Burden of Autoimmune Disorders; An updated Review

Abstract:

When immunologic tolerance to auto-reactive immune cells is lost, autoimmune illness manifests as the immune system attacking self-molecules. Numerous autoimmune diseases have been found to be strongly predisposed by genetic, viral, and/or environmental factors. Autoimmune diseases include insulin-dependent diabetic mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis. They are characterized by a variety of problems and symptoms that range from organ-specific to systemic. Additionally, autoimmune pathology may have a role in conditions like arteriosclerosis, inflammatory bowel disease, schizophrenia, and specific forms of infertility. A brief explanation of the immune system and tolerance maintenance, an analysis of a few autoimmune disorders, a look at potential immune auto-reactivity mechanisms, and a review of experimental autoimmune models are all provided in this topic.

1. Introduction:

When the immune system is unable to distinguish between healthy tissue and potentially dangerous antigens, it results in autoimmune diseases. The idea of molecular mimicry can be used to explain the immune system attacking its own host. The immune system will typically fight foreign antigens and develop a reaction in response to the antigens. In autoimmune illnesses, the immune system is unable to tell its own host cells apart from foreign antigens. A mechanism called molecular mimicry is where a foreign antigen resembles a self-antigen structurally.[1-4]. Molecular mimicry continues to be a significant mechanism that may be implicated in the beginning of autoimmunity despite the study surrounding its association with autoimmune disorders. Self-destructive attacks brought on by molecular mimicry can result in a wide range of bodily reactions, from insignificant to potentially fatal. Different autoimmune diseases appear in different ways, and their onset ages vary [5-9]. Autoimmune disorders have a complicated origin, with genetic, hormonal, and environmental factors all contributing. Although autoimmune disorders are typically assumed to be relatively uncommon, their death

and morbidity rates are rather high. In the United States, autoimmune illnesses rank among the top killers of young and middle-aged women (under 65 years of age) [10]. Numerous of these disorders are chronic, which has an impact on quality of life, use of medical services, and direct and indirect economic expenditures[11]. The complex immune system evolved with the primary purpose of defending hosts against infectious pathogens. However, this pleiotropic immune system can cause pathology in two main ways: first, immune deficiency syndromes, in which one or more immune system cells are unable to react in a protective way to a pathogen; and second, autoimmune illnesses.[12-14]. Previously thought to be uncommon, autoimmune diseases are now known to impact 3-5% of the population, with type I diabetes (T1D) and autoimmune thyroid disease (ATD) being the most prevalent of these ailments. The presence of almost 100 different autoimmune illnesses is more significant, some of which are organ-specific (like primary biliary cirrhosis, or PBC) and others of which are indicative of immunological dysfunction affecting a number of organs (like systemic lupus erythematosus) (SLE). The advent of innovative molecular immunology technologies and sophisticated evidence-based clinical laboratory testing have combined to produce considerable gains in prognosis, diagnosis, and illness classification over the past ten years [15].

The more ancient innate immune system and the more recently evolved adaptive immune system are the two components of the immune system. The innate immune system lacks memory and is non-specific to particular infections. The skin, saliva, tears, bacterial flora, and a variety of cells and proteins, such as complement, lysozyme, white blood cells, red blood cells, and platelets, make up the first line of defense. The adaptive immune system, on the other hand, may create targeted immune responses against pathogens that it has previously met since it has the ability to form memories. The adaptive immune system makes use of B- and T-lymphocytes and their byproducts, immunoglobulins, and cytokines to produce a highly specialized response that improves with each consecutive encounter to a particular disease [16-23].

Host receptors on lymphocytes go through substantial gene rearrangement and somatic mutation processes to develop a repertoire of receptors that can recognize a wide range of antigens in order to defend against a wide range of pathogens. The adaptive immune system responds to identification by sending a message of either immunity or tolerance. When "self" antigens present naturally in the body are tolerated, "non-self" antigens elicit the proper immune response

but "self" antigens do not. Autoimmunity may arise when the tolerance process is unsuccessful. Tolerance at the central and peripheral levels is essential for preventing autoimmunity [24-28].

2. The emergence of immunological tolerance:

In 1948, Macfarlane Burnet of the Walter and Eliza Hall Institute for Medical Research in Melbourne, Australia, made the claim that immunological tolerance to oneself is a trait learned throughout development as opposed to an innate trait. A few years later, in 1953, Peter Medawar and his associates experimentally proved that inbred mice could be trained to develop immunological tolerance. Immune tolerance was finally explained as the capacity of the immune system to refrain from attacking self-molecules, cells, or tissues [29].

Although it is intriguing that Paul Ehrlich's groundbreaking work at the beginning of the 20th century had already established the concept of "horror autotoxicus," many researchers did not believe in the concept of autoimmunity. The earliest murine model of autoimmunity, the New Zealand black (NZB) mouse, was initially published in 1959. Thyroid auto antibodies were later discovered, and autoimmune thyroiditis was established as the archetypal autoimmune disease [30, 31]. To comprehend immunological tolerance, a number of fundamental ideas should be introduced, such as central tolerance, peripheral energy, T regulatory cells (Tregs), and the homeostasis brought on by cytokines and chemokines and their corresponding receptors. Immune system homeostasis is mostly shaped by central tolerance, which is found in the thymus and bone marrow. Before growing and leaving the thymus, developing lymphocytes go through positive selection in the brain. Notably, the thymic medulla of an otherwise healthy host undergoes negative selection and deletion of cells with potential self-peptide sensitivity. Importantly, mature T cells undergo secondary selection (peripheral tolerance) after leaving the thymus, during which the majority of self-reactive T cells are eliminated or became anergic. Additionally, immature B cells are destroyed through a process known as clonal deletion or clonal anergy if they express surface IgM that detects common self cell-surface antigens. Receptor editing is a technique that allows deletion-resistant auto reactive B cells to survive. Peripheral tolerance also has an impact on mature B cells [32, 33].

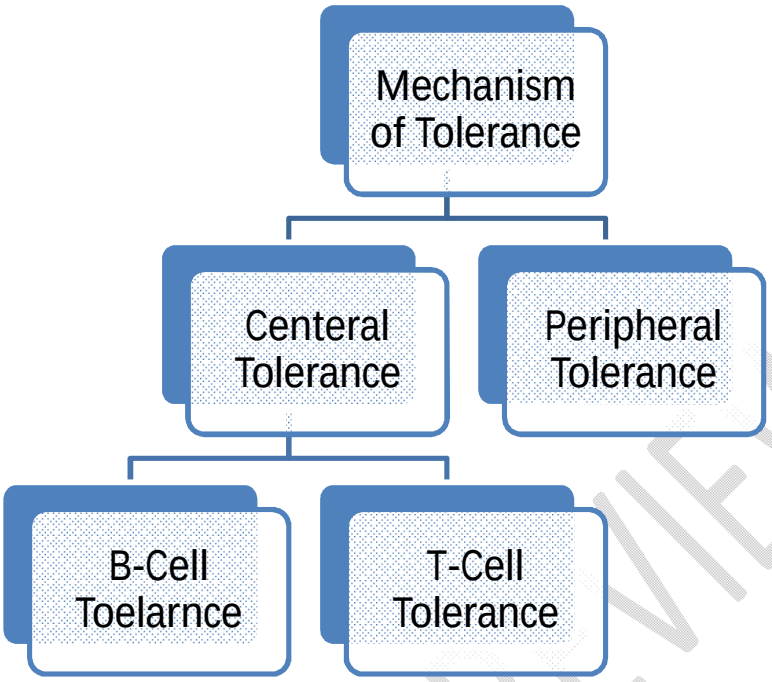

Figure 1 Emergence of immunological Tolerance

2.2. Central Tolerance:

The thymus and bone marrow, respectively, are the primary sites of T- and B-lymphocyte maturation. As a result, central tolerance refers to the processes of tolerance found in these places.

2.2.1. T- cell tolerance:

When immature T-cells enter the thymus from the bone marrow and come into contact with proteins attached to major histo-compatibility complexes, the process begins (MHC). MHC molecules are cell-surface antigens found in vertebrates; they are also known as human leukocyte antigens in humans (HLA). MHC Class I is made up of the three subtypes HLA-A, HLA-B, and HLA-C. Almost all cell types in the body express MHC I antigens. HLA-DP, HLA-DQ, and HLA-DR are additional subtypes that fall under MHC Class II. Less frequently, MHC II molecules are seen in reticuloendothelial system cells such macrophages and B-lymphocytes. The type of T-lymphocytes that each MHC molecule interacts with determines its relevance. When MHC I molecules bind to CD8+-T lymphocytes, a cytotoxic response is triggered, and

when MHC II molecules connect to CD4+-T cells, a helper T-cell response is triggered [34, 35]. The cortical epithelial area of the thymus is where the central tolerance process starts. In order to interact with immature double-positive T cells that express both CD4+ and CD8+, endogenous proteins are linked to either MHC I or MHC II molecules. T-lymphocytes that bind with a medium affinity are indicated to continue living and develop into single-positive lymphocytes, producing either CD4+ or CD8+ lymphocytes. Positive selection is what we call this. Each CD4+ or CD8+ T-lymphocyte is then exposed to MHC molecules that are coupled to self-peptides as these cells travel to the corticomedullary junction region. If there is strong binding at this point, the corresponding T-cell will die through apoptosis. Negative selection is what we call this [36-40]. The first line of defense against auto-reactive T-cell spread into the systemic circulation is central tolerance. The medullary epithelial cells of the thymus play a significant role in the effectiveness of this process. These cells produce autoimmune regulator transcription factors (AIRE), which lead to enhanced production of tissue-specific antigens prevalent in other parts of the body, to display a comprehensive array of self-peptides found in all organs of the body. Effective negative selection is aided by the expression of tissue-specific antigens. When AIRE mutations occur and less tissue-restricted antigen expression occurs, autoimmune disease may result. An illustration of this is the illness known as autoimmune poly-glandular syndrome type I (APECED), which is defined by Addison disease, hypoparathyroidism, and at least two of the following three disorders [41-44].

2.2.2. B-Cell Tolerance:

In the bone marrow, the immature B-cell central tolerance process takes place. B-cells produce antibodies, also known as immune-globulins, which are crucial for the immune response to a variety of infections. These antibodies are heavy- and light-chained glycoprotein molecules that attach to antigens, including those of microbial origin, and aid in their destruction. Immunoglobulins come in five classes: IgG, IgM, IgA, IgE, and IgD. Each class has a different purpose in defending the body against both acute and chronic infections as well as different sorts of pathogens, such as bacteria, viruses, parasites, and fungi. Recurrent infections are more likely to happen when people are unable to manufacture some or all antibodies [45]. The membrane-bound version of the B-antibody cell's interacts with the antigen on the antigen-presenting cell to activate it. In response to this encounter, the B-cell transforms into a plasma cell and secretes

significant amounts of certain immunoglobulins that are intended to attack the antigen. This procedure is essential for defense against foreign antigens. However, autoimmunity develops when B-cells identify and eliminate self-antigens. There are tolerance mechanisms in place to stop this from happening, just like T-cells do [46].

2.3. Peripheral Tolerance:

T- and B-lymphocytes penetrate peripheral immunological organs and tissues, such as the spleen and lymph nodes, after leaving the thymus and bone marrow. In these areas, peripheral tolerance mechanisms guard against the development of autoimmunity in the event that auto-reactive cells get past all central tolerance checks. Peripheral tolerance can take many different forms [47]. The first primary peripheral tolerance mechanism is energy. A lack of immunological response brought on by the lack of costimulatory signals is referred to as energy. T-lymphocytes go through the following process. In addition to the MHC: T-cell receptor connection, mounting an immune response necessitates the delivery of a second signal via costimulatory molecules. There are other costimulatory pathways, but the CD28:B7 axis is a significant one. T-lymphocytes have a receptor called CD28 that interacts to B7, a lig and found on antigen-presenting cells. The interaction between the MHC: TCR and CD28:B7 helps the T-lymphocyte develop and survive by causing the cytokine interleukin-2 to be produced. Therefore, the immunological response will not continue if the second costimulatory signal is not supplied [48-51]. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 are two proteins that help to maintain anergy (PD-1). T-lymphocytes have the CTLA4 receptor, which has a stronger affinity for B7 than CD28. When a T-lymphocyte detects a self-antigen, CTLA4 binds to B7 and triggers its clearance by clathrin, blocking the costimulatory signal. The PD-1 operates similarly. It detects the ligands PD-L1, and PD-L2 located on antigen-presenting cells and is expressed on different kinds of T-cells. The phosphorylation of PD-1's tyrosine motifs upon interaction with either of its ligands has the downstream impact of downregulating TCR signalling. Autoimmunity can be brought on by any anomaly in the peripheral tolerance pathway [52-55]. Another mechanism of peripheral tolerance is clonal ignorance. Through a variety of methods, autoreactive T-lymphocytes disregard self-antigen during this process. The inability of lymphocytes to access self-antigens may be the result of a physical barrier, such as the blood-brain barrier. It can also be because lymphocytes were not exposed to enough self-antigen to

trigger an autoimmune reaction. In other instances, apoptosis leads to peripheral tolerance. The Fas-Fas ligand system becomes activated when auto reactive T-cells bind to self-antigen complexes. T-lymphocytes contain both Fas and its ligand, and their interaction causes the T-lymphocyte to die by inducing the caspase cascade. Therefore, a mutation in the Fas gene can cause both lympho proliferative diseases and autoimmunity. This is how the disease autoimmune lympho proliferative syndrome develops (ALPS)[56].

3. Epidemiology of different autoimmune diseases:

The prevalence and incidence of autoimmune disorders differ. When variations in age, gender, ethnicity, and other demographic variables are taken into account, the geo-epidemiology becomes more complex.

Table 1 Data From [57]

Types	Age Onset	Female/Male	Incidence at USA and Europe	Incidence at Middle east and asia
Multiple sclerosis	20–40	2/1	2.7–7.5	0.7–3.6
Type 1 diabetes	6–13	1/1	10–20	<1
Primary biliary cirrhosis	50–60	10/1	2.7 (USA)	0.34–0.42
Autoimmune hepatitis	<40 (T1) 2–14 (T2)	4/1 (T1) 10/1 (T2)	0.5 (USA)	0.08–0.15 (Japan)
Graves' disease	50–60	5/1	38	120
Crohn's disease	15–30, 60–80	1/1.2	6.9–20.2	0.24–1.34
Ulcerative colitis	15–30, 60–80	1/1	8.3–19.2	0.36–6.02

Coeliac disease	Childhood	1/1	0.9–9.1 (all ages)	Unclear
Addison's disease	15–45	0.8–2.4/1	1 (USA)	Unclear
Sjogren's syndrome	40–50	9/1	3–5 (USA)	6.57
Systemic lupus erythematosus	30–50	9/1	1.2–8.7	0.9–3.1
Rheumatoid arthritis	44–55	2/1	31–45	8–42

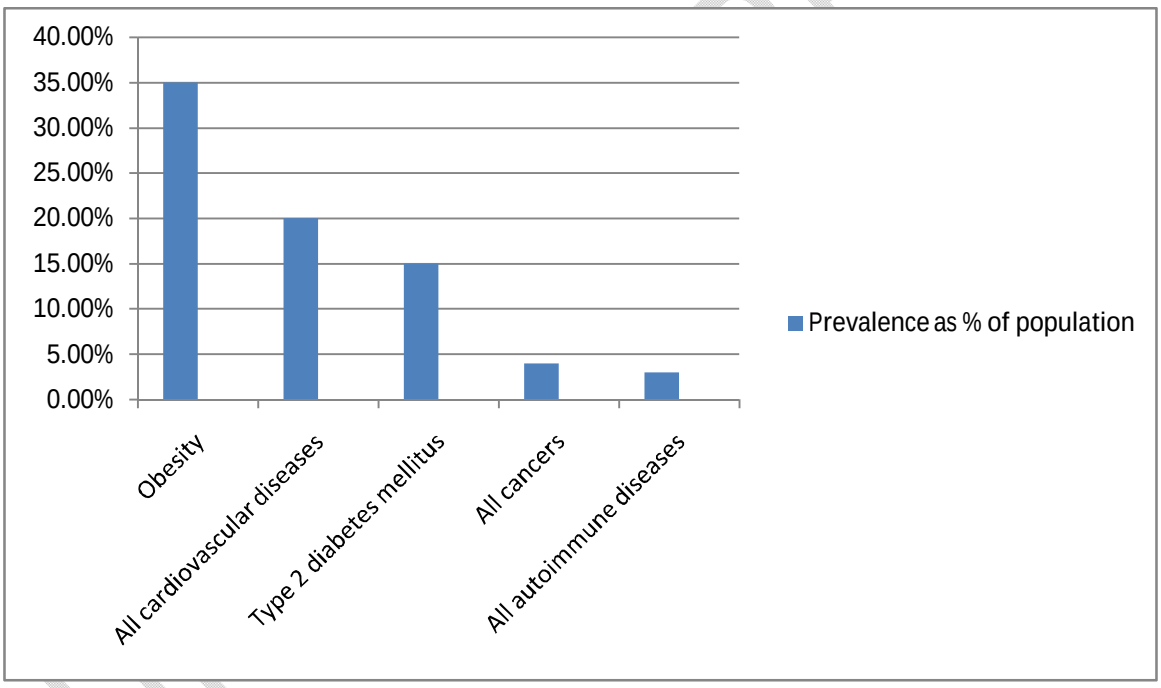

Figure 2 Prevalence of some autoimmune diseases [58]

4. Clinical significance:

In 2009, between 7.6 and 9.5% of Americans reported having one of 29 common autoimmune disorders [59]. It's possible that the prevalence is now significantly higher. In addition, autoimmune illnesses afflict women more frequently than men. Numerous clinical symptoms,

many of which are disabling and significantly affect quality of life, result from an aberrant cellular response to self-antigen recognition. Systemic and localised consequences are also possible with autoimmune diseases. The following list includes the key clinical features of several significant autoimmune disorders from both categories. It is significant to note that this is not a comprehensive list, and even organ-based autoimmune disorders can proceed to different systemic symptoms [60-63].

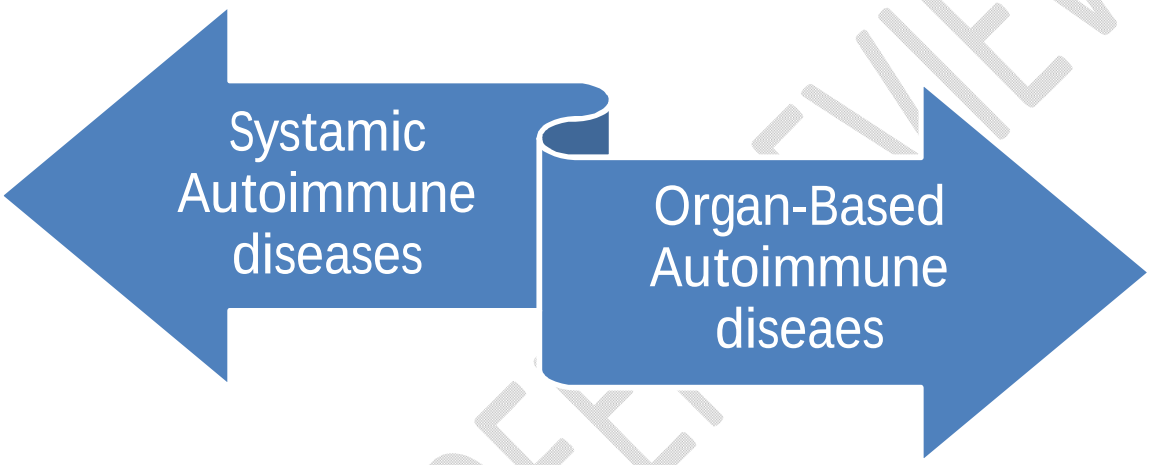

Figure 3Catagories Of autoimmune Disorders

Table 2 : List of Systemic Autoimmune Diseases

Types	Symptoms	Diagnosis	Possible Treatments	Reference
Systemic Lupus Erythematosus:	Malar rash, discoid rash, photosensitivity, mouth ulcers, arthritis, serositis, kidney disease, hematologic disorder,	By assessment of different symptom, physical examination, X-rays, and lab tests.	Hydroxychloroquine, corticosteroids	[64-67]

	neurologic disorder, immunologic disorder, and antinuclear antibody positive.			
Sjogren Syndrome	xerophthalmia, xerostomia, and numerous manifestations affecting the neurological system, lungs, kidneys, and skin.	antibodies , pattern of inflammation, found most often on the salivary glands lips,	Hydroxychloroquine (Plaquenil), certain immunosupressors	[68-71]
Scleroderma	excessive buildup of collagen in the skin and internal organs, which can manifest locally or systemically (limited cutaneous systemic and diffuse cutaneous systemic). The CREST syndrome of calcinosis, Raynaud's	physical exam and biopsy	Using corticosteroids or non-steroidal anti-inflammatory drugs to relieve pain	[72, 73]

	phenomenon, esophageal involvement, scleroderma, and telangiectasia are all linked to the limited cutaneous systemic variant.			
Sarcoidosis	Noncaseating granulomas can develop in any organ of the body, including the eyes, skin, heart, gastrointestinal tract, nervous system, and endocrine system. Sarcoidosis most frequently manifests as bilateral hilar lymphadenopathy in the lungs.	biopsy	Corticosteroids	[74]
Rheumatoid Arthritis	Symmetric synovial inflammation, morning stiffness lasting more than	Magnetic resonance imaging (MRI) and ultrasound	Methotrexate	[75]

	30 minutes, and numerous extra-articular symptoms such as rheumatoid nodules, amyloidosis, and systemic vasculitis			

Table 3 : List of organ-based Autoimmune disorders

Types	Symptoms	Diagnosis	Possible Treatments	References
Type 1 Diabetes	Autoantibodies to pancreatic islet cells in type 1 diabetes prevent the pancreas from producing insulin, which causes hyperglycemia, polyuria, and polydipsia.	blood sample	Intensive insulin therapy	[76-78]
Crohn Disease	patchy, transmural lesions that can	Colonoscopy, Biopsy	Steroid medicines	[79]

	affect the entire gastrointestinal tract.			
Bullous Pemphigoid	symmetric, tense bullae on the trunk, inner thighs, and flexures as well as urticaria, pruritus, and eczema.	skin biopsy and immunofluorescence testing of skin and serum	Topical corticosteroids, systemic corticosteroids, and doxycycline	[80]
Ankylosing Spondylitis	Sacroiliac joint soreness, lower back pain, peripheral arthritis, and dactylitis	X-Ray	Nonsteroidal anti-inflammatory drugs (NSAIDs) — such as naproxen (Aleve, Naprosyn, others) and ibuprofen (Advil, Motrin IB, others)	[81]
Multiple Sclerosis	demyelination resulting in spinal cord syndromes, ocular neuritis, brainstem and cerebellar syndromes, and	a thorough neurological examination and medical history of the patient. The neuroaxis using magnetic resonance imaging.	injectable, oral and infusions medications.	[82]

	cognitive impairment as a result of persistent central nervous system inflammation	testing for evoked potentials. a spinal fluid analysis		

5. New Insights into treatment of Autoimmune Disorders:

Type 1 diabetes, multiple sclerosis, and rheumatoid arthritis are examples of autoimmune diseases brought on by immune system dysfunction. In these illnesses, the body's own cells are attacked rather than protected by T lymphocytes, which normally coordinate the immune response against viruses and bacteria and harm the target organ. Current medications lack the mechanisms to discriminate between defective and normal cells, making it difficult to eradicate the disease's defective cells. The medications used to treat certain autoimmune diseases also lower healthy immunity, making the patient more prone to infection. The use of a novel class of nanoparticles coated with protein targets targeted at the T-cells responsible for autoimmune illnesses allows for their reprogramming into regulatory T cells and the selective removal of the disease, according to a study published in Nature. A brand-new biological mechanism that controls the immune response is responsible for this.

Multifactorial treatments are being tried to treat pathologic conditions and restore immunological tolerance in affected people as the pathogenetic processes of autoimmune disorders are revealed. Immune-regulatory cell populations are used in cell therapies, which are promising approaches that can help researchers in the domains of immunology and rheumatology reach their long-term objectives. We can easily anticipate that the aggressively continuous development of biotechnologies for producing and controlling in vitro expanded cell therapies will hasten the use of these drugs in clinical trials for a variety of autoimmune illnesses. Future clinical studies will offer uniform efficacies and safety thanks to protocols for each cell therapy that have received international agreement regarding the best manufacturing techniques and regimens, including sources, doses, and intervals. There are still a lot of difficulties to overcome. However,

significant efforts being made all over the world will improve the standing of the present cell therapies used to treat autoimmune illnesses [83-91].

Conclusion:

From diagnosis to management and treatment, the identification and management of immunosuppressive/immunocompromised disorders remains a challenge. More than 100 different syndromes are being studied actively in order to better define the pharmacologic medicines that particularly target the illness pathways of many of these syndromes. The medical community's capacity to properly handle autoimmune disorders continues to be complicated by knowledge gaps. Providers do not think to inquire about the presence of a family history of autoimmune illnesses, and patients do not think to discuss it, as a result of this lack of awareness among the American public and the medical community. Biologic drugs that alter particular inflammatory effector pathways are still a popular and effective pharmacologic strategy. Hope exists for potential modification of the host immune system to return balance and immune tolerance to the human body through research to further create drugs that will entirely reverse, if not cure, these disorders.

References

1. Invernizzi, P., et al., *Female predominance and X chromosome defects in autoimmune diseases.* J Autoimmun, 2009. **33**(1): p. 12-6.
2. Talal, N., *Sjögren's syndrome: historical overview and clinical spectrum of disease.* Rheum Dis Clin North Am, 1992. **18**(3): p. 507-15.
3. Fessel, W.J., *Systemic lupus erythematosus in the community. Incidence, prevalence, outcome, and first symptoms; the high prevalence in black women.* Arch Intern Med, 1974. **134**(6): p. 1027-35.
4. Linos, A., et al., *The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality.* Am J Epidemiol, 1980. **111**(1): p. 87-98.
5. Gartler, S.M. and A.D. Riggs, *Mammalian X-chromosome inactivation.* Annu Rev Genet, 1983. **17**: p. 155-90.
6. Willard, H.F., *Tales of the Y chromosome.* Nature, 2003. **423**(6942): p. 810-1, 813.

7. Plath, K., et al., *Role of histone H3 lysine 27 methylation in X inactivation.* Science, 2003. **300**(5616): p. 131-5.
8. Syrett, C.M., et al., *Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases.* JCI Insight, 2019. **4**(7).
9. McCain, J., *The Disease Burden of the Most Common Autoimmune Diseases.* Manag Care, 2016. **25**(7): p. 28-32.
10. Cooper, G.S., F.W. Miller, and D.R. Germolec, *Occupational exposures and autoimmune diseases.* International Immunopharmacology, 2002. **2**(2): p. 303-313.
11. Cooper, G.S. and B.C. Stroehla, *The epidemiology of autoimmune diseases.* Autoimmunity Reviews, 2003. **2**(3): p. 119-125.
12. Eaton, W.W., et al., *Epidemiology of autoimmune diseases in Denmark.* J Autoimmun, 2007. **29**(1): p. 1-9.
13. Walsh, S.J. and L.M. Rau, *Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States.* Am J Public Health, 2000. **90**(9): p. 1463-6.
14. Kong, M.F. and W. Jeffcoate, *Eighty-six cases of Addison's disease.* Clin Endocrinol (Oxf), 1994. **41**(6): p. 757-61.
15. Yu, C., M.E. Gershwin, and C. Chang, *Diagnostic criteria for systemic lupus erythematosus: A critical review.* Journal of Autoimmunity, 2014. **48-49**: p. 10-13.
16. Laakso, M., et al., *Death certificate and mortality in rheumatoid arthritis.* Scand J Rheumatol, 1986. **15**(2): p. 129-33.
17. Calvo-Alén, J., et al., *Lack of recording of systemic lupus erythematosus in the death certificates of lupus patients.* Rheumatology (Oxford), 2005. **44**(9): p. 1186-9.
18. Mühlhauser, I., et al., *Reliability of causes of death in persons with Type I diabetes.* Diabetologia, 2002. **45**(11): p. 1490-7.
19. Broadley, S.A., et al., *Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey.* Brain, 2000. **123 (Pt 6)**: p. 1102-11.
20. Cooper, G.S., et al., *The prevalence and accuracy of self-reported history of 11 autoimmune diseases.* J Rheumatol, 2008. **35**(10): p. 2001-4.
21. Anaya, J.M., L. Gómez, and J. Castiblanco, *Is there a common genetic basis for autoimmune diseases?* Clin Dev Immunol, 2006. **13**(2-4): p. 185-95.

22. Cohen, R., et al., *Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002.* Inflamm Bowel Dis, 2008. **14**(6): p. 738-43.
23. Somers, E.C., et al., *Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder?* Am J Epidemiol, 2009. **169**(6): p. 749-55.
24. Kyurkchiev, D., et al., *Secretion of immunoregulatory cytokines by mesenchymal stem cells.* World J Stem Cells, 2014. **6**(5): p. 552-70.
25. Ren, G., et al., *Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression.* J Immunol, 2010. **184**(5): p. 2321-8.
26. Jiang, D., et al., *Suppression of Neutrophil-Mediated Tissue Damage-A Novel Skill of Mesenchymal Stem Cells.* Stem Cells, 2016. **34**(9): p. 2393-406.
27. Ryan, S.T., et al., *Extracellular Vesicles from Mesenchymal Stromal Cells for the Treatment of Inflammation-Related Conditions.* Int J Mol Sci, 2021. **22**(6).
28. Maccario, R., et al., *Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype.* Haematologica, 2005. **90**(4): p. 516-25.
29. Wang, L., et al., *Breach of Tolerance: Primary Biliary Cirrhosis.* Semin Liver Dis, 2014. **34**(03): p. 297-317.
30. Silverstein, A.M., *Paul Ehrlich, archives and the history of immunology.* Nature Immunology, 2005. **6**(7): p. 639-639.
31. Rose, N.R. and E. Witebsky, *Studies on organ specificity. V. Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts.* J Immunol, 1956. **76**(6): p. 417-27.
32. Salinas, G.F., et al., *The role of B lymphocytes in the progression from autoimmunity to autoimmune disease.* Clinical Immunology, 2013. **146**(1): p. 34-45.
33. Hang, L., R.M. Nakamura, and R. Tubbs, *Current Concepts and Advances in Clinical Laboratory Testing for Autoimmune Diseases.* Critical Reviews in Clinical Laboratory Sciences, 1997. **34**(3): p. 275-311.
34. Khan, U. and H. Ghazanfar, *T Lymphocytes and Autoimmunity.* Int Rev Cell Mol Biol, 2018. **341**: p. 125-168.
35. Simpson, E., *Function of the MHC.* Immunol Suppl, 1988. **1**: p. 27-30.

36. Wu, D., et al., *Prevalence of Type 1 diabetes in New Zealanders aged 0-24 years.* N Z Med J, 2005. **118**(1218): p. U1557.
37. Moore, K.R., et al., *Three-year prevalence and incidence of diabetes among American Indian youth in Montana and Wyoming, 1999 to 2001.* J Pediatr, 2003. **143**(3): p. 368-71.
38. Peter, S.A., et al., *The incidence and prevalence of type-1 diabetes mellitus.* J Natl Med Assoc, 2005. **97**(2): p. 250-2.
39. Al-Herbish, A.S., et al., *Prevalence of type 1 diabetes mellitus in Saudi Arabian children and adolescents.* Saudi Med J, 2008. **29**(9): p. 1285-8.
40. Moussa, M.A., et al., *Prevalence of type 1 diabetes among 6- to 18-year-old Kuwaiti children.* Med Princ Pract, 2005. **14**(2): p. 87-91.
41. Boberg, K.M., et al., *Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population.* Scand J Gastroenterol, 1998. **33**(1): p. 99-103.
42. Hurlburt, K.J., et al., *Prevalence of autoimmune liver disease in Alaska Natives.* Am J Gastroenterol, 2002. **97**(9): p. 2402-7.
43. Lee, Y.M., et al., *Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women.* J Gastroenterol Hepatol, 2001. **16**(12): p. 1384-9.
44. Rautiainen, H., et al., *Prevalence and incidence of primary biliary cirrhosis are increasing in Finland.* Scand J Gastroenterol, 2007. **42**(11): p. 1347-53.
45. Taussig, M.J., *Molecular genetics of immunoglobulins.* Immunol Suppl, 1988. **1**: p. 7-15.
46. Nemazee, D., *Mechanisms of central tolerance for B cells.* Nat Rev Immunol, 2017. **17**(5): p. 281-294.
47. Rose, N.R., *Mechanisms of autoimmunity.* Semin Liver Dis, 2002. **22**(4): p. 387-94.
48. Kim, W.R., et al., *Epidemiology and natural history of primary biliary cirrhosis in a US community.* Gastroenterology, 2000. **119**(6): p. 1631-6.
49. James, O.F., et al., *Primary biliary cirrhosis once rare, now common in the United Kingdom?* Hepatology, 1999. **30**(2): p. 390-4.
50. Delgado, J., et al., *The epidemiology of primary biliary cirrhosis in southern Israel.* Isr Med Assoc J, 2005. **7**(11): p. 717-21.

51. Hollowell, J.G., et al., *Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III).* J Clin Endocrinol Metab, 2002. **87**(2): p. 489-99.
52. Mayr, W.T., et al., *Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985-2000.* Neurology, 2003. **61**(10): p. 1373-7.
53. Hader, W.J. and I.M. Yee, *Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan.* Neurology, 2007. **69**(12): p. 1224-9.
54. Warren, S.A., L.W. Svenson, and K.G. Warren, *Contribution of incidence to increasing prevalence of multiple sclerosis in Alberta, Canada.* Mult Scler, 2008. **14**(7): p. 872-9.
55. Svenson, L.W., et al., *Prevalence of multiple sclerosis in First Nations people of Alberta.* Can J Neurol Sci, 2007. **34**(2): p. 175-80.
56. Kuehn, H.S., et al., *FAS haploinsufficiency is a common disease mechanism in the human autoimmune lymphoproliferative syndrome.* J Immunol, 2011. **186**(10): p. 6035-43.
57. Wang, L., F.-S. Wang, and M.E. Gershwin, *Human autoimmune diseases: a comprehensive update.* Journal of Internal Medicine, 2015. **278**(4): p. 369-395.
58. *<Prevalence of Autoimmune Diseases - Autoimmune Disease _ Johns Hopkins Pathology.pdf>*.
59. Päivönsalo-Hietanen, T., J. Tuominen, and K.M. Saari, *Uveitis in children: population-based study in Finland.* Acta Ophthalmol Scand, 2000. **78**(1): p. 84-8.
60. Stephen, C., *Capture-recapture methods in epidemiological studies.* Infect Control Hosp Epidemiol, 1996. **17**(4): p. 262-6.
61. Ginn, L.R., et al., *Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases.* Arthritis Rheum, 1998. **41**(3): p. 400-5.
62. Anaya, J.M., et al., *Autoimmune disease aggregation in families with primary Sjögren's syndrome.* J Rheumatol, 2006. **33**(11): p. 2227-34.
63. Dandona, L., et al., *Population based assessment of uveitis in an urban population in southern India.* Br J Ophthalmol, 2000. **84**(7): p. 706-9.
64. Gershwin, M.E., *Bone marrow transplantation, refractory autoimmunity and the contributions of Susumu Ikehara.* J Autoimmun, 2008. **30**(3): p. 105-7.

65. Whittingham, S., M.J. Rowley, and M.E. Gershwin, *A tribute to an outstanding immunologist - Ian Reay Mackay.* J Autoimmun, 2008. **31**(3): p. 197-200.
66. Mackay, I.R., N.V. Leskovsek, and N.R. Rose, *Cell damage and autoimmunity: a critical appraisal.* J Autoimmun, 2008. **30**(1-2): p. 5-11.
67. Tsokos, G.C., *Systemic lupus erythematosus.* N Engl J Med, 2011. **365**(22): p. 2110-21.
68. Rose, N.R., D.A. Neumann, and A. Herskowitz, *Autoimmune myocarditis: concepts and questions.* Immunol Today, 1991. **12**(8): p. 253-5.
69. Lieberman, E.B., et al., *Clinicopathologic description of myocarditis.* J Am Coll Cardiol, 1991. **18**(7): p. 1617-26.
70. Rose, N.R., *Autoimmunity in coxsackievirus infection.* Curr Top Microbiol Immunol, 2008. **323**: p. 293-314.
71. Rashtak, S. and M.R. Pittelkow, *Skin involvement in systemic autoimmune diseases.* Curr Dir Autoimmun, 2008. **10**: p. 344-58.
72. Shoenfeld, Y., et al., *The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity.* J Autoimmun, 2008. **31**(4): p. 325-30.
73. Rongioletti, F., et al., *Scleroderma with an update about clinico-pathological correlation.* G Ital Dermatol Venereol, 2018. **153**(2): p. 208-215.
74. Llanos, O. and N. Hamzeh, *Sarcoidosis.* Med Clin North Am, 2019. **103**(3): p. 527-534.
75. Lebwohl, B., D.S. Sanders, and P.H.R. Green, *Coeliac disease.* Lancet, 2018. **391**(10115): p. 70-81.
76. Alkhateeb, A., et al., *Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families.* Pigment Cell Res, 2003. **16**(3): p. 208-14.
77. Somers, E.C., et al., *Autoimmune diseases co-occurring within individuals and within families: a systematic review.* Epidemiology, 2006. **17**(2): p. 202-17.
78. Lettre, G. and J.D. Rioux, *Autoimmune diseases: insights from genome-wide association studies.* Hum Mol Genet, 2008. **17**(R2): p. R116-21.
79. Cushing, K. and P.D.R. Higgins, *Management of Crohn Disease: A Review.* Jama, 2021. **325**(1): p. 69-80.
80. Miyamoto, D., et al., *Bullous pemphigoid.* An Bras Dermatol, 2019. **94**(2): p. 133-146.
81. Zhu, W., et al., *Ankylosing spondylitis: etiology, pathogenesis, and treatments.* Bone Res, 2019. **7**: p. 22.

82. Ömerhoca, S., S.Y. Akkaş, and N.K. İçen, *Multiple Sclerosis: Diagnosis and Differential Diagnosis.* Noro Psikiyatr Ars, 2018. **55**(Suppl 1): p. S1-s9.
83. Cronstein, B.N. and T.M. Aune, *Methotrexate and its mechanisms of action in inflammatory arthritis.* Nat Rev Rheumatol, 2020. **16**(3): p. 145-154.
84. Hardy, R.S., K. Raza, and M.S. Cooper, *Therapeutic glucocorticoids: mechanisms of actions in rheumatic diseases.* Nat Rev Rheumatol, 2020. **16**(3): p. 133-144.
85. Nikiphorou, E., M.H. Buch, and K.L. Hyrich, *Biologics registers in RA: methodological aspects, current role and future applications.* Nat Rev Rheumatol, 2017. **13**(8): p. 503-510.
86. Rendas-Baum, R., et al., *Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor-α inhibitors.* Arthritis Res Ther, 2011. **13**(1): p. R25.
87. Kuijper, T.M., et al., *Flare Rate in Patients with Rheumatoid Arthritis in Low Disease Activity or Remission When Tapering or Stopping Synthetic or Biologic DMARD: A Systematic Review.* J Rheumatol, 2015. **42**(11): p. 2012-22.
88. Murphy, G. and D.A. Isenberg, *New therapies for systemic lupus erythematosus - past imperfect, future tense.* Nat Rev Rheumatol, 2019. **15**(7): p. 403-412.
89. Mosanya, C.H. and J.D. Isaacs, *Tolerising cellular therapies: what is their promise for autoimmune disease?* Ann Rheum Dis, 2019. **78**(3): p. 297-310.
90. Dominici, M., et al., *Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement.* Cytotherapy, 2006. **8**(4): p. 315-7.
91. Wang, Y., et al., *Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications.* Nat Immunol, 2014. **15**(11): p. 1009-16.