Review Article

Impact of COVID-19 on thyroid gland functions with reference to Graves' disease: A systematic review

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Abstract

Coronavirus disease 2019 (COVID-19) is caused due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Both immediate and long-term adverse effects arise out of this disease's aftermath. It involves various organs, which include endocrine glands, nervous system, musculoskeletal system, and other organs. The long-term outcomes of the SARS-CoV-2 infection are influenced by preexisting comorbidities. Genetic, environmental, and immunological factors contribute to the development of various autoimmune diseases, which include Graves' disease (GD). The growing mystery surrounding this virus is exacerbated by auto-inflammatory diseases, such as pediatric inflammatory multisystemic syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C), which raises concerns about the nature of the virus' connection to the autoimmune and auto-inflammatory sequelae. There is a need to understand the underlying mechanisms of developing GD in post-COVID-19 patients. There are limited data regarding the pathogenesis involved in post-COVID-19 GD. Our goal was to understand the various mechanisms involved in post-COVID-19 GD among patients with confirmed COVID-19 infection. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for 2020, a literature search of medical databases (PubMed, Cochrane Central Register of Controlled Trials, and Scopus) from February 2021 to February 2022 was performed by five authors. The keywords used were "Post COVID-19," "Grave's disease," "Cytokine storm," "Autoimmunity," and "Molecular mimicry." This review revealed three underlying mechanisms that resulted in post-COVID GD, which included cytokine storm, molecular mimicry, ACE2 receptor concentration, and cell-mediated immunity. The full spectrum of the effects of COVID-19 needs to be researched.

Keywords: ACE2, autoimmune diseases, autoimmunity, COVID-19, cytokine storm, Graves' disease, molecular mimicry

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), discovered in the Chinese city of Wuhan in December 2019.[1]

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Severe and critical cases are distinguished by respiratory system damage and multiple organ failure caused by an excess of pro-inflammatory cytokines, resulting in a large number of deaths worldwide.[2] SARS-CoV-2 attaches to the angiotensin-converting enzyme (ACE2) receptor and then primes S proteins with the transmembrane serine protease 2 (TMPRSS2). It is interesting to note that the thyroid gland expresses ACE2 and TMPRSS2 in higher quantities than the lungs.[3-5] Many endocrine tissues, including thyroid gland, express ACE2 receptors and serine

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proteins.[6] The ACE2 host receptor, expressed in respiratory epithelial cells, interacts with the receptor-binding domain (RBD) area of virus spike glycoprotein to facilitate SARS-CoV-2 entry and reproduction in the host cell (S).[7] When viral particles have been released, antigen-presenting cells (APCs), including dendritic cells, macrophages, and B cells, can endocytose them and use MHC class II to present peptide antigens to CD4+ T cells. As a key mediator, activated CD4+ T cells aid in the release of pro-inflammatory cytokines, the activation of macrophages, the priming of CD8+ T cells, the stimulation of B cells to produce antibodies, and the targeting of SARS-CoV-2.[8,9]

Molecular mimicry, a process where the antibody interacts deceptively with the host surface proteins, is common. It typically occurs when microbial peptides have antigenic sequences that are similar to those of host self-proteins.[10,11] Molecular mimicry may be a significant factor in the development of autoimmunity in COVID-19, according to several studies.[12] Two investigations have published the thyroid gland's histological findings in patients with SARS-CoV-2 infection. According to these studies, few patients had lymphocytic infiltration in the interstitium.[13,14] There was also follicular epithelial cell disruption in two patients. These histological findings affecting the thyroid gland in COVID-19 patients may or may not be significant. The deregulated immune response and increased pro-inflammatory cytokines induced by SARS-CoV-2 contribute to pathogenic mechanisms in COVID-19, which are similar to those of autoimmune diseases.[15] The immune system's job is to discriminate among self- and non-self-antigens, and if it fails to do so, it generates autoantibodies against tissues, which triggers off a sequence of events that leads to autoimmune disorders.[16] COVID-19 has caused a pandemic that has affected several organs in the human body, causing individuals to develop metabolic or endocrine malfunctions, which can be abrupt or delayed.[17] It is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells. There is evidence that after 8 weeks of COVID-19 infection, there is a risk of autoimmune thyroid diseases such as Kawasaki disease, Guillain–Barre syndrome (GBS), Graves' disease (GD), rheumatic musculoskeletal diseases, and autoimmune hemolytic disease.[18-20] Multiple studies have highlighted the importance of the mechanistic underpinnings of such autoimmune-like responses involved in disease severity. There are various hypotheses proposed for the autoimmune response in the thyroid occurring during COVID-19, such as the effect of cytokine storm, immune deregulation, molecular mimicry, and other immunological mechanisms that remain unknown.[21-23] As a matter of fact, the purpose of this review was to investigate the various underlying mechanisms focusing on similarities in immune responses and development of post-COVID-19 GD.

Search strategy and selection criteria

According to the PRISMA guidelines for 2020, a systematic literature search of medical databases (PubMed, Cochrane Central Register of Controlled Trials, and Scopus) from January 2021 to January 2022 was performed by five authors. The keywords used were "COVID-19," "SARS-CoV-2," "novel Coronavirus," "Post COVID-19," "Grave's disease," "Cytokine storm," "Autoimmunity," and "Molecular mimicry." The search was limited to English articles and publications in peer-reviewed journals. All published articles that were in line with national and international guidelines and under the recommendations of the International Committee of Medical Journal Editors were included in the current review. Even some of the cross-references from the published articles were also reviewed. Isolated case reports, case series with a sample size <5, and suspected cases of COVID-19 without positive reverse transcription polymerase chain reaction (RT-PCR) test results were excluded. The remaining suitable articles were analyzed [Table 1].

Graves' Disease and COVID-19

COVID-19 has a deleterious impact on many endocrine organs, either directly or indirectly, and GD is one of them.[23] The thyroid hormone is a very vital hormone that regulates cell metabolism and other significant physiological mechanisms. GD is an autoimmune disease that is linked to high levels of thyroid-stimulating immunoglobulin, which stimulate the thyroid-stimulating hormone (TSH) receptor in the same way that the thyroid-stimulating hormone does. There is also an associated rise in the antibodies, such as thyroid-stimulating antibody (TSAb), thyroid-stimulating blocking antibody (TSBAb), thyrotropin-binding inhibitory immunoglobulin (TBII), anti-thyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin antibody (anti-TGAb).[24] The disease prevalence is rapidly increasing among women, and the male-to-female ratio is 1:10. Many environmental, genetic, immunological, and other factors have an impact on GD. Tobacco use and the use of interleukin-1α (IL-1 alpha) and interleukin-2 (IL-2) for therapeutic purposes are examples of environmental factors.[25] Immunological factors include thyroid

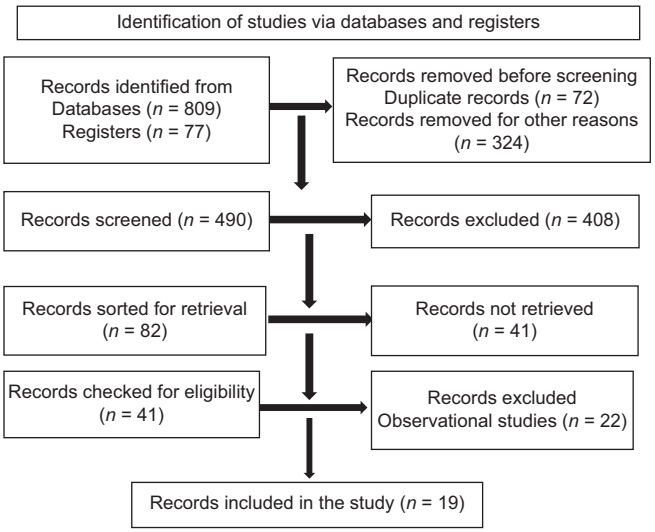

Table 1: Search strategy and selection criteria

stimulation by cytokines and antigen cross-reactivity between environmental and thyroid antigens. Other factors include psychic trauma and sympathetic hyperactivity.[26,27]

In 287 consecutive COVID-19 patients hospitalized in non-intensive care units, retrospective research looking at thyroid function found a higher frequency of hyperthyroidism and an inverse relationship between TSH, IL-6, and age.[22] In another recent prospective study comparing 125 patients with mild COVID-19 pneumonia to 125 patients with severe COVID-19 pneumonia, hyperthyroidism was found in 12% of the patients with severe pneumonia (6.4% overt and 5.6% subclinical). 1.6% overt and 4.8% subclinical hyperthyroidism were less common in the group of people who were only mildly unwell. The results did not seem to be negatively impacted by thyrotoxicosis.[28] Only two patients had overt hypothyroidism, while 31 had overt illness and 15 (5.2%) had hypothyroidism. Two letters to the editor were published describing two cases of each GD post-COVID-19 (29), (30). The first of the two cases was the concurrent presentation of SARS-CoV-2 infections and GD in a woman aged 47 years with a 12-year history of GD and GD relapsed on being infected with COVID-19. The treatment with methimazole (MMI) 40 mg/daily quickly stabilized her thyroid status without complications. The second patient was a 61-year-old woman with atrial fibrillation (AF), and GD one month following infection with COVID-19 hyperthyroidism was diagnosed and treated with MMI 10 mg/daily for 3 months, thus achieving euthyroidism.[29] In a few cases, there is no history of thyroid disease and later developed GD two months post-COVID-19 infection. The entire immunological and thyroid assessment was consistent with the diagnosis of GD. Later, the patients were successfully treated with MMI 10 mg/day.[30] Additionally, the severe SARS-CoV-2 infection-related hyper-inflammatory state may have caused an immunological cascade that led to the reactivation of GD, as has been observed in other autoimmune diseases. It is interesting to note that while the pathophysiology of GD appears to be mediated by Th2 autoimmune response, the hyper-inflammation caused by SARS-CoV-2 is thought to be primarily mediated by Th1 cytokines and IL-6. This suggests that SARS-CoV-2 may cause GD by modifying the immune system in those who are susceptible.

Cytokine storm

It has been well reported that COVID-19-mediated infection led to cytokine storm mainly governed by Th1 cytokines and IL-6. An abnormal innate and acquired immune response, loss of tolerance to self-antigens and antibodies, and worsening in patients with antibody diseases are all results of SARS-CoV-2 infection, which increases the release of serum cytokines, primarily TNF, IFN, IL-6, IL-1, IL-17, and IL-18.[31] By preventing effector T cells from acting in a pro-inflammatory manner, $CD4^+$ T-regulatory (Treg) cells regulate immunological homeostasis and reduce immunity after the end of an immune response.[32] They can be recognized by the expression of the particular transcription factor FOXPE, as well as by the high concentrations of several inhibitory molecules, including CTLA-4, GITR, CD39, and CD73. TGF-beta, IL-10, and IL-35 are examples of immunosuppressive cytokines that can inhibit autoimmune disorders that are secreted by Tregs.[33] Studies show that severe COVID-19 patients have decreased malfunctioning Treg cells.[34] In addition, some Treg cells will also change their phenotype to Th17 cells in an inflammatory environment, which will intensify the inflammatory response and mobilize neutrophils.[35] Therefore, the harmony between these two cell populations is a crucial component of immunological homeostasis and disruption of this harmony is known to contribute to the pathogenesis of autoimmune diseases.[36,37]

IL-6 has been reported to be produced by the thyroid gland and TSH and IL-l stimulate its production, perhaps by TSH receptor antibodies. Therefore, the control of IL-6 synthesis and secretion may be important to inhibit its signal that affects cells. The suppression of IL-6 expression strategies can also be chosen to negatively regulate the IL-6 transcription.[38] Elevated interleukin-6 levels in COVID-19 patients are considered the most significant parameter in predicting the most severe course of the disease and the need for intensive care.[39] In the lungs, IL-6 demonstrates a striking effect in response to COVID-19 infections. All these reports suggest the significance of "cytokine storm," particularly IL-6 and its downstream signaling pathways in COVID-19 disease. Elevated serum IL-6 levels have been reported in patients with thyroid-destructive processes.[40] Patients with SARS-CoV-2 infection have a moderate-to-severe reaction. As a result of hypercytokinemia, it might lead to multi-organ failure.[41] One of the causes of acute respiratory distress syndrome is cytokine storm. The term "cytokine storm" was coined to describe the immune system's activity during acute graft-versus-host disease.[42] This cytokine storm is thought to be a vicious inflammatory loop caused by the virus' direct action on cells or immune activation. All stromal cells, B lymphocytes, macrophages, monocytes, dendritic cells, and mast cells release IL-6. This IL-6 binds to the IL-6 soluble receptor, resulting in enormous chemotactic secretion. When thyrotoxicosis patients and COVID-19-infected individuals were compared, both had greater serum levels of IL-6, indicating that IL-6 plays a role in GD pathogenesis.[43] The cytokines, such as IFN, TNF, and IL-6, work together to aggravate the disease.[44] In patients with COVID-19, there is a link between serum IL-6 and the severity of thyrotoxicosis.[45] The damage to epithelial and endothelial cells also occurs, resulting in vascular leakage and an increase in permeability. Adaptive immunity mediated by T cells is turned on. Two examples of autoimmune hyperthyroidism found in Italy following SARS-CoV-2 infection are described by Mateu-Salat *et al.*[30] One of them had a history of GD that had been in remission for more than 30 years, while the other was known to be thyroid disease-free. These cases of hyperthyroidism were identified 1 and 2 months, respectively, following the clinical beginning of COVID-19. Both instances had positive thyroid stimulating hormone receptor (TSHR), thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies. Both instances' symptoms and thyroid function are improved with the administration of thiamazole and propranolol.

Expression of ACE2

The thyroid gland may be susceptible to SARS-CoV-2 infection because the thyroid parenchyma contains a large number of ACE2 receptors.[27] It was discovered that the serum concentration of ACE was favorably correlated with that of 3,5,30-triiodothyronine (T3) and thyroxine (T4), suggesting that it could serve as a helpful marker for the evaluation of peripheral thyroid hormone activity.[27] There was also a discovery of ACE2 receptor mRNA expression in thyroid follicular cells, and SARS-CoV-2.3 may be targeting the thyroid.[46] The intricate interaction between the thyroid gland and viral infection involves thyroid hormones and immune modulatory signaling molecules. The immunological and inflammatory reactions brought on by viruses may have a major impact on thyroid function.[14] Thyroid health may directly influence the course of COVID-19 because thyroid hormones influence numerous organ systems. Furthermore, because patients with these issues are more likely to contract COVID-19, and thyroid abnormalities have been linked to disorders, including diabetes, obesity, kidney failure, and liver disease, an underlying, poorly controlled thyroid ailment may exacerbate SARS-CoV-2 infection.[47]

Concept of Molecular Mimicry

Molecular mimicry and bystander activation are two potential explanations for the connection between autoimmune disease and COVID-19.[48] The former happens when similarities between self- and foreign-derived peptides encourage the activation of autoreactive T or B cells in a susceptible person by foreign-derived peptides.[49] According to a description of SARS-CoV-2 proteome, three proteins, DAB1, AIFM, and SURF1, which are found in the brainstem respiratory pacemaker, also known as the pre-Bötzinger complex, share three sequences of six amino acids (GSQASS, LNEVAK, and SAAEAS).[50] The authors argued that these some, but not all, similarities could be the source of central respiratory depression caused by an autoimmune disease. Also, the pulmonary surfactant and associated proteins shared pentapeptides with SARS-CoV-2, which may explain autoimmune-directed pulmonary damage.[51] This may imply that autoimmunity is likely to occur in vulnerable people through molecular mimicry and could account for some autoimmune-like symptom manifestations that patients with COVID-19 experience. Cross-reactivity occurs as a result of this type of molecular similarity, which can either start an autoimmune illness or feed an existing disease. SARS-COV-2 possesses a proteome that resembles the three human proteins.[11] Another supporting hypothesis is the resemblance between the spike glycoprotein and the immunologically reactive portions of human surfactant-related proteins.[52] There is still a lot of work to be carried out to rule out another molecular mimicry as a cause of autoimmunity caused by COVID-19 infection.

Conclusion

Our review suggests that there is a temporal relationship between COVID-19 and autoimmune thyroid manifestations. There are long-term consequences of COVID-19 infections affecting the thyroid glands. SARS-CoV-2 can disturb the self-tolerance of host antigens through molecular mimicry and cytokine storm. Therefore, thyroid function assessment in COVID-19 patients may be considered in the diagnostic workup and thereby helps to decrease the incidence of thyroid disorders in the community.

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Conflicts of interest

There are no conflicts of interest.

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