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Oxidative Stress in Systemic Lupus Erythematosus Causes Inflammation and Cellular Damage

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Abstract: Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting various organs, driven by a combination of genetic, environmental, and hormonal factors leading to immunological dysregulation. The disease is characterized by the production of autoantibodies, inflammation, and end-organ damage, with oxidative stress playing a significant role by inducing functional changes in DNA, lipids, and proteins. Current understanding of SLE pathophysiology highlights the importance of oxidative stress biomarkers in predicting disease progression and guiding treatment. Despite available treatments like corticosteroids and immunosuppressants, there remains a need for more effective therapies with fewer side effects. This research aims to investigate the relationship between oxidative stress and SLE progression, utilizing biomarkers to improve early diagnosis and treatment decisions. By analyzing oxidatively modified molecules in SLE patients, the study seeks to enhance our understanding of disease mechanisms and identify new therapeutic targets to reduce morbidity and mortality.

Keywords: Systemic Lupus Erythematosus (SLE), Autoantibodies, Inflammation, Oxidative Stress, Immunomodulation, Autoimmune Disease

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1. Introduction

Women, particularly those that identify as Asian, Hispanic, or African-American, are the majority of people who suffer with SLE, a chronic, disabling condition 2011 [1]. Disease is challenging to diagnose, has no known cure, and progresses in an unpredictable manner through flare-ups and remissions. The majority of therapy is immunosuppressive drugs, which make patients vulnerable to opportunistic infections. For a variety of reasons, like genetic defects, hormones, environmental exposures like UV light, medications, or viral mechanisms, the immune system malfunctions and begins attacking cells, crippling organs including the Joints, Skin, Brain, and Kidneys, resulting in SLE. Several of the symptoms of the condition involve skin rashes (such as the 'butterfly' rash on the face), mouth ulcers, arthritis (pain and swelling in the joints), and neurological symptoms (dementia, convulsions). Thrombocytopenia, which refers to low platelet counts, leukopenia, which refers to low levels of white blood cells, and hemolytic anaemia, which refers to the destruction of red blood cells are the three symptoms that are associated with blood cell damage. It is possible for renal failure to be the consequence of other problems in vital organs like the kidneys, which would contribute to an even greater rate of morbidity and death 2017 [2].

Due to the disease's great heterogeneity, various patient combinations of clinical symptoms may be present. Cell mediated pathways lead to the creation of inflammatory cytokines, loss of regulatory function, and infiltration into organs, causing pathology. On the other hand, autoantibodies travel through the body, accumulate in tissues, and play a role in tissue destruction. 2017 [2]. Steroids and cytotoxic medications are currently used in therapeutic approaches to slow or stop the progression of disease and organ damage. Better therapeutic strategies, however, are required to directly target pathogenic pathways while protecting the defense mechanisms of the immune system. In order to manage this complex condition more effectively, it is crucial to identify biomarkers that can anticipate the development, progression, and exacerbation of the disease 2017 [2].

2. Review

Self reactive antibodies are produced at varying rates as the disease progresses, and the condition's pathophysiology is believed to be significantly impacted by various types of cells that secrete antibodies. A diverse spectrum of isotypes, affinities, and idiotypes are secreted as a result of the many methods in which these cells are generated and activated Every one of them functions differently, involving the attachment to a specific antigen and multiple receptor detection. The reactions triggered by the effector lead to persistent tissue inflammation. dsDNA autoantibodies have been extensively researched and were the first to be identified as having a pathogenic role in lupus nephritis. Which, certain cases are gaining attention due to their links to specific organ damage, like Anti-2GP1 antibodies in 2016 or Anti-NMDAR antibodies in neuropsychiatric clinical symptoms [3].

Massive cellular death happens in association with infections, oxidative stress, or overall tissue damage. Various processes, including necrosis, apoptosis, or NETosis (the formation of Neutrophil Extracellular Traps, or NETs), may occur individually or simultaneously 2012 [5]. Failure to promptly eliminate dead cells from the body can lead to the accumulation of cellular waste, triggering inflammation and the release of various autoantigens such as DNA, histones, and ribonucleoproteins. There is a possibility that follicular dendritic cells could generate autoreactive B cells due to somatic hypermutation, leading to the presentation of autoantigens if cellular remnants in secondary lymphoid organs are not cleared properly [5]. The potential of rupturing nuclear autoantigen self-tolerance therefore exists in this sensitive location when nuclear autoantigens are exposed improperly. Actually, the autoantibody germline variations frequently lack autoreactivity. The ensuing generation of autoantibodies is crucial to the emergence of the complicated immune dysfunction that supports SLE. Immune complexes made up of autoantigens and autoantibodies produced from cells are formed and deposit in many organs, including the kidney, causing serious organ damage. They could potentially be created on-site by circulating autoantibodies attaching to planted antigens 2015 [4].

Around a million people with systemic lupus erythematosus (SLE) experience organ damage, either from the autoimmune disease itself or from the long-term use of medications like steroids. For this study, data on the relationship in mid-organ damage and mortality in patients with SLE in 2020 was gathered. [6].

From the 10 420 papers that the search turned up, 21 longitudinal studies were chosen. 85 percent of the studies were deemed to be of exceptional quality. In 10 research examining organ damage (SDI) as a continuous variable and using HR as a quantify of society, a link was observed between a higher danger of mortality and One-Unit increase in SDI. Q p = 0.027, I2=52.1%; pooled HR for these trials was 1.34 [95% CI: 1.24 to 1.44, p0.001]. The elimination of one putative outlier study had little effect on the consolidate HR 1.33 (95% CI: 1.25 to 1.42), p0.001, Q p = 0.087, and I2=42.0% 2020 [6].

Thus, research from many countries has consistently shown a greater death-rate in SLE patients with organ destruction. Reversing the progression of SLE patients' condition with influential therapies and steroid-free technique may decrease organ destruction, enhance

results, and lower death-rate 2020[6].

A higher risk of several cancers has been related to autoimmune diseases like Systemic Lupus erythematosus often recognized as 'lupus' or 'SLE' and other autoimmune conditions. Particularly, those with lupus may have a higher chance of developing lymphoma and other malignancies, like cervical cancer 2022 [7]. Individuals with clement SLE who have had the condition for over a decade face a three to four times higher likelihood of cardiovascular occurrences and mortality approximated to those without SLE who exhibited equivalent traditional cardiovascular risk factors, cIMT, and carotid plaque. A subset of people with SLE who may have a worse prognosis can be recognized by subclinical atherosclerosis 2021, SLICC, and SLE-APS [8].

An autoimmune condition called systemic lupus erythematosus (SLE) has a high mortality rate. The majority of current therapeutic approaches primarily rely on corticosteroids, which have a high morbidity burden, and immunosuppressives, who are limited by poor efficacy, elevated infections, and cancers. Because the immunosuppressive drugs in our arsenal have serious side effects, immunomodulatory therapies are crucial because they offer the chance to avert disease flare-ups and the resulting accumulation of damage. Immunomodulators such as belimumab, hydroxychloroquine, vitamin D, and prosterone (synthetic dehydroeipandrosterone) are available today. These treatments have demonstrated the ability to regulate the abnormal immune reactions linked to SLE without the need for immunosuppression, utilising various cellular and cytokine pathways (2016) [9].

Despite improvements in immunosuppressive drugs and treatments for infections and kidney illness, life expectancy in SLE patients has increased. However, mortality rates remain about three times higher than average. Accelerated atherosclerosis and cardiovascular disease (CVD) are significant contributors to mortality in SLE 2015 [12]. Traditional risk factors were insufficient to anticipate the higher occurrence of CAD and atherosclerosis in SLE patients when compared to controls. In 2013, the high mortality rate among SLE patients due to cardiovascular disease highlights the ongoing significant risk it poses to this population [13].

To avoid autoimmunity, it is a standard procedure to modify or remove self-reactive B cells produced through V(D)J recombination in the bone marrow or due to random mutations in secondary lymphoid organs. However, 10 – 20 percent of mature naive B cells in healthy people have self-reactive B cell receptors (BCRs). In individuals with systemic lupus erythematosus (SLE) that is active serologically, the number increases to 50%. Severity of the disease is associated with a high level of self-DNA reactivity. Within certain autoimmune conditions, such as SLE, a significant antigen is endogenous or "self" DNA. The regulation of anti-DNA antibody production remains uncertain at this time. One probable explanation for DNA-reactive B cells' resistance to activation in healthy individuals is the absence of endogenous DNA, which is normally eliminated during DNA processing by efferocytosis and other mechanisms [15].

3. Discussion

Systemic Lupus Erythematosus is an Autoimmune disorder characterised due to a dearth of tolerance to nuclear antigens. During an active disease, T and B cells, along with other immune cells, are hyperactive, and this hyperactivity may be due to pathogenesis, which involves alterations in the signal transduction pathways involving T-cell and B-cell receptors, such as an increase in protein phosphorylation. For years, the significance of these enzymes in cellular signalling and their role in the development of autoimmune ailments has been widely recognised. Significant advancements have been achieved in comprehending tyrosine kinases and their role in immune cell signalling pathways. Based on research involving animals with lupus and human patients with SLE, this review will explore the role of tyrosine kinases and the newly discovered inhibitors in 2014 [16]. When discussing the causes of autoimmune

diseases, the focus has usually been on autoimmunity, whether it manifests as antibodies or effectors 2013 [17]. Studies on autoimmune diseases such as SLE, MS, type 1 diabetes, and RA in 2011 revealed a common set of genes that impact immune reactivity 2011 [18]. No research has focused on how the effector cells or antibodies affect the target organs' reactivity. The root cause of this duality is not readily apparent. Maybe it's because the term "autoimmune diseases" inherently implies that 2013 [19].

There are a few links between lupus and cancer that have been clarified by researchers. Immunosuppressant medications, like azathioprine (Imuran) and mycophenolate mofetil (Cellcept), are known to increase the likelihood of cancer. Despite this, one of the bigger studies investigating this link concluded that immunosuppressive medication exposure was not the only factor between lupus and cancer, and that the cancer risk was actually greatest in the early stages of the disease. Medical experts still don't fully understand the link in the middle of lupus and cancer 2022 [7]

Inclusion criteria included mild disease, an SLE Diseases Activity Index Score of 3 (1-6), and a SLICC Damage Index Score of 0 (0-1) for individuals with systemic lupus erythematosus. The average patient had been ill for 12–13 years, and the median patient age was 47. The controls, numbering 109 and consisting of 91% females, had an average age of 49 (12). The groups did not vary in baseline carotid intima-media thickness (cIMT) (p=0.068), despite the fact that patients had a higher plaque prevalence. After 10.1 (9.8-10.2) years (p=0.022), 12 patients and 4 controls eventually got the result. With demographics like age, gender, and waist and hip measurements taken into account, C reactive, family history of CV, history of smoking and diabetes, and baseline body mass index in comparison to the manages, the probability of the unfavorable result in patients increased three to four times Protein, total cholesterol, HDL and LDL levels, dyslipidaemia, cIMT, and the Existence of carotid plaque are all factors to consider. The odds ratios (HRs) for a bad outcome were (1.66 [95% CI 1.20 - 2.28]) and (9.08 [95% CI 2.71 - 30.5]) , respectively, for a Above SLICC Score, SLE-antiphospholipid syndrome (SLE-APS), and cIMT in patients. Combining SLICC and SLE-APS with cIMT greatly beset the forecast of the unfavourable result (p 0.001)2021 [8].

Supplementing with vitamin D seems to have a favorable effect on disease activity, notably proteinuria, which is significant in SLE. Belimumab is a successful medication for people with certain serological and clinical features predictive of response because it has particular immunomodulatory qualities. With effects on numerous molecular pathways, hydroxychloroquine is an essential background treatment for SLE. Advantages specific to certain conditions include decreasing flare, feasting cutaneous sickness, and inflammatory arthralgias, complementing general advantages such as longer longevity, enhanced lipids, more acceptable glycemic management, and blood pressure. One SLE immunomodulator that shows promise in lowering disease activity and bone risk is dehydroeipandrosterone 2016 [9].

Despite its tiny size, increased-density lipoprotein (HDL) is well-renowned for its Anti-Oxidative, Anti-Inflammatory, Anti-Thrombotic, and Anti-Apoptotic characteristics, all of which contribute to its atheroprotective effects independent of cholesterol mobilisation 2014 [10]. Consequently, inferior HDL levels were associated with an increased risk of CVD. Low HDL levels and malfunctioning HDL are associated with revved atherosclerosis in SLE patients. Several investigations have looked at HDL-targeted medicines as a possible treatment option for SLE patients who have cardiovascular disease 2020 [14]. Based on these findings, HDL appears to be an untapped potential for lowering CVD risk in SLE patients. This review will discuss the possibilities for HDL-targeted therapy methods, the quantitative and qualitative functions of HDL in healthy and SLE states, and more 2012 [11].

These defense checkpoints may be bypassed by genetic flaws, physiological malfunctions, and/or pathological circumstances, resulting in autoimmunity. A possible explanation for the reactivation of inert DNA-reactive B cells is an increase in the availability of immunogenic

self-DNA. Mutations affecting genes involved in nucleic acid metabolism (including DNases, RNases, and their sensors), as well as systems for removing apoptotic cells, are understood to cause autoimmune illnesses like SLE. Pathogenic anti-DNA antibodies and subsequent clinical illness presentations like SLE may be caused by increased DNA availability as an immunogen, adjuvant, or both, according to a 2019 paper that discusses the relevant research. Let's explore the key elements involved in Anti-DNA reactions, including the physical signs and reasons for immunogenic DNA in autoimmunity, DNA-Protein complexes that trigger immune responses, the regulation of DNA by intracellular and extracellular DNases, autoimmune disorders linked to their malfunction, detectors of immunogenic DNA in cellular compartments, and inflammatory cytokines like interferons that drive disease processes. One potential treatment strategy we suggest for managing SLE is to decrease DNA Availability by boosting extracellular DNase activity 2019 [15].

4. Conclusion

Lupus erythematosus systemic (SLE) is a difficult-to-diagnose and -treat autoimmune illness that impacts several organs. Autoantibodies, inflammation, and end-organ damage are outcomes of immunological dysregulation, which is itself triggered by a combination of genetics, environmental factors, and hormones. By inducing functional oxidative changes to DNA, lipids, and proteins, oxidative stress is a major contributor to cellular damage and inflammation in SLE. Biomarkers that have been oxidatively changed and measured in SLE patient samples may provide light on the pathophysiology of damage caused by oxidative stress, aid in disease prognosis prediction, and guide early treatment decisions. Several treatment options exist for SLE at the moment, but more effective methods are needed to safeguard the immune system's defense systems while directing them towards harmful pathways. In order to better manage this complicated disorder, biomarkers that can predict the onset, course, and worsening of the disease are crucial. To find new biomarkers that can help SLE patients have better outcomes and lower death rates, more study is required..

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