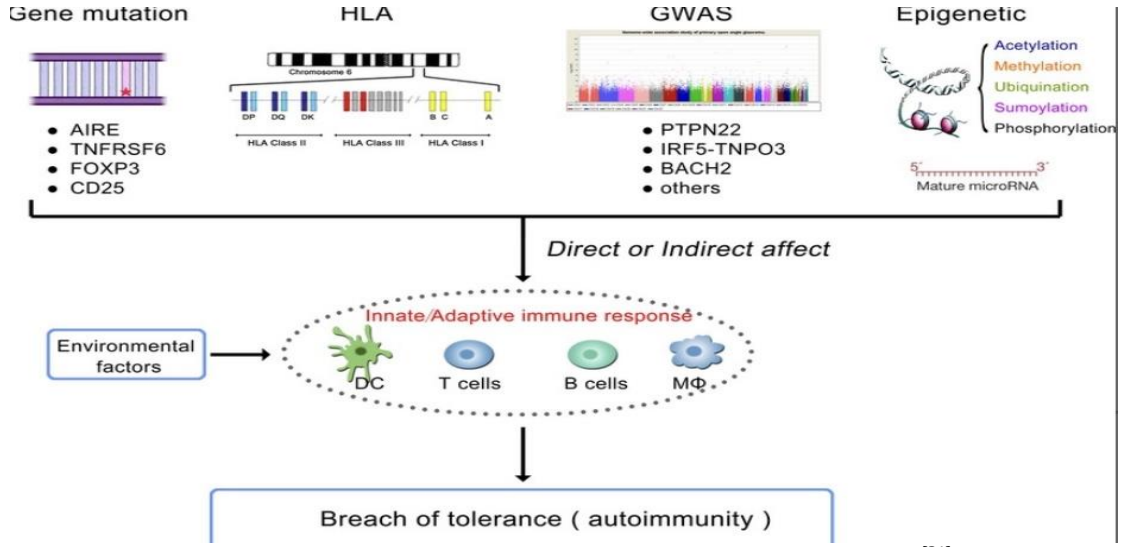

Figure 2: Genetic factor is the main causes of autoimmune illness [21]

Environmental Factors

Environmental factors may be involved in autoimmune disease development, promotion, or modulation in a number of ways. When and how specific environmental factors trigger autoimmune disorders might affect when symptoms initially manifest, how they manifest, or even if an autoimmune disease that already exists in an individual will manifest at all [22] .

Environmental determinants are pivotal in influencing the onset and nature of autoimmune diseases. Within families predisposed to autoimmunity, the specific manifestation of disease may be dictated by a unique confluence of various infectious agents, chemical exposures, pharmaceuticals, and immunizations [23] .

A/ Hormones: According to conservative estimates, approximately 80% of those with autoimmune illnesses are women, making them more common in women than in males. Ankylosing spondylitis, inflammatory heart disease, and diabetes mellitus are examples of exceptions. In addition to the body's natural synthesis of steroids, hormones can also be acquired externally via foods like soy, medicines like birth control pills, or skin care products. Sex hormones interact directly with immune system cells through their surface receptors, and steroid hormones are known to have an impact on the synthesis of antibodies and the proliferation of immune cells. Hormones can therefore enhance or suppress the immunological response [24] .

B/ Exposure to toxic metals: It is expected that 25% of people are poisoned by heavy metals in some way. According to studies, the autoimmune process can be triggered by exposure to harmful metals, including mercury, arsenic, nickel, aluminum, cadmium, and lead. This may result in autoimmune diseases [25] .

C/ Exposure to toxic chemicals: Autoimmune illnesses have been connected to industrial toxins, pollutants, hair dyes, insecticides, and particular household cleansers [26] .

D/ Diet: An insufficient diet that is high in toxins but low in nutrients might cause inflammation. There is a magnesium deficit in many illnesses, including Alzhe].r's, epilepsy, migraine, fibromyalgia, and chronic tiredness, which can lead to autoimmune disorders. Supplemental magnesium is used to prevent epilepsy episodes [27] .

E/ Vaccines/ Immunizations: Certain immunizations have been linked by researchers to several autoimmune illnesses. For example, there is evidence linking the controversial anthrax vaccine to the emergence of some autoimmune illnesses [28] .

F/ Infections: There are a number of theories as to how infections could result in autoimmune illness that involves bystander activation, cryptic self-peptide synthesis, antigen diffusion, molecular mimicry, direct virus harm, and the adjuvant impact. According to the theory of molecular mimicry, when an infection takes place, autoimmunity is triggered because the microorganism's antigens resemble self-antigens very closely. When the immune system is unintentionally activated by an infection, a condition known as bystander activation may develop. This causes autoimmunity to become active in those who are genetically predisposed to it. The main activation of innate immunity by microbial antigens which can use as adjuvant effect like adjuvants that administered in vaccinations. Self-antigens with adjuvants, such as collagen for rheumatoid arthritis and cardiac myosin for myocarditis, can be used to experimentally generate a variety of autoimmune disorders [29] .

G/ Smoking and autoimmune disorders: One of the most potent risk factors for autoimmune diseases is tobacco use Systemic lupus erythematosus (SLE) has been associated with smoking; It has been established that the predominance rate for both past and current smoking for the onset of the condition are link with rheumatoid arthritis . Smoking increases the likelihood of sickness by up to a 21-fold estimate when combined with genetic risk factors, such as the alleles of HLA-DR. Smoking can accelerate apoptosis and induce tissue damage by producing free radicals, releasing metalloproteinase, and inducing the expression of Fas on lymphocytes, among other methods. Additionally, smoking increases inflammation because it raises fibrinogen levels, produces leukocytosis, and leads to an increase in intercellular adhesion molecule-I, C-reactive protein, and E-selectin levels [1,2] as in Figure 3.

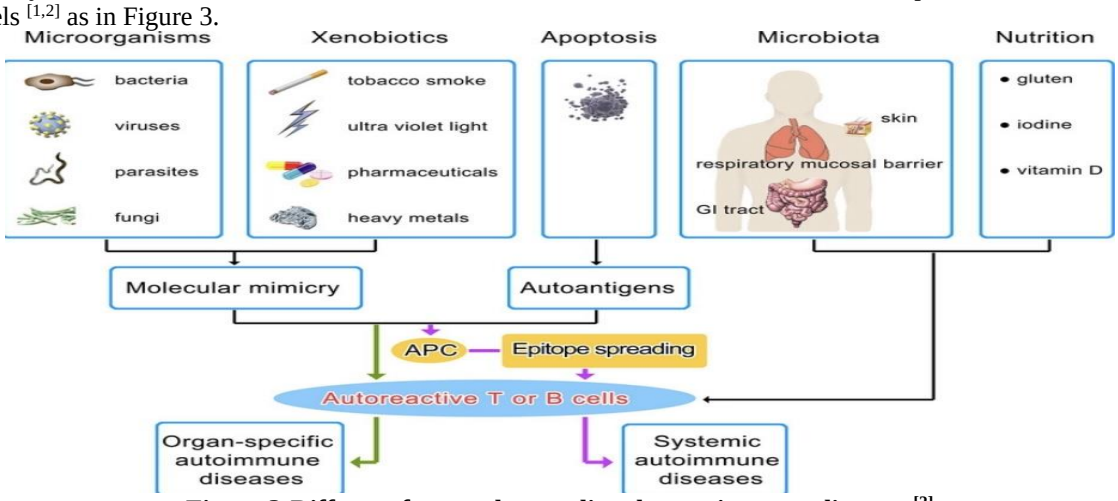

Figure 3:Different factoes that mediated auto-immune diseases [2]

Cell-Mediated Damage

Numerous autoimmune disorders are mostly pathogenicly caused by damage brought on by immune system cells. The preponderant cellular infiltrate in autoimmune responses typically comprises neutrophils, autoreactive CD4+ T helper cells, autoreactive CD8+ cytotoxic cells, phagocytic macrophages, with a lesser representation of NK, mast cells, and DC. The cells of immune system can harm the tissues directly by enhancing cells death or indirectly by producing substances such as prostaglandins, RNS, ROS, and cytotoxic cytokines [30] .

Tissue macrophages and monocytes can function as effector cells after the immune response has begun, or as antigen-presenting cells to start an autoimmune reaction. The extremely cytotoxic proteins nitric oxide and hydrogen peroxide are released by neutrophils and macrophages to harm tissues. The inflammatory site attracts neutrophils and T lymphocytes through the production of cytokines and other mediators by macrophages [31] .

Antibody-Mediated Damage

All animals' serum and tissue fluids include a class of glycoproteins called antibodies or immunoglobulins. In addition to serving as receptors on the surface of B-cells, antibodies can also exist freely in the blood and lymph. B-cells generate a significant quantity of antigen-specific antibody in response to particular antigen binding. These antibodies are the main protective immune response elicited by vaccination and offer crucial defense against pathogenic microorganisms soon following infection. Likewise, self-reactive or autoantibodies play a crucial role in removing cellular waste brought on by inflammation or physical injury to the body [32] .

Autoantibodies are an essential component in the diagnosis or categorization of autoimmune disorders and are a common characteristic of all autoimmune diseases. Autoantibodies manifest long before clinical symptoms since most autoimmune disorders are chronic. Indeed, the likelihood of developing an autoimmune disorder escalates from approximately 10% with the presence of a single autoantibody to roughly 60–80% when three

autoantibodies are detected for a specific autoimmune condition.By adhering to self-tissues, autoantibodies can harm the body by causing lysis, activating the complement cascade, and binding to self-tissues. Autoantibodies attach to antigens on the surface of red blood cells in certain types of hemolytic anemia, causing the cells to lyse [33].

Hormones

The majority of autoimmune illnesses are more common in women than in males. According to conservative estimates, women make up over 80% of those who have autoimmune illnesses. A few exceptions include males are more likely to develop diabetes mellitus, ankylosing spondylitis, and inflammatory heart disease. In addition to the body's natural synthesis of steroids, hormones can also be received externally via foods like soy, medicines like birth control pills, or skin care items. Sex hormones, both natural and synthetic [34].

interconnection with the cells of immune system through receptors on their surface or inside of them. It is well known that steroid hormones, such as oestrogens and androgens, affect the development of antibodies and immune cells. Hormones have the ability to either enhance or suppress the immunological response. Men frequently have more severe inflammation than women, whereas women exhibit higher antibody responses. Studies using animal models have added significantly to our conception of sex differences and the immune system. Similar to human autoimmune illnesses, several animal models exhibit a sex bias in disease incidence and severity. An active topic of research is how sex hormones control the immune system[35].

Regulating the immune response

To keep the immune system in balance and avoid or minimize tissue damage, an immune response must be induced and then downregulated. Similarly, if pro-inflammatory responses are correctly down regulated, inflammation related to autoimmune illness can be diminished or even averted. Inhibitory receptors such as CTLA-4 and Tim-3, anti-inflammatory cytokines including IL-10 and TGF-β, and specialized cell populations such as Treg cells, represent a selection of the inhibitory pathways that modulate the immune response. Recently, it has been established that innate immunity initiates the signals that control and activate the immune response. Depletion of regulatory T cells enhances inflammation in autoimmune disease animal models caused by adjuvants, whereas administration of these cells lowers or even stops disease progression. As a result, whether or not an autoimmune illness manifests itself can depend on the balance between regulatory and effector T cells. Recent research indicates that microbial activation of TLR reduces the quantity of regulatory T cells, which may help to explain the link between the start of an autoimmune disease and infection. Therefore, alterations in the mechanisms regulating inflammation, whether due to genetics or environmental factors, may accelerate the onset of autoimmune disease from autoimmunity [36, 37].

Immunotherapy

Patients typically seek medical care only after autoimmune escalation and antigenic dissemination have significantly widened the immune response, making treatment difficult when the sickness first appears. Immuno-suppressive or antiviral/antibacterial medications have previously been used as therapy for autoimmune illnesses. Recent treatments, however, focus on pathways shared by a number of autoimmune illnesses. Pro-inflammatory cytokines like TNF and IL-1b are the aim of some therapies. Others use therapeutic vaccination with regulatory T cells or block costimulatory molecules. Well-known oral medications, such as statins and angiotensin-blocking agents, which are widely used to treat various medical disorders, such as allergies and hypertension, have been shown in recent research to reduce autoimmune inflammation. Several effector mechanisms will likely need to be addressed in order to successfully cure autoimmune disease, on the other hand ,there are multiple effector mechanisms participate to the immunopathogenesis of autoimmune disorders [38,39].

Common Autoimmune Diseases

There are more than 80 autoimmune diseases. Here are 14 of the most common ones [40,41].

1- Type 1 diabetes	2- Rheumatoid arthritis (RA)
3- Psoriasis/psoriatic arthritis	4- Multiple sclerosis
5- Systemic lupus erythematosus (SLE)	6- Inflammatory bowel disease
7- Addison’s disease	8- Graves’ disease
9- Sjögren’s syndrome	10- Hashimoto’s thyroiditis
11- Myasthenia gravis	12- Autoimmune vasculitis
13- Pernicious anemia	14- Celiac disease

Conclusion:

A strong immune response(cellular and humoral) play an important in disrupts immune system regulation and can lead to autoimmunity .It is important to identify some parameters whether genetic markers or hormonal markers that help in early diagnosis of autoimmunity.

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