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Chapter 5

Biochemical, Pathophysiological, and Clinical Characteristics of Covid-19

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Abstract

COVID-19 is a new acute respiratory syndrome caused by the SARS-CoV-2. The pathophysiological processes may be asymptomatic or may cause a wide range of mild manifestations (upper respiratory tract infection) to severe sepsis or even death. COVID-19 mainly demonstrates respiratory manifestations, although it affects other vital systems as well, and its acute form is often associated with long-term complications. Such complex manifestations indicate that SARS-CoV-2 disrupts host immune responses and causes inflammatory, thrombotic, and widespread parenchymal disorders. In this study, the pathophysiology of the COVID-19 is briefly discussed.

1. Introduction

SARS-CoV-2 is a pneumotropic virus that is transmitted mainly from one person to another through respiratory secretions such as cough drops, sneezes, or even talking. Transmission occurs through personal contact, contaminated surfaces, or fumes (especially in environments where public hygiene such as hand hygiene, masks, and appropriate social distancing are not consistently applied [1].

The worldwide mortality rate from COVID-19 is 3.4%, which is higher than the seasonal flu. Male and female mortality rates have also increased in all age groups. Deaths are mainly due to Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, blood clotting, septic shock, metabolic acidosis, and cardiovascular complications [2].

Although a complete analysis of the underlying causes is not available, studies have shown sexual dimorphism (73% of infected men and a mean age of 49 years) based on diagnosed cases and mortality from COVID-19. Combination is also observed during this epidemic and 32% of these people suffer from underlying diseases such as diabetes, hypertension and cardiovascular diseases [3].

Genomic monitoring utilizes next-generation sequencing applications, makes the entire genome data available, and develops phylogenetic methods. These methods offer new tools for detecting species that differ in phenotype or antigen. Genomic monitoring facilitates further early prediction as well as the initiation of effective strategies to reduce and control the spread of SARS-CoV-2 and other new viruses.

The aim of this study was to investigate the pathophysiological aspects of Covid 19 disease in order to make a connection between theoretical concepts and clinical findings.

2. Methods

The present study focused mainly on the analysis of the biochemical, pathophysiological, and clinical characteristics of Covid-19. To conduct the investigation, reputable sources were searched through reputable websites such as: WHO, Science Direct, Elsevier, Pub Med, Lit Covid, Med Rxiv and the like using appropriate keywords. We then selected, prioritized, and used articles on general and specialized topics related to Covid-19 pathophysiology, randomized clinical trials, systematic reviews, and clinical practice guidelines.

2.1. Structure of SARS-CoV-2

SARS-CoV-2 is a single-stranded, non-segmented RNA virus with a volume of ~29.9 kB with a diameter of 50-200 nm. Structurally, it has a double-layered lipid envelope that includes spike glycoprotein (S), envelope protein, membrane glycoprotein, and nucleocapsid

protein. The viral spike glycoprotein has a receptor binding domain (RBD) to interact with host cell receptors [4].

Membrane glycoproteins are responsible for the accumulation of viral particles. The envelope protein also plays a role in pathogenesis, while it interacts with a tight junction protein, called "Protein Associated with Caenorhabditis elegans Lin-7 protein 1 (PALS1)" [5].

2.2. Mechanisms of cellular infection and dissemination

Some studies have suggested that SARS-CoV-2 attacks ciliated cells in the superficial epithelium of the nasal cavity. Unlike influenza viruses, which mainly infect airway cells and immune cells, SARS-CoV-2 can infect a wider range of cells, including cardiocytes and endothelial cells, the testes, and bile ducts. Viral spike glycoprotein (S) binds to ACE2 on the surface of epithelial cells, a process supported by the serine-transmembrane protease (TMPRSS2), which mediates virus entry [6].

ACE2 expression is high in nasal epithelial cells and supports primary local infection by SARS-CoV-2. How SARS-CoV-2 is released in the lower respiratory tract is unknown. Two theories prevail: First, (micro) aspiration of SARS-CoV-2 particles causes diffusion from the oropharynx to the lungs; second, airborne microparticles are transported directly through the air stream to the lower respiratory tract and bypass the upper airways. The involvement of other receptors (eg, neuropilin1) that act as influencing factors in SARS-CoV-2 and tropical cell entry has been suggested [7].

3. Host cell infection

SARS-CoV-2 infects the cell surface protein of the angiotensin-converting enzyme (ACE2) via the receptor binding domain (RBD), and its spike protein (S) infects human cells. Spike glycoprotein has two subunits, S1 and S2. The S1 subunit consists of the receptor binding domain (RBD), which binds to the receptor binding motif (RBM) of the cell surface receptor, as well as the S2 subunit, and mediates fusion with the host cell membrane [8].

The spike protein is cleaved by host proteases (located in subunit S2) to make the structural changes necessary for membrane fusion. Serine proteinase type II (TMPRSS2) is the major host protease and mediates the activation of protein S and the initial entry of the virus into primary target cells [9].

Camostat mesylate, a TMPRSS2 serine protein inhibitor, blocks the entry of coronaviruses into cells and plays an important role in the preparation of S glycoproteins as a result of infection, and Furin is another host protease that is extremely important. It has COVID-19 in cellular pathogenesis [10].

The main route of entry of SARS-CoV-2 is through the upper respiratory tract or mucosal surfaces in the upper respiratory tract. Virus particles first bind to ACE2 receptors and then reach cells through receptor-mediated endocytosis. This mechanism has been experimentally confirmed by the introduction of anti-ACE2 monoclonal antibodies into cell cultures, their establishment, and blocking virus entry. Uncoating of viral genetics and proteins allows RNA and translation proteins, including RNA-dependent polymerases, to be transcribed and assembled by the virus and subsequently eliminated by the virus until the replication cycle is complete [7].

The primary physiological function of ACE2 is to convert angiotensin I and II peptides to angiotensin 1-9 and angiotensin 1-7, which provide cardiovascular protective functions through mechanisms (including vasodilation and endothelial permeability control). SARS-CoV-2 infection results in decreased ACE2 levels as well as disruption of the Renin Angiotensin Aldosterone System (RAAS), which amplifies signaling through the angiotensin II pathway and leads to relatively severe inflammatory and circulatory dysfunction. [11].

Increased expression of ACE2 or concomitant expression at high levels of ACE2, TMPRSS2 and CTSB/L proteins in SARS-CoV-2 target cells / tissues is likely to be associated with a higher risk of viral infection. According to some studies, the genes/ proteins ACE2, TMPRSS2, and CTSB/L are widely expressed in human tissues (especially kidney, heart, as well as respiratory and gastrointestinal tissues). ACE2 and TMPRSS2 genes are expressed at least in blood cells and tend to be regulated simultaneously [12]. It has also been shown that SARS-CoV-2 entry factors are also expressed at high levels in nasal epithelial cells [13].

The relatively high prevalence of COVID-19 in people with hypertension or diabetes has raised concerns about the role of ACE2 receptors in these vulnerable groups, especially given that a significant proportion of them may be associated with inhibitors. ACE (ACEIs) or angiotensin II receptor blockers (ARBs) are being treated. Despite initial concerns that concomitant treatment of patients with COVID-19 with ACEIs or ARBs may increase ACE2 expression and thus predispose to infection and pathophysiological complications, fortunately clinical evidence has not confirmed this [14].

4. Histopathology

COVID-19 accounts for most cases of acute lung injury and acute respiratory distress syndrome (ARDS) [47]. The lungs have high RAAS activity and ACE2 control is essential to maintain homeostasis. AT2 cells synthesize pulmonary surfactant, which prevents lung collapse. Alveolar cells (AT1 and AT2) make up 31% of lung cells [15]. However, ACE2 expression is concentrated in a population of AT2 cells that also express genes involved in the viral process [16]. Because SARS-CoV-2 attacks AT2 cells, the physiological balance of ACE/ACE2 is disrupted by infection, and local overactivity of RAAS leads to increased vascular

permeability and edema.

Analysis of lungs obtained from autopsies of patients who died of COVID-19 have shown that diffuse alveolar damage with intracellular alveolar cell necrosis, AT2 hyperplasia, interstitial fibrin deposition, and interstitial edema. In the lungs of patients with COVID-19 and the lungs of patients with influenza, the relative number of ACE2-positive cells for alveolar epithelial cells, endothelial cells, and lymphocytes was higher than in non-infected individuals [17].

The female reproductive system also expresses ACE2 and has been shown to be a target for SARS-CoV-2. Because of this, pregnant women are at risk for COVID-19. Pregnancy itself increases ACE2 expression in the kidney, uterus, and placenta and increases RAAS activation. ACE2 has a time-dependent expression in the placenta, so that in the late stages of pregnancy, ACE2 is also detected in several fetal tissues [18].

Extensive lung infection by SARS-CoV-2 in COVID-19 causes capillary leakage which, if persisted, can lead to viremia, localized over-activation of ACE/ANGII /AT1R signaling due to decreased ACE2, widespread inflammation, and "storm" "Cytokines". Although the cause of the "cytokine storm" remains largely obscure, it may be caused by mechanisms that are not directly related to ACE2 through the modulation of pulmonary macrophages, dendritic cells, and/or neutrophils [19]. Suppression of ACE2 expression and local increase in ANGII production can cause pulmonary vascular leakage [20].

Enrichment of all cellular modules associated with SARS-CoV-2 infection in the gastrointestinal tract well explains the cause of diarrhea as one of the main symptoms of COVID-19. Since SARS-CoV-2 genetically infects human intestinal enterocytes (60) or human intestinal organoids, isolation of SARS-CoV-2 RNA from feces is acceptable because, of course, the intestinal tract is the main site of entry and proliferation for SARS-CoV-2 [21].

There has also been a significant association between liver dysfunction and mortality in COVID-19 patients, which may be due to the relatively low expression level of ACE2 in the liver and lead to direct viral infection or indirect damage to the cause of drug-induced liver damage or systemic inflammation due to COVID-19 [22].

Analysis of severe biochemical changes induced by COVID-19 in the liver has shown higher liver enzymes and significantly lower albumin levels. Therefore, liver markers should be monitored continuously throughout the course of COVID-19. In the case of the pancreas, ACE2 is expressed in the microvascular tissues of the exocrine tissue and in the pancreatic duct subset with TMPRSS2 expression restricted to duct cells [23].

4.1. Susceptibility to SARS-CoV-2 infection

Children and adolescents account for 1 to 3 percent of all reported cases of coronavirus 2019 (COVID-19) nationwide and even a small number of severe cases and deaths. They are more likely to develop asymptomatic infections than adults, and analyzes based on the clinical signs of infections in children are often underestimated. The viral load sufficient to transmit, and their potentially infectious contact with others, depends on the number of social contacts in the age group and the behavior during these contacts. There is preliminary evidence that children and adolescents are less sensitive to SARS-CoV-2 (0.56 odds ratio for infected contact compared to adults). Also, there is weak evidence that children and adolescents play a lesser role in the SARS-CoV-2 transmission population than adults.

4.2. ARDS related to COVID-19

Cases of COVID-19-related acute respiratory distress syndrome (ARDS) have some of its general features, such as impaired gas exchange and CT findings. However, the combination of different pathological mechanisms in COVID-19-induced ARDS leads to more variable clinical manifestations. COVID-19-related ARDS cases, unlike non-COVID-19 ARDS cases, are often associated with near-normal respiratory compliance. However, compliance can vary depending on the predominant pathogenesis of the infection [24].

4.3. Translation results

Two simplified phenotypes of SARS-CoV-2 ARDS are proposed: Type H, with low compliance, high-intensity right-to-left shunt, high lung weight, and high absorption capacity (severe ARDS associated with COVID-19, similar to classic ARDS); Type L, which is characterized by high compliance, low ventilation to perfusion ratio, low lung weight, and low absorption capacity (mild ARDS associated with COVID-19) [25]. Increased respiratory rate in COVID-19-related ARDS (usually within the first few days of ARDS onset) is different from non-COVID-19 ARDS and is likely to be underestimated, potentially obscuring the true extent of hypoxemia. Theoretically, COVID-19 provides a unique opportunity to decipher the etiology and pathogenesis of ARDS. It is also clear that ARDS is not a separate disease, but a syndrome that occurs in different conditions of intensive care.

4.4. Pulmonary fibrosis

Pulmonary fibrosis is a condition characterized by poor lung function and respiratory failure, with a poor and irreversible prognosis. Approximately 50% of people with severe COVID-19 develop ARDS, of which pulmonary fibrosis is a known complication. Approximately 50% of people with severe COVID-19 develop ARDS, of which pulmonary fibrosis is a known complication. Normally, the secretion of TGF-β from the damaged lung repairs the

damage caused by the infection, 84 but in severe COVID-19, the infection can cause excessive TGF-β signaling [26].

Significant signs of pre-fibrotic processes such as epithelial to mesenchymal transmission and endothelial to mesenchymal transmission have been observed in COVID-19.87. Follow-up of SARS and MERS survivors showed that older patients often developed residual pulmonary fibrosis [27].

The development of the Ground glass opacity (GGO) pattern on chest CT scan peaks 10-11 days after the onset of symptoms and before the onset or gradual elimination of irregular fibrosis.19 Accordingly, those who were severely affected by the progression of the disease and whose inflammatory response was increased were more likely to develop pulmonary fibrosis. Symptoms such as interstitial thickening, irregular interface, thick reticular pattern, and a parenchymal band on CT imaging are known to predict COVID-19 early pulmonary fibrosis.

4.5. Coagulation and endothelial damage

Coagulopathy and endothelial injury are critical events in severe covid-19 that include arterial and venous thromboembolism. Venous thromboembolism has been reported to affect approximately 21 to 69% of critically ill patients with Covid-19. This is much higher than other surgical patients (7.5%) who were admitted to the intensive care unit.99 In addition, COVID-19 had a higher prevalence of thrombosis than the flu [28].

Reports from available data suggest that there is a link between coagulation disorders and the severity of lung failure and mortality. Patients with severe COVID-19 are often diagnosed with symptoms of excessive coagulation - such as high circulating D-dimer concentrations (about 3 to 40 times normal), increased fibrinogen, increased prothrombin time and partially active thromboplastin time, and thrombocytopenia. D-dimer concentrations in patients with severe COVID-19 are consistently higher than in patients admitted to the general ICU 107 and patients with severe pneumonia (but not related to COVID-19) [29].

The pathophysiology of hypercoagulation in COVID-19 are likely to include virus-induced endothelial damage and subsequent inflammation (mediated by cytokines, reactive oxygen species, and acute phase reactants). Although some studies suggest that SARS-CoV-2 may infect vascular endothelial cells, but other studies have not confirmed it. Pulmonary thrombosis due to endothelial injury has been confirmed by evidence of alveolar damage in COVID-19, which is often associated with thrombotic microangiopathy [30]. Findings from endotheliopathy also describe different types of diffuse pulmonary intravascular coagulation, both of which involve dysfunctional interactions between leukocytes and endothelial cells, which manifest as vascular immunopathology and mainly lead to exacerbation of vascular hypoxemia [31].

However, blood coagulation and endothelial injury or endotheliitis are not unique to COVID-19 but are generally a common feature of ARDS. Presumably, endothelium is partly responsible for COVID-19-resistant ARDS with disturbed, hyperperfused intrapulmonary blood flow, and alveolar damage, most severely including edema, hemorrhage, and intra-alveolar fibrin.

In patients with COVID-19, the increased risk of mortality is not limited to pulmonary infection and ARDS, but to systemic vascular disorders including stasis, endothelial barrier dysfunction and permeability control, cell membrane disruption. Local inflammation of the endothelium, and Active prothrombotic endothelial cells (clinically) is also associated with intracellular virus particles that are localized to the lungs, brain, heart, kidneys, intestines, and liver [32].

Extensive endotheliitis is usually a clear sign of a severe infectious disease associated with viral sepsis and shock. The mentioned disorders are mainly caused by abnormal nitric oxide metabolism and regulatory regulation of reactive oxygen species, which are exacerbated by oxidative stress by reducing antioxidant (endothelium-related) defense mechanisms [33].

5. Host response to SARS-CoV-2

5.1. Cytokine response

Usually after SARS-CoV-2 damage occurs, endothelial, epithelial, and other parenchymal cells release inflammatory mediators that activate immune cells. Together, these events release several proinflammatory cytokines and chemokines [34].

In patients with Covid-19 admitted to the ICU, 10 kDa of interferon-induced gamma protein (IP10) was increased compared with outpatients. Patients with COVID-19-related respiratory failure decreased HLA DR Isotype expression on circulating monocytes, but they retained their high cytokine production capacity [35].

Although the increase in systemic cytokine response in COVID-19 is definite, the comparison of concentrations of TNF, IL-6 and IL-8 in acute conditions - ARDS induced by COVID-19 - is stronger than in other similar conditions. Therefore, if cytokine storm syndrome in COVID-19 can be different from other acute conditions in terms of sensitivity scale or response characteristics (eg inflammatory mediators or different profiles). Comparison of the expression of the inflammatory gene in bronchoalveolar lavage fluid (BALF) in patients with Covid-19, patients with community-acquired pneumonia, and healthy individuals showed a specific signature of COVID-19 activation in proinflammatory genes [36].

In critically ill patients, circulating ferritin is also a marker for secondary hemophagocytic lymphohistocytosis (HLH) as well as macrophage activation syndrome (MAS-HLH) [37].

5.2. Non-cytokine mediators

In severe Covid-19 (ferritin concentration of at least 4420μg/L) indicates a phenotype similar to MAS-HLH. Various studies have shown that ferritin is both a good indicator for assessing disease severity and a predictor of hospital mortality (94). Thus high circulating ferritin may be a potential marker for guiding anti-inflammatory therapies (e.g., an IL-1 receptor antagonist) in patients with severe COVID-19 [38].

Some studies have shown that high CRP concentrations are associated with Covid-19 intensity. Such patients admitted to the ICU showed CRP kinetics similar to those of bacterial sepsis, such as high concentrations of CRP at admission and subsequent gradual decline [39].

Regarding the complement system, the activation peptide of complement component 5a (C5a) and membrane attack complex (MAC; C5b-9) increased due to the severity of the disease in the blood (and BALF for C5a) of patients with COVID-19. C4d concentrations were also associated with ferritin concentrations in patients with COVID-19 during hospitalization [40].

5.3. Covid-19 and endocrine factors

Hypertension, type 2 diabetes, and obesity are comorbidities associated with the risk of Covid-19 complications and mortality. In key metabolic tissues such as thyroid, endocrine pancreas, testes, ovaries, adrenal glands and pituitary gland, ACE2 is expressed [41].

Infection of pancreatic β cells with SARS-CoV-2 impairs blood sugar regulation, and may occur in patients without prior diabetes163. The data confirm that glycemic control affects the outcomes of patients with COVID-19 diabetes [42].

Increased prevalence of cardiovascular disease, increased ACE2 expression, decreased viral clearance, and metabolic disorders may increase the severity of COVID-19 in patients with diabetes. However, hyperglycemia and inadequate blood sugar control may cause endothelial damage by increasing oxidative stress and excessive inflammation in severe infections. In addition, Covid-19 is often associated with hypokalemia, which affects glucose control in diabetes [43].

The renin-angiotensin-aldosterone (RAAS) system is highly activated in patients with severe COVID-19. Angiotensin II may increase inflammation by inducing IL-6 in endothelial and vascular smooth muscle cells. As aldosterone levels increase, angiotensin II also causes blood vessels to constrict and reabsorb water. TMPRSS2 expression is controlled by androgen hormones. This phenomenon probably partially explains the sex differences in critically ill patients with COVID-19, so that the severity of Covid-19 and the number of deaths in men are about twice as high [44].

The innate immune response is usually disrupted during SARS-CoV and MERS-CoV infection by their non-structural proteins, which affect the overall production of cytokines. Just as SARS-CoV-1 inhibits IFN-I, so too, SARS-CoV-2 lacks strong IFN-type I/III signatures, and patients with severe COVID-19 compared to cases Mild to moderate, have impaired IFN-I signature [45].

Neutralizing antibodies have been key components of humoral immunity against emerging viral infections. The main role of these antibodies is to bind antigen and interact with Fcγ receptor carrier cells to modulate subsequent targeted immune responses.

The humoral immune response to SARS-CoV-2 infection is mediated by antibodies to viral surface glycoproteins. They are mainly Spike (S) glycoproteins and nucleocapsid proteins. These antibodies can be detected by RT-PCR approximately 6 days after confirmation of infection and have the ability to neutralize, clear the virus and prevent infection. After the onset of acute SARS-COV-2 infection, the time period for the emergence of IgM (early) and late IgG antibodies is between 6 and 28 days [46].

The response of IgG, IgM, and IgA antibodies to cysteine proteases such as SARS-CoV-2 is also associated with nucleocapsid protein antibody titers in patients with COVID-19. Viral clearance probably requires the coordinated function of B and T cells, but its long-term safety is crucial to the effectiveness of vaccination. Detectable antibodies were observed in less than 40% of patients within 1 week and increased to 100, 94.3 and 79.8% for IgM or IgG or both within 2 weeks, respectively [47].

Studies show that IgA antibodies are produced in the first week after infection and peak after 20 to 22 days, while IgM antibody titers peak after 10-12 days and later 18 days after symptoms began to disappear. Another study showed that IgG titers increased in the first 3 weeks after the onset of symptoms and decreased for up to 8 weeks [48].

Cell-mediated safety studies show that the detection of SARS-CoV-2 antigens by pre-existing and cross-reactive T cells contributes to the recurrent presence of T cells in the SARS-CoV-2 response. A strong T cell immune response has been shown in asymptomatic or mild COVID-19 recovering individuals. CD4+T helper cells have been shown to interact with CD8 + T cells, along with natural killer cells, to direct the cytotoxic response to kill infected cells [49].

Virus-specific CD4+T cell responses and virus-specific CD8+T-cell responses have been identified in a number of patients and indicate that most people can be infected. The response of CD4+T cells mainly consisted of T-helper-1 (Th1) cells, which were characterized by high concentrations of IFN-γ secretion against structural and non-structural proteins [50].

One of the primary features of COVID-19 infection is a general and significant reduction in the total number of lymphocytes, especially CD4+ and CD8+T cells which can determine the severity as well as the vital effects of the disease. Neutralizing autoantibodies against type I IFNs have been observed in 10% of patients with pneumonia, suggesting a potential therapeutic role for IFNs [51].

In most patients with SARS-CoV-2, in the first 2 weeks after the onset of symptoms, both CD4+T cell and CD8+T cell responses are observed, leading mainly to the production of Th1 cells.

Inflammatory features of patients with Covid-19 indicate that either the systemic cytokine component is not a significant factor in the severity of Covid-19 or that the disease has a specific inflammatory profile, which is less well known and at the same time harmful.

The fourth characteristic is incompatible immune responses in the host that are unable to fight the virus. For example, there is a clear association between high viral loads, manifestations, and host response size, indicating that a weak immune response in controlling SARS-CoV-2 virus leads to severe COVID-19.

6. Conclusions and Perspectives

COVID-19 is a two-stage disease. The first stage involves increasing the rate of virus transmission and infection due to the widespread expression of the human ACE2, TMPRSS2 and CTSB/L genes associated with the main infection in specific respiratory and gastrointestinal tissues. The second stage also involves host-specific uncontrolled inflammatory immune responses and possibly sex and/or age that increase cytokinemia, invasive inflammation, and (due to extensive SARS-CoV-2 organotropism) lateral and systemic tissue damage.

Compared to influenza and SARS, multiple organ involvement and thromboembolic events are more common in COVID-19. The results showed that endothelial and epithelial infections (instead of alveolar infection) are the predominant pathological complication in this disease. Disorders of the alveolar epithelial-endothelial barrier play a major role in the development of severe pneumonia and ARDS, and in fact SARS-CoV-2 is an endotheliophilic virus.

The inflammatory features observed so far in patients with Quid-19 indicate that either the systemic cytokine component is not a significant factor in the severity of Quetting-19 or that the disease has its own unique, unknown, and yet harmful inflammatory profile. On the other hand, the host incompatible response is not able to fight the virus. In fact, there is a clear association between high viral loads and host irregular response characteristics, indicating that a weak immune response to the virus leads to severe COVID-19. All of these factors determine preventive, therapeutic, prognostic and vaccination strategies.

7. References

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