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Inflammatory Biomarkers and Chronic Diseases: The Link to COVID-19

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1. Abstract

The COVID-19 disease and pandemic eruption have caused a major concern for patients and healthcare systems globally. Immunological therapies are among the areas that require a lot of attention as the immunological consequences of the infection are neither well defined nor well understood. All medical reports indicate that severe acute respiratory syndrome-coronavirus-2 infection has a fatal outcome often results from alveolar injury that impedes airway capacity and multi-organ failure. Both of these complications are associated with the hyper production of cytokines that is known by the term cytokine storm and also called cytokine release syndrome. Strong body of clinical reports show that both mild and severe forms of disease result in cytokine secretion through changes in circulating leukocyte subsets. This is accompanied by elevated level of cytokines production. The milieu of cytokines produced includes IL-6, IL-1β, IL-10, TNF, GM-CSF, IP-10 (IFN-induced protein 10), IL-17, MCP-1, MCP-3 and IL-1ra. With no surprise immune-therapies that target the immune response and curtail the cytokine storm in coronavirus 2019 (COVID-19) patients have become a focus of recent clinical trials. In this mini-review we are also highlighting the importance of monitoring closely the levels of the cytokines as a true measure for the patient`s status and immunity level.

2. Keywords: COVID-19; Inflammation; Clinical biochemistry; Molecular diagnostic endocrinology; Rheumatic diseases; Obesity and diabetes

3. Introduction

3.1. What is COVID-19?

The outbreak of the novel corona virus disease 2019 (COVID-19), has been first reported in December 2019 [1]. This eruption had put the world into a state of global pandemic throughout 2020 and had a significant burden on economies, healthcare systems and the lives of individuals globally. What has been crystalized over the few months, COVID-19 is a disease caused by a new virus from Corona (SARS) virus' family. COVID-19 disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. I is characterized by symptoms including but not limited to fever, dry cough, rhinitis, asthenia, headache and dyspnea [3], pneumonia, lymphopenia, exhausted lymphocytes and a cytokine storm [4]. SARS viruses have a viral envelope with a positive RNA genome and a kilobase capsid.

These viruses are classified as nidovirals and are

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single stranded RNA viruses with the ability to mutate and recombine [1].

Risk factors are documented to play a major role in the severity and risk of mortality of the COVID-19 disease. The major risk factors such as diabetes, obesity, high blood pressure, chronic obstructive lung disease, coronary heart disease, chronic kidney disease and immunocompromised individuals are having a major contribution for the disease development [4]. In addition, environmental factors may also play a role in the severity of COVID-19 symptoms. Environmental factors are to include smoking, air pollution and other factors that may impact the overall functioning of the cardiovascular and respiratory systems [3]. In particular, the inflammatory response and cytokine storm may result in COVID-19 disease progression. This shapes the way we practice to use the inflammatory biomarkers (cytokines) as a screening and monitoring COVID-19 treatment efficacy by implementing the testing strategy in our diagnostic laboratories.

3.2. Chronic Diseases and the Link to COVID-19

Chronic diseases are a classification of a wide variety of diseases characterized by long lasting symptoms or disease progression and is often characterized by chronic inflammation [5,6]. In this mini-review article we are focusing our discussion on chronic diseases, specifically rheumatic diseases, diabetes and obesity in relation to COVID-19. First, autoimmune rheumatic diseases are a group of heterogeneous diseases that result in the significant activation of the host immune system. Common rheumatoid disease pathologies are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic rheumatism, ankylosing spondylitis, scleroderma and systemic vasculitides [7]. Inflammatory rheumatism does not appear to be linked directly with a higher risk of infection of COVID-19 [8]. Instead, it may be a higher risk category for facing infectious complications. It is well understood that individuals with autoimmune rheumatic diseases such as rheumatoid arthritis are at a higher risk of facing infectious complications in comparison to the general public. As a result of the presence of risk factors are the same as those reported with COVID-19 generally [7].

Similar to rheumatoid diseases, diabetes as a second chronic disease, serves as a potential comorbidity for COVID-19. It imposes a higher risk of infectious complications as a result of the similar risk factors associated [9]. Globally, type 2 Diabetes Mellitus (T2DM) is a major health crisis caused by insulin resistance. It impacts skeletal muscle, liver, adipose tissues and consequential islet β-cell exhaustion. As a result, it leads to reduced β-cell function and loss of β-cell mass [10-12]. Diabetes is a significant risk factor in the progression of COVID-19 prognosis although it does not necessarily affect the risk of infection [13].

Third, obesity is a major public health crisis especially in North America. It modifies individual's physiological responses through proinflammatory factors putting patients at a higher risk of facing complications in the prognosis of COVID-19 similar to other chronic diseases as discussed above [14]. Obesity can alter the immune response by impacting both the innate and adaptive immune responses. It causes the immune system to be more prone to infections and less responsive to treatments [15,16]. Hence, obesity is suggested as an independent risk factor for SARS-CoV-2 infection. The proportion of patients presented with obesity have a much higher risk of being placed in intensive care as a result of the virus [17]. It can be seen evidently that rheumatoid diseases, diabetes and obesity along with a host of other chronic diseases play a large role in the progression of the prognosis of COVID-19. This is tightly linked with a compromised immune system.

3.3. The link between COVID-19 and Cytokines

Inflammation is a protective process to clear any strange pathogen. However, excessive inflammation can cause severe collateral tissue damage. The cytokine milieu and inflammatory mediators are

operating through a complex network that include interleukins, interferons, chemokines and growth factors that are manifested in severe COVID-19 patients. A strong body of literature have shown a suboptimal and inappropriate T-cell activation. This leads to producing pro-inflammatory cytokines that may contribute to tissue damage in critically ill COVID-19 patients [18,19]. Laboratory findings and results have demonstrated that patients associated with severe COVID-19 are manifesting Lymphopenia, hyper ferritinemia and increased D-dimer. Mechanistically, this is resulted through the phenomenon that is known as the cytokine storm and over production of cytokines [20,21]. A number of published reports suggest that the hyper inflammation seen in severe COVID-19 may be driven by considerable levels of C-reactive protein (CRP) and Interleukin (IL)-6 that are seen in other comparable conditions. COVID-19-related cytokine storm syndrome was documented to parallel the chimeric antigen receptor-T cell cytokine release syndrome [22]. This highlights the importance of immunomodulatory therapies by targeting IL-6 or IL-1 receptors. The underlying importance the cytokines could possibly be of great value in COVID-19 treatment strategies [23-25]. This mini-review is focused on illustrating the importance for understanding the pathogenesis of severe COVID-19 for the development of targeted immune therapy [26]. There is an immediate need for identifying a prognostic biomarker in order to early identify patients that will progress into critical COVID-19 through the measurement of cytokine levels. Jørgensen MJ, et al. reported an elevated cytokine levels in patients with Respiratory failure (RF), acute respiratory distress Syndrome (ARDS) and hyperinflammation. These findings are consistent with earlier reports of SARS-CoV-10 and SARS-CoV-2 as seen in intensive care units (ICU) [27]. The cytokine release syndrome has been suggested as an important cause of ARDS and RF in COVID-19 patients [28-29]. It has been demonstrated the increase in the levels of a wide range of inflammatory cytokines in these patients. This includes cytokines such as IL-1ra, IL-6, IP-10, G-CSF, MCP-1, MIP-1α and TNF. All are rapidly released upon innate immune activation manifesting an important role for shaping the adaptive immune response through the induction of T cell activation [30-32]. IL-6 and MCP-1 were reported consistently as being associated with RF [27]. It has been recently suggested that IL-6, IL-1ra, IP-10 and MCP-3 could serve as predictive markers for disease progression in COVID-19 [33,34]. Studies have reported the link between high IL-6 level secretion and disease severity in COVID-19. This is a strong evidence to suggest IL- 6 involved in down-regulation of HLA-DR and lymphopenia with contribution to the cytokine levels found in severe COVID-19 [30,35]. From the clinical and diagnostic perspective, plasma inflammatory cytokines serve as valuable biomarkers in the diagnosis, management and prognosis of several inflammatory diseases [36]. Recently reported that IL-6 and MCP-1 should be added to the list of candidate markers for disease prediction in COVID-19 patients with RF. Further, it was reported, the exploration should continue to decipher other targets utilized for immune therapy with cytokine antagonist's effect [27]. It is important to characterize and predict which patients that will progress to severe COVID-19 through finding a surrogate biomarkers involved. Research work is still progressing to facilitate rapid detection of critically ill COVID-19 patients who could benefit from targeted immunotherapy implementation for resulting in improved treatment outcome.

3.4. Clinical Significance

During the course of COVID-19 infection, the mature virion enters the endosome and interacts with toll-like receptors (TLR). This will lead to stimulation of down stream inflammatory pathways. Both chloroquine and hydroxychloroquine used interfere with endosomal

acidification and inhibits such TLR activation. These drugs also interfere with downstream inflammatory pathways and resultant cytokine production. It dampens the inflammatory response via upregulation of regulatory anti-inflammatory molecules [37-45]. Janus kinases (JAK) 1 and 2 are involved in inflammation. The enzyme AP-2-associated protein kinase 1 (AAK1) plays a role in viral cellular entry. Based on information generated by bioinformatics analysis, baricitinib may help reduce SARS-CoV-2 infection by inhibiting AAK1. Consequently, it possibly leads to dampening the inflammation through JAK1/2 inhibition [46]. The resultant cytokine storm responsible for severe COVID-19 is associated with secondary Hemophagocytic lymphohistiocytosis (HLH) which is also known as hemophagocytic syndrome (HPS). HLH may respond to immunosuppressive agents used for such as tocilizumab (IL-6 blockade) and anakinra (IL-1 blockade) [24]. A recent pre-print retrospectively evaluated the use of a single dose of intravenous tocilizumab 400 mg in 21 patients with COVID 19 from China who had respiratory distress and hypoxemia that required intensive care support. The report showed that 19 of these 21 patients demonstrated clinical improvement with discharge from hospital by 2 weeks. The findings of this study was cautiously interpreted in the context of a small sample size. Another limitation, was the lack of a control group for comparison and background treatment with antiviral therapies and corticosteroids [47]. Ongoing clinical trials are further evaluating the role of IL-6 blockade with tocilizumab and sarilumab in severe COVID-19. The former drug is approved in China for this indication [48,49]. Cepharanthine, selamectine and mefloquine hydrochloride are other categories of drugs that have been proven to be cytopathic to viral cultures of SARS-CoV-2. The precise mechanisms of their action are still unclear [50]. Based on previous studies of other viruses [51,52] it has been hypothesized that vitamin C and D supplementation may boost immunity and help patients fight COVID-19 and its aggressive impact. Related clinical research studies are warranted. In addition, other different treatments strategies that are currently utilized in the clinical setting. Among these therapy regimens, inhibitors of RNA polymerase such as remdesivir [53] and favipiravir [54] and protease inhibitors lopinavir and ritonavir [55]. These drugs affect intracellular virion assembly; however, their efficacy remain under investigation with a rationale to further evaluate these drugs in COVID-19 [56]. Here, in this mini-review we have focused on addressing the immunity and concept of inflammation and its link to COVID-19 outcome.

The intention here, is to draw more attention of the efficacy of the immunotherapy as it requires more focus. In addition, it is important to having a fully utilized laboratory protocol for cytokine measurements. Inflammatory mediators as IL-6 and MCP-1 are among other mediators that are considered as a key biomarker involved with the pathogenesis of COVID-19 disease.

4. Conclusion

In summary, physicians are advised to monitor closely the current COVID-19 pandemic by raising national and global awareness of the virus characteristics and its targets. We also need to explore different strategies on how to minimize the incidence of severe cases. The whole world is working at a high speed for developing and distributing the vaccines while waiting for evidence-based recommendations supported with strong data. The empirical preventive measures should also be implemented with full consideration for the immunotherapy treatment as an option among other therapeutic regimens available. We have to rely on the expert's opinion and rapidly accumulate the proper evidences that are important for standardizing our best practice. A True balanced and well-informed actions are needed urgently by all medical specialists and the society officials. The ongoing assumption is concerning the potential

immune-mediated injury in severe COVID-19 because of its important application. In such situations, physicians may be called upon to decide on the appropriate immunosuppressive strategies to be taken (Personalized medicine approach, a case by case-based approach). Using the inflammatory cytokine testing panel is considered as a mirror image of the status of patient`s immune system. The implementation of such screening and diagnostic tool has to be generalized in clinical practice to avoid major mistakes in diagnosing and treating COVID-19 patients. As a result, strategies being followed that will have a great impact on the mortality and morbidity rates. COVID-19 disease is evolving very rapidly and will continue to have our attention for the years to come. Scientists and physicians must put their minds together to decipher the COVID-19 mystery that brought the world to a moment of silence to ponder on the true power of science and its applications in medicine.

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