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SARS-Cov-2 Contributing Factors, Triggering the Risk of Autoimmune Diseases

Amen asghar[1], Aftab sarwar[2], Zubair sharif[3]

[1,2,3] Department of Medical Laboratory Sciences, Superior University, Lahore, Pakistan,
Email: bsmls-f21-029@superior.edu.pk

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Abstract

SARS-CoV-2 leads to irregularities in immune response regulation and is believed to contribute to autoimmune diseases, highlighting a significant link between viral infections and autoimmune diseases. This connection arises from the molecular and immunological interactions between the SARS-CoV-2 virus and the host. Autoimmunity can be triggered by various factors that create an overly stimulated immune system. The virus activates both innate and adaptive immunity, which can result in disease progression. COVID-19 disrupts normal antiviral immunity and plays a role in the onset of autoimmune diseases. Several factors contribute to this phenomenon, including molecular mimicry, bystander activation of T-cells, transient immunosuppression, and inflammation. Additionally, vaccination against SARS-CoV-2 may also provoke autoimmunity. In this review, we explore the various factors through which SARS-CoV-2 may contribute to autoimmune diseases, aiming to minimize the risk of developing such conditions following COVID-19 and SARS-CoV-2 vaccination.

Keywords

SARS-COV-2, Autoimmune Disease, Molecular Mimicry, Bystander Activation,

Introduction

Beta-coronaviruses (β-CoVs)are zoonotic viruses, a family of corona virus genus, with the newly emerged β-CoV is named SARS-CoV-2 have been identified in Wuhan-China, December 2019.[(1)] SARS-COV-2 is defined as severe acute inflammatory syndrome which is the cause of coronavirus disease 2019. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic from the early months of 2020. There have been over 414,179 confirmed cases of COVID-19 reported in 197 countries, with 332,331 cases outside of China and 81,848 cases in China.[(2)] There have been reported 7,057,132 confirmed COVID-induced deaths worldwide**.** The highest death toll due to coronavirus has been reported in the united states .[(3)]An immune response regulation is perturbed by SARS-COV-2 At its most severe, acute respiratory distress syndrome entails the rapid onset of diffuse inflammation throughout the lung. SARS-CoV-2 is transmitted via aerosols and respiratory droplets, with a normal incubation period of 4–5 days and subsequent development of symptoms. Most patients arrive at healthcare facilities with mild to moderate illness, featuring headache, myalgia, fever, coughing and diarrhea but some do not have symptoms.[(4)]Autoimmune diseases a possible sequel to SARS-COV-2. There are a number of ways in which autoimmunity can be induced, often through the creation of an over stimulated state of the immune system. Many years before, it was already known that viruses are an important part of the environmental triggers for autoimmune antibodies and thus autoimmune diseases[(5)] SARS-CoV-2 activates both innate and adaptive immunity, which can lead to disease progression. Research indicates that Covid-19 interferes with normal antiviral immune responses, especially in individuals with comorbidities, older adults, and those with certain genetic predispositions. This disruption results in lymphopenia (affecting CD4+ T, CD8+ T, NK, and B cells), a decrease in regulatory T-cells (Treg), excessive T cell activation, an overproduction of pro-inflammatory cytokines

(including IL-2R, IL-1, IL-6, IL-8, IL-10, IL-17, and TNF-α), T cell exhaustion, and an increase in antibody levels.[6-8] SARS-CoV-2 is associated with autoimmune diseases, influenced by various factors such as molecular mimicry, bystander activation of T-cells, transient immunosuppression, and inflammation which have also been observed in post-COVID-19 autoimmunity. Numerous studies have indicated a connection between the presence of autoantibodies in patients and the severity of COVID-19. When a virus infects the respiratory epithelium, the immune system becomes hyperactive, activating both innate and acquired immunity. This hyper-activation can lead to a "cytokine storm," and any factor that contributes to chronic inflammation can play a role in the development of autoimmune diseases.[9] In addition to chronic inflammation, another significant risk factor that can lead to autoimmunity is molecular mimicry. The interaction between viruses and the immune system can also trigger autoimmune diseases. Specifically, the hexa-peptide sequences of SARS-CoV-2, particularly the Spike glycoprotein, share similarities with human proteins, which can result in various complications, including pulmonary disorders, cardiac and vascular failure, neurological issues, and auto-inflammatory syndromes, as well as autoimmune diseases. [10] Vaccination against SARS-CoV-2 may also lead to autoimmunity. One potential mechanism for this is molecular mimicry, along with bystander activation, adjuvant-induced inflammation, and immune dysregulation. Various autoimmune disorders, including Immune Thrombocytopenic Purpura (ITP), Guillain-Barré Syndrome (GBS), Miller Fisher Syndrome (MFS), and Kawasaki-like disease in children, have been reported in relation to COVID-19.[11] [12] [13, 14] Recognizing the autoimmune effects of COVID-19 is essential for managing its impacts during the ongoing pandemic and in the long-term aftermath. Additionally, a better understanding of COVID-19's pathophysiology may hinge on exploring the molecular mechanisms of other viruses that trigger autoimmune responses. The specific ways in which the virus interacts with the immune system to induce auto-reactivity, as well as the factors that lead to autoimmunity following SARS-COV-2 vaccination, remain unclear. In this review, we discuss the various factors through which SARS-COV-2 may contribute to autoimmune diseases, aiming to minimize the risk of developing such conditions after COVID-19 and vaccination

SARS-Cov-2 and Autoimmunity: A Connection

Viruses play a significant role in the environmental factors that influence the immune system. Examples of viruses that have a well-established link to various autoimmune diseases include Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and human T lymphotropic virus 1 (HTLV-1).[15-17] In a similar way, SARS-CoV-2 can be associated with similar outcomes, as many studies show that COVID-19 patients have a higher likelihood of developing various types of autoantibodies and autoimmune diseases. Several autoimmune disorders such as Immune thrombocytopenic purpura (ITP), Guillian-Barrė syndrome (GBS), Miller Fisher syndrome (MFS), Kawasaki-like disease in children, etc. have been recorded in connection with COVID-19. Some patients with Long COVID have been found to have elevated levels of autoantibodies, which are thought to be involved in other autoimmune diseases like lupus (SLE), rheumatoid arthritis, or Sjögren's syndrome. Recent studies had shown an increment of new-onset diabetes type 1 in healthcare centers during the current pandemic, as well as case reports of SARS-CoV-2-infection followed by new-onset of diabetes type 1 in children.[18-20] SARS-COV-2 virus has the potential to interfere with the immune system's self-tolerance mechanism,[21] leading to the development of autoimmune disorders. Autoimmune diseases can be systemic or organ-specific chronic conditions impacted by environmental and genetic factor [22, 23] SARS-COV-2 causes autoimmune diseases and different factors are involved in this process such as molecular mimicry, bystander activation of T-cells, transient immunosuppression, and inflammation.

Chronic Inflammation and Post Covid-19 Autoimmunity

SARS-CoV-2 activates both innate and adaptive immunity, which can lead to hyper-activation of the immune system. This result in excessive secretion of cytokines, commonly referred to as a "cytokine storm." In some instances, either due to genetic factors or acquired defects in the immune system, both NK cells and CD8+ T cells may fail to eliminate the infected cells, thereby prolonging the immune response. Consequently, pro-inflammatory cytokines are continuously produced without a regulatory feedback mechanism, causing a sharp increase in IL-1, IL-6, IL-18, IL-33, and

TNF, ultimately resulting in a cytokine storm.[24] COVID-19 patients have a significantly high level of cytokines in their plasma, especially in ICU patients. A study identified the overwhelming presence of IL-6 in ICU patients as compared to non-ICU COVID-19-positive patients.[25] High levels of cytokines can lead to serious issues, including organ failure, tissue damage, and potentially death. The severity of COVID-19 and its complications, like multi-organ failure and acute respiratory distress syndrome (ARDS), have been linked to this phenomenon.[26]

Cytokine-Storm Triggering Autoimmunity

Some patients who recover from severe COVID-19 have been reported to develop autoimmune diseases or autoantibodies months later, which suggests that the cytokine storm and immune dysregulation during infection may predispose some individuals to such conditions.[27] Auto-inflammatory pathways play a significant role in connecting cytokine storms to autoimmune disorders. In a typical autoimmune condition, the immune system mistakenly attacks the body's own tissues. Increased levels of cytokines can provoke responses similar to autoimmune reactions by enhancing the aggressiveness of immune cell.[28] This cytokine is associated with the onset of autoimmune diseases such as lupus [29] and rheumatoid arthritis,[30] as well as the inflammatory response seen in COVID-19. An overactive inflammatory response due to high levels of IL-6 during a cytokine storm can lead to tissue damage.[31]Additionally, T-cells, which play a crucial role in autoimmune conditions, can be affected by these cytokine storms. Elevated cytokine levels can lead to abnormal T-cell responses that mistakenly attack the body's own cells, worsening autoimmunity. In some cases, the virus or its components may resemble host proteins, triggering an immune response that targets both the virus and the body's own tissues. This phenomenon, known as molecular mimicry, can further contribute to the development of autoimmune conditions.[32]

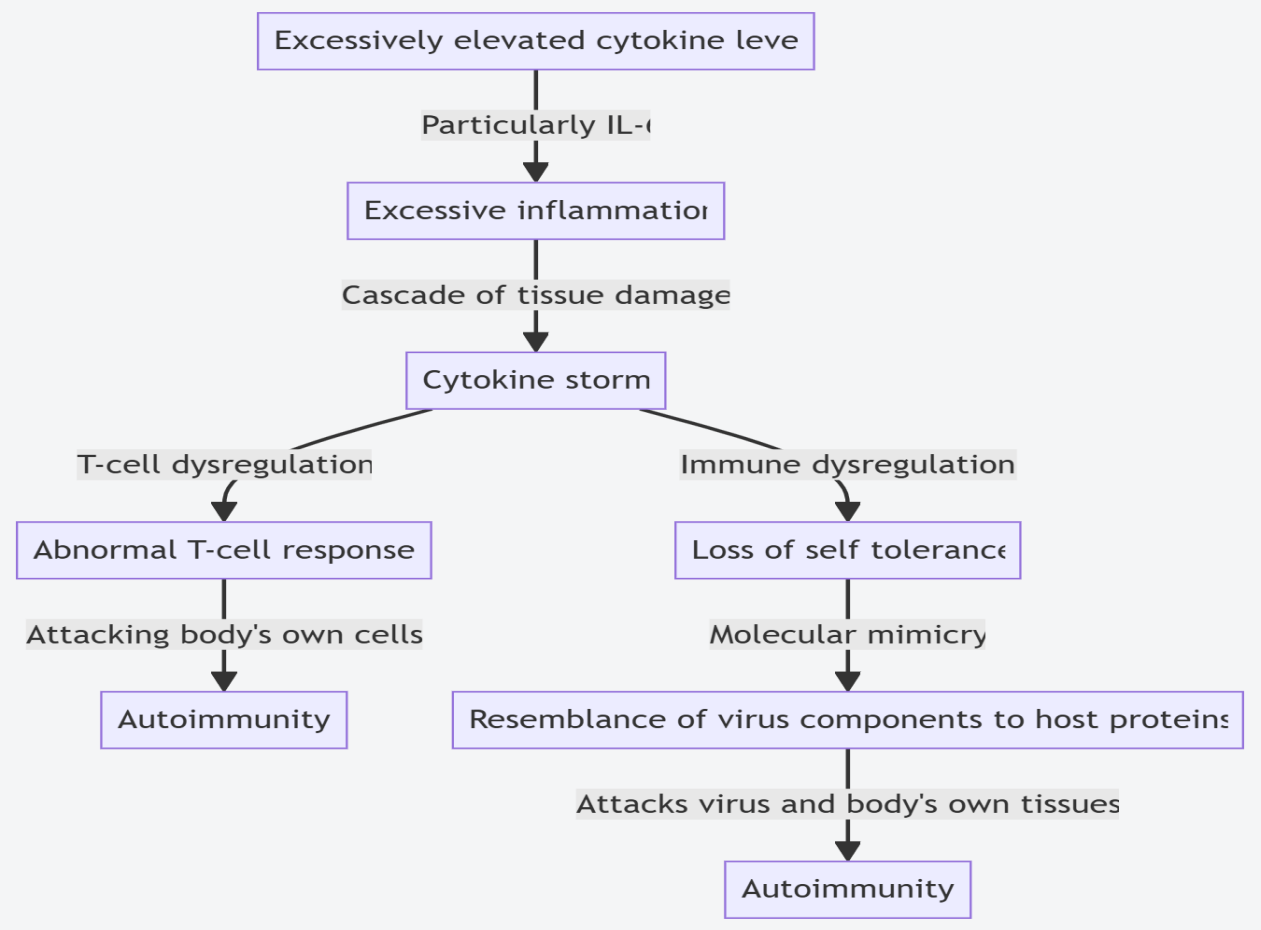

Figure.1 showing that the excessively elevated cytokine levels, particularly IL-6, in severe COVID-19 can exacerbate inflammation and immunological dysregulation, raising the risk of autoimmune diseases. In addition to causing direct tissue damage, cytokine storms may trigger autoimmune-like reactions as a result of molecular mimicry, T-cell dysregulation, or chronic inflammation.

Molecular Mimicry and Post Covid-19 Autoimmunity

In a process called "Molecular mimicry," antibodies often interact misleadingly with the host's surface proteins.[33] This phenomenon typically arises when the self-proteins of the host and microbial peptides share similar antigenic sequences.[34] Several studies suggest that molecular mimicry could play a significant role in the onset of autoimmunity in COVID-19.[35] Research has shown that certain hexapeptide sequences from SARS-CoV-2 (including nucleocapsid (N), membrane (M), ORF7b, ORF7a, ORF71a, ORF71b, and especially the S glycoprotein) share sequences with human proteins, potentially leading to various complications such as neurological issues, pulmonary problems, cardiac and vascular failure, autoinflammatory syndromes, and autoimmune diseases.[36, 37]

Common Peptides Sequences With Sars-Cov-2 And Human Protein

Three human proteins—DAB1, AIFM, and SURF1—play crucial roles in neuronal development and mitochondrial metabolism, and they show notable similarities to the hexapeptides of N and the surface glycoprotein of SARS-CoV-2.[38] The amino acid sequences from SARS-CoV-2 can cross-react with human proteins like OR7D4, PARP9, and SLC12A6, which are present in the cytoplasmic matrix of B cells and macrophages, the endothelial cells of various organs, and the plasma membrane of olfactory neurons. This interaction can lead to dysfunction in the affected organs.[39] Furthermore, the amino acid sequence of Ankyrin 1 (ANK-1) (323-LLLQY-327) closely resembles that of the S glycoprotein of SARS-CoV-2 (752-LLLQY-756), which is associated with autoimmune hemolytic anemia related to SARS-CoV-2 infection.[40] Additionally, the immune system may target heat shock proteins (HSP)/chaperones that are remarkably similar across different organisms.[35] Patients with rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis have serum containing a similar heptapeptide-sequence (LDKYFKN/Follistatin-related protein 1) that is found between the SARS-CoV-2 spike and human proteins.[41, 42] Two important hexapeptides (KDKKKK and EIPKEE) associated with Guillain-Barré syndrome, myasthenia gravis, and multiple sclerosis (MS) are found in both SARS-CoV-2 and the human heat shock proteins 90 (HSP90B and HSP90B2) and 60 (HSP60), respectively.[33] SARS-CoV-2 has at least six immunological determinants (KTVLK, TPEEH, RETMS, PFVVS, GLEAP, ICLLQ) in common with the Kawasaki antigen Inositol-triphosphate 3-kinase.[42]

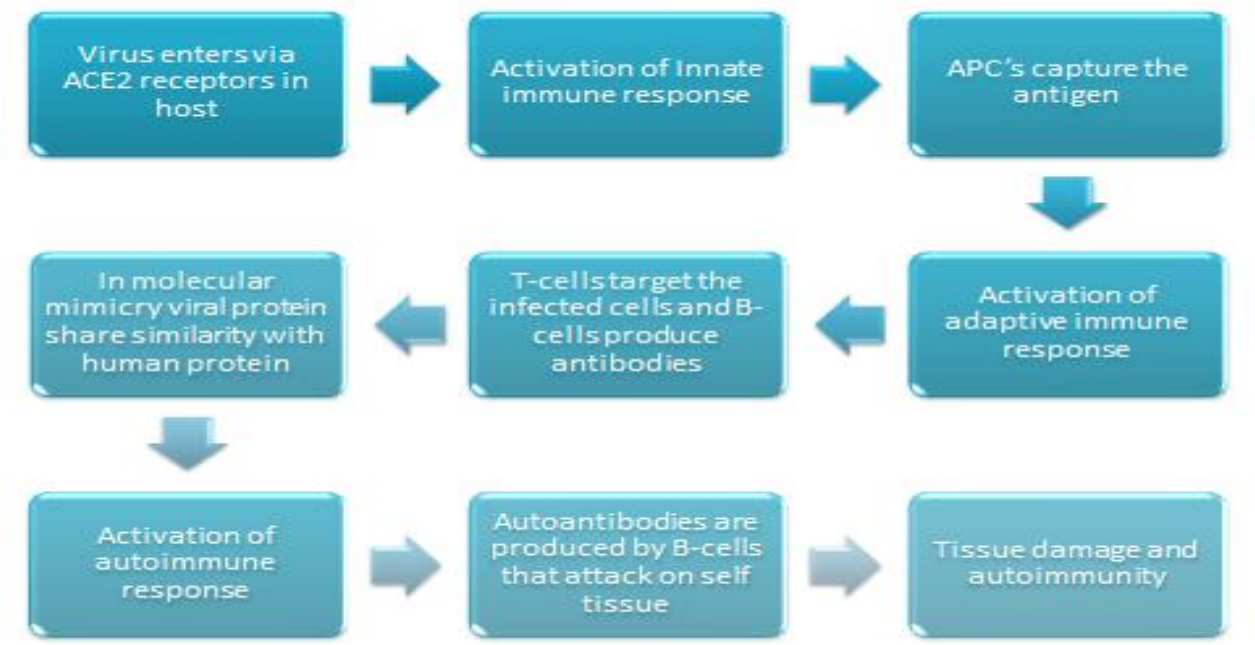

Figure.2 showing that SARS-CoV-2 infection leads to immune activation involving B-cells and T-cells. Some viral proteins, like the spike protein, resemble human proteins (such as ACE2 and those found in cardiac and neural tissues). In response, the immune system produces antibodies and T-cells that target these viral proteins, which can result in the formation of autoantibodies. Cross-reactivity happens when these antibodies and T-cells inadvertently attack host tissues that share similar structures.

Bystander Activation of T-Cells and Post Covid-19 Autoimmunity

When an infection occurs, the immune system employs various regulatory and checkpoint mechanisms to protect host tissue from damage. However, a robust immune response to an invading microbe can disrupt this balance and lead to autoimmunity. Damage to both peripheral and central tolerance, often observed in early immunodeficiencies, may contribute to the failure of these responses.[(43)] Research shows that severe Covid-19 patients often have reduced and dysfunctional T-regulatory cells.[(44)]

Bystander Activation of T-Cells Triggering Autoimmunity

Bystander activation of T cells can lead to autoimmune diseases after COVID-19 by creating an inflammatory environment that improperly activates T cells, which then may cross-react with self-tissues due to similarities between viral and self-antigens. Additionally, IL-6, the most significant cytokine produced in Covid-19 patients, suppresses CD4+ CD25+ FOXP3 T-reg cells, contributing to the onset of various autoimmune diseases.[(32)] This inappropriate immune activation can result in sustained autoimmune responses and tissue damage. Several autoimmune diseases like rheumatoid arthritis, type-1 diabetes , multiple sclerosis, autoimmune hepatitis, SLE, can occur as a result of bystander activation of T-cells after covid-19.[(45)]

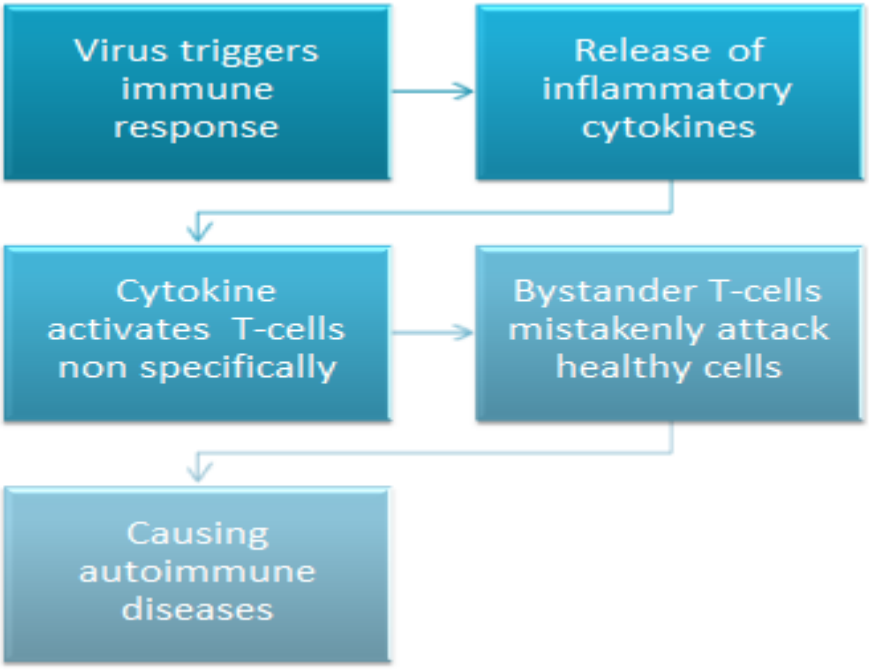

Figure.3 Cytokines like TNF-α, IL-6, and IL-17 that are released during the acute phase of an infection can trigger nonspecific T-cell activation. This phenomenon is a hallmark of bystander activation, where these cytokines foster an environment that prompts T-cells to activate, even if they don't recognize the viral antigens. Inflammatory cells, including macrophages and dendritic cells that get activated during an infection, can present altered self-antigens amid inflammation. This process may result in T-cells being activated against the host's own tissues. Once these T-cells are activated, they move to areas of tissue damage or inflammation, such as the lungs, heart, and kidneys, where they may attack normal cells that are mistakenly identified as foreign due to the ongoing inflammation or tissue injury.

Transient Immunosuppression and Postsars-Cov-2 Autoimmunity

The temporary immunosuppression experienced during illness, along with a type of immune reconstitution after recovery, may contribute to the loss of tolerance to specific self-antigens, leading to autoimmunity in SARS-CoV-2 infections. In COVID-19, there is a significant reduction in lymphocytes from various lineages, including CD4+ T lymphocytes, CD8+ T lymphocytes, and regulatory T lymphocytes.[46, 47] Decrease in T-regulatory cells after COVID-19 could potentially contribute to the development or worsening of autoimmune diseases by disrupting immune tolerance and increasing inappropriate immune responses. This heightened immune response may affect Treg populations and function. The virus might directly influence Tregs or their precursors, potentially reducing their numbers or impairing their function. A reduction in Tregs can lead to a loss of tolerance, where the immune system begins to recognize and attack self-antigens, triggering autoimmune responses. It also causes enhanced production of autoantibodies and produced effector T-cells that attacks body own tissues.[48, 49]

Viral Persistence and Epitope Spreading in Aggravating Autoimmunity Post Covid-19

The development of long-term autoimmunity is greatly affected by the persistence of viruses. When a virus remains in the body, it can keep the immune system in a state of chronic activation, leading to immunological dysregulation, molecular mimicry, and the production of autoantibodies. For individuals with genetic predispositions or other risk factors, this can increase the likelihood of autoimmune diseases emerging months or even years after the initial infection.[50, 51] Epitope spreading, which refers to the polyclonal activation caused by the ongoing presence of viral antigens that drive immune-mediated injury, can heighten the risk of autoreactivity. After the immune system responds to viral epitopes, it may begin to target self-antigens that share structural similarities with the virus. This mechanism could lead to the onset of autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus (SLE), Guillain-Barré syndrome, and myocarditis, among others. Epitope spreading helps explain how chronic autoimmunity can develop following an infection like COVID-19.[52] [53]

SARS-Cov-2vaccination And Autoimmunity

Several autoimmune diseases and other complications were reported after covid-19 vaccination. The possible factors by which the virus causes autoimmunity is molecular mimicry, bystander activation, adjuvant-induced inflammation.Research studies have suggested a possible link between COVID-19 vaccination and a heightened risk of autoimmune diseases or adverse reactions associated with autoimmunity, such as autoimmune glomerulonephritis, autoimmune rheumatism, and autoimmune hepatitis.[54-57] Molecular mimicry is the phenomenon where certain disease-causing elements in vaccines resemble specific human proteins. This similarity can cause the immune system to mistakenly identify human proteins as threats, which may lead to autoimmune diseases.[58] Adjuvants are substances that enhance immune responses to antigens without having their own distinct antigenic properties. They boost the effectiveness of vaccines by stimulating the immune system.[59] To initiate immune responses, adjuvants can act as ligands for Toll-like receptors (TLRs), which are present on innate immune cells. However, studies have shown that adaptive antibody responses can still occur even without TLR ligands, and there is a possibility that adjuvants could trigger immune-related disorders.[60] [61] Bystander pathways can activate T cells in vaccinations that contain adjuvants or adjuvants alone.Movement of these activated auto-reactive cells to sites of inflammation, along with their significant release of cytokines, could be enough to trigger autoimmune conditions. Analyzing the degree of molecular similarity between SARS-CoV-2 and the human proteome is a necessary first step before developing a vaccine. In fact, due to the commonality of pathogen-host peptides, one possible side effect of vaccination could be a particular type of autoimmune reaction that targets self-antigens.[62]

Prevention of Autoimmunity After Covid-19

Prescribing such medication that can modulate immune response to prevent excessive activation, certain immunosuppressive drugs or biologics can help control immune activity in autoimmune conditions. Anti-inflammatory medications can help manage inflammation that might contribute to inappropriate T-cell activation. This includes corticosteroids or other anti-inflammatory drugs prescribed by a healthcare provider. Understanding genetic predispositions to autoimmune diseases and discuss with healthcare providers about personalized prevention strategies based on genetic risk

factors. Early antiviral therapy and prophylactic antiviral drugs use can also prevent the onset of autoimmunity.[63-65] We can also prevent autoimmune diseases by increasing lymphocytes or reducing inflammation represents a promising treatment approach. Immunomodulators, convalescent plasma therapy, and NK cell-based therapy are some methods for boosting lymphocytes. Techniques like blood purification , regulatory T (Treg) cell-based therapy, mesenchymal stem cell (MSC)-based therapy, blocking IL-6 signaling, and using Janus kinase (JAK) inhibitors can all be used to reduce inflammation. Patients with COVID-19 exhibit lymphopenia and high cytokine levels, which can be considered potential biomarkers for disease progression. Autoantibody testing might help in detecting the early onset of autoimmune disease.[66-73]

Conclusions and Future Perspectives

The cases of autoimmune diseases after covid-19 increases, indicating a strong correlation between autoimmunity and the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection. This current review is aimed to comprehensively provide an updated understanding on different factors which are contributing in autoimmune diseases after covid-19. There is a strong relation between viral infections autoimmune diseases that occurs due to the molecular and immunological interaction between the SARS-COV-2 virus and the host. Different mechanism are involved in triggering autoimmune diseases like molecular mimicry, bystander activation of t-cells,cytokine strom and transient immunosuppression. Whereas other mechanisms like viral persistence and epitope spreading plays a role in aggravating the autoimmune reactions. As with other vaccines, auto-immunity may also be triggered by the SARS-CoV-2 vaccination.Understanding molecular mimicry related to SARS-CoV-2 peptide sequences, along with thorough research on the human proteome, can play a crucial role in developing safe and high-quality vaccines. These studies are essential to minimize the risk of acute autoimmune reactions to vaccination and the potential onset of autoimmune diseases after COVID-19. More research is require to precisely understand the underlying mechanism by which SARS-CoV-2 is triggering autoimmune diseases.

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