Metabolic disorders associated with coronavirus disease-2019 in conjunction with different chronic diseases and the increased vulnerability to infection

Maha Z. Rizk, Hanan F. Aly

Department of Therapeutic Chemistry, National Research Centre (NRC), Cairo, Egypt

Correspondence to Hanan F. Aly, Professor of Biochemistry, Department of Therapeutic Chemistry, National Research Centre, ElBehouth St., P.O. 12622, Dokki, Cairo, Egypt. Celluar Phone: 00201011005557; e-mail: hanan_abduallah@yahoo.com

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The severe acute respiratory-syndrome coronavirus 2 is a viral pathogen that is responsible for the coronavirus disease-2019. Since first being reported, severe acute respiratory-syndrome coronavirus 2 has infected millions of people and eventually caused millions of deaths worldwide, with these numbers rising daily during successive waves. So far, the risk factors associated with poor clinical outcomes (death or admission to an ICU) have been reported to be old age and several comorbidities associated with compromised immune system to help the patient fight the infection. The most common of these comorbidities are obesity, hypertension, diabetes, cardiovascular diseases, dementia, and malignancies. These comorbidities, individually or in combination with age, were reported to be linked with poor prognoses. In the present review, vulnerability of patients with different chronic diseases to infection with coronavirus disease-2019 is discussed with different treatment strategies during coexistence of viral infection with any of these diseases. Also, biochemical markers (e.g., angiotensin-converting enzyme 2, cytokine storm, or inflammatory markers) and the underlying mechanisms associated with viral infection together with the different chronic diseases are described.

Keywords:
Alzheimer, cardiovascular disease, coronavirus disease-2019, diabetes, obesity

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Introduction

Coronavirus disease-2019 (COVID-19), the world viral crisis, is an infectious disease caused by a new type of coronavirus that has lately emerged with its possible origin linked to the Wuhan seafood market in China [1]. COVID-19 represents the seventh member of the coronavirus family that infects humans. There are several types of coronaviruses. Some are less serious and cause mild illness, while others, including COVID-19, can be more vigorous and affect breathing or respiration and result in lung complications leading to high morbidity and mortality. The symptoms of COVID-19 include fever, fatigue, dry cough, dyspnea, and sore throat, with patients presenting with abnormal chest computed tomography scans in the form of pulmonary ground-glass opacity changes. The virus is prevalent worldwide, and hence, the WHO officially considered it as pandemic [2]. This virus mainly spreads among people through sneezing or coughing or it might be released through tiny droplets into the air during talking, singing, or laughing. These droplets can reach any person around within a small distance and hence can get infected with the virus. In addition, infection may spread by touching solid surfaces bearing the virus on which it persists up to three days.

Coronavirus 2 or severe acute respiratory-syndrome coronavirus-2 virus (SARS-CoV-2), which has been identified as the pathogen of COVID-19, is a novel enveloped RNA beta-coronavirus that shares similar genetic identity with two bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21 [3]. The affinity of SARS-CoV-2 for angiotensin-converting enzyme 2 (ACE2) as a cell receptor is 10–20-fold higher than that of SARS-CoV although they are structurally similar. However, ACE2 expression is not only limited to the lung, but it may also be found in many other organs, such as the oral epithelium, adipose tissue, and heart, which could demonstrate the higher infectivity and multiple-organ dysfunction caused by SARS-CoV-2 [4,5]. SARS-CoV-2 infectivity is related to the rate of shedding of ACE2. The extracellular domain of ACE2 forms the receptor for the spike (S) protein of SARS-CoV-2, and this is the basic site for the pathogenesis of SARS-CoV-2 infection [3].

Although many COVID-19 patients are presented with mild symptoms such as fatigue and cough, several others develop severe or critical pneumonia, regarded as acute respiratory-distress syndrome (ARDS), multiorgan failure, and even death [6]. Therefore, the medical sector should focus on identifying populations at high risk for developing severe or critical COVID-19 [7].

Primarily, age is a main factor for prediction of the disease and mortality rates are significantly higher in elder individuals. The case-fatality rate in databases exceeded 1% around the age of 50–55 years and 10% above 80–85 years. The positive association of sociodemographic factors (age and male sex) with severe COVID-19 is consistent with reports of other infectious diseases (e.g. influenza virus and SARS in 2003) [8]. Older age is linked to reduced immune reaction, more comorbidities, and limited organ reserve [9]. Also, those with health problems, such as type-2 diabetes, cardiovascular diseases, obesity, neurological disorders, hypertension, kidney or liver or lung disorders, and smoking, weakened immune system, and cancer, are more vulnerable to COVID-19 infection.

Obesity

Obesity is a huge healthcare concern because it is a milestone in the development of several serious chronic diseases and is considered a major risk factor that may lead to death when subjected to COVID-19 attack [10,11]. Obese patients are liable to increased prevalence of many diseases, including renal insufficiency, lung and respiratory disorders, cardiovascular diseases, type-2 diabetes mellitus, certain types of cancers, and a significant degree of endothelial dysfunction. These conditions impose major risk for COVID-19 severity, worse outcomes, and significantly reduce the quality of life, leading to high mortality rates, which makes obesity particularly ominous in COVID-19 [12]. Strong evidence has demonstrated that obesity results in significant changes in both innate and adaptive immune response and obese individuals are subjected to chronic and low-grade inflammation [13]. The overall result is a reduced immune response to infectious agents, resulting in poorer outcomes post infection [14].

During the 2009 HIN1 pandemic, patients with severe obesity were more likely to require hospitalization, ICU admission, and death due to the disease. Further data have indicated that obesity negatively impacts host immune defense, leading to many infectious diseases. Excess adiposity causes pronounced changes in the resident immune-cell composition of adipose tissue, which alters the balance between proinflammatory and anti-inflammatory immune cells in favor of the former. This results in chronic low-grade inflammation, which may be amplified by acute inflammation from COVID-19, resulting in a more severe disease phenotype and poorer outcomes [13,14].

Interestingly, many reports suggest that insulin may be a key regulator of T-cell metabolism and function [15,16]. Insulin signaling exerts critical immune-stimulatory effects on these cells, positively controlling their growth and proliferation, glucose metabolism, and production of cytokines, and in turn strengthens the host defense against infections. Concerning obesity, a complex phenomenon known as ‘insulin resistance‘ occurs, which is characterized by reduced insulin signaling in peripheral tissues, including immune cells causing different metabolic disorders and induced adipose dysfunction due to expansion of adipose mass [17]. Thus, insulin-stimulated signaling pathway is impaired in lymphocytes of individuals with obesity [18] and type-2 diabetes [19], impacting the functioning of lymphoid tissue [20]. On the other hand, excess lipid deposition affects the integrity and architecture of primary lymphoid tissues and hence impacts the immune-cell development and activation. Several studies have reported that obesity leads to increased lipid deposition in tissues other than adipose like primary lymphoid organs (bone marrow and thymus). Excess lipid deposition in these tissues impacts the distribution of leukocyte population, the activity of lymphocytes, resulting in a marked change in the overall immune defense [20,21]. Lipid accumulation of lymphoid organs is known to occur in older people and adversely affects their immunity. Consequently, obesity is assumed to promote premature ‘aging’ of the immune system [22].

Besides insulin resistance, metabolic changes associated with obesity include leptin resistance and these negatively impact immune-cell function. Leptin was found to regulate both innate and adaptive immune responses via the modulation of immune-cell metabolism, proliferation, and activity. Circulating leptin levels are significantly elevated in obese patients, but the response of target tissues to leptin is severely compromised due to leptin resistance [23,24]. Therefore, leptin resistance would profoundly impact the proper development and activity of immune cells in

obese patients, weaken the host defense, and increase the chances of severe disease and poor outcome in COVID-19 patients. Together, these changes have a substantial influence on immune-cell growth and proliferation, glucose metabolism, and activation, which ultimately results in impairment of host immune defense.

Furthermore, it is evidenced that adipose ACE2 may be involved in the spread of COVID-19 to other tissues. ACE2 is required for the entry of COVID-19 into the cells through the receptors found on cells in the nose lining, the lungs, pancreas, kidneys and gut, adipose, and in the lining of blood vessels, in the heart muscle, and cells circulating in the blood. It is assumed that increased expression of ACE2 would boost the entry of the virus into the cells and therefore, cause severe disease with worse clinical outcomes. It is worth mentioning that ACE2 expression is increased in obese and overweight patients compared with lean participants [25]. Interestingly, ACE2 expression is higher in adipose compared with lung tissue, which is the primary target of COVID-19 [26]. Adipose tissue has been shown to act as a reservoir for other human pathogens [27]. More importantly, lipid droplets that are present in adipose tissue have been shown to play a key role in the production of the hepatitis- C virus [28]. Therefore, it is reasonable to assume that adipose tissues might act as a reservoir for COVID-19 and lipid droplets might facilitate viral production and spread. Consequently, excess adipose tissue in obesity would facilitate virus entry and spread and therefore, cause severe clinical disease manifestations. It should be pointed out that adipose tissue acts not only as a metabolic reserve but also as an endocrine organ that induces chronic low-grade inflammation, characterized by elevated levels of proinflammatory cytokines, such as leptin, interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α), and decreased levels of anti-inflammatory cytokines such as adiponectin and IL-10 [29]. In case of obesity, the constant low-grade inflammation leads to T-cell exhaustion, which greatly impairs the immune response and hence the ability to attack the virus from the host and its eradication [30]. Another main feature of obesity is activity deficiency, which could also impair immune-cell activation and disrupt adaptive immunity, associated with a pronounced decrease in anti-inflammatory CD4+ and CD8+ cells and an increased percentage of proinflammatory immune cells such as Th17 and Th22 cells [31]. Additionally, because of the large volume of adipose tissue, the population with obesity significantly possesses a large amount of ACE2 and stocks a huge amount of virus, which results in increased viral shedding, immune inactivation, and cytokine storm [32]. In brief, the mentioned unfavorable chronic inflammation, dysfunction of the immune system, and higher ACE2 concentration in adipose tissue might partly explain the high risk of poor outcomes in obese COVID-19 patients.

Obese patients with influenza shed the virus for a longer period of time than lean participants, which increases the transmitting ability of the virus. In addition, the reduced and delayed capacity of producing interferons allows more viral RNA replication, increasing the possibility of novel viral strains, and the unfavorable hormone milieu of obese patients also leads to defects in innate immunity and B-cell and T-cell responses. Consequently, emerging evidence indicates an association between obesity and the severity of respiratory infectious diseases [10,11].

Dysregulated fatty acid metabolism, cellular hypertrophy and death, endoplasmic reticulum stress (ER stress), hypoxia, and mitochondrial dysfunction, because of excess fat, leads to a substantial alteration of cellular architecture of adipose tissue. This rearrangement favors a proinflammatory environment and perpetuates local as well as systemic inflammation [14].

Alzheimer disease (AD)

Dementia, including AD, is a health problem, which affects elderly people and causes serious complications leading to morbidity and mortality [33]. The brain of AD patients is featured by the deposition of amyloid plaques and the presence of neurofibrillary tangles, neuronal damage and synapse loss, as well as oligodendroglia degeneration and myelin impairment [34]. Most people with dementia are usually bearing one or two additional chronic health diseases. Strong risk factors for cognitive decline and dementia include cardiovascular diseases, diabetes, obesity, and hypertension [35]. Many of these disorders in patients with dementia are also considered high-risk factors for COVID-19 and are associated with worse clinical manifestations.

In patients with dementia including vascular dementia and AD, the blood–brain barrier (BBB) is damaged, which makes it easier for certain bacteria and viruses to enter the brain more easily and hence those patients are more susceptible to these infections. In addition, the memory disabilities in these patients may impair their understanding to comply with preventive measures for COVID-19, such as social distancing, mask wearing, and frequent hand sanitizing [36].

SARS-CoV-2, as well as all members of the human coronavirus (CoVs) family, is an opportunistic pathogen of the central nervous system (CNS) [37] and symptoms, such as confusion, headache, hypogeusia/ageusia, hyposmia/anosmia, dizziness, epilepsy, and acute cerebrovascular disease [38], are caused by the direct invasion of the virus into the CNS. Postmortem studies revealed the presence of both SARS-CoV-2 antigen and RNA in the brain tissue of COVID-19 patients [39,40].

It has been hypothesized that SARS-CoV-2 could cause damage in the CNS by direct neurotoxicity or indirectly through the activation of the host immune response, leading to demyelination, neurodegeneration, and cellular senescence causing features of encephalitis and thrombotic events. This causes progressive brain aging favoring the development of neurodegenerative diseases, including dementia [41]. However, after the acute recovery phase, the long-term consequences of SARS-CoV-2 infection on accelerated aging and age-related neurodegenerative disorders are still to be considered. Noteworthy, SARS-CoV-2 could strongly impact cognitive decline in AD patients. On the other hand, dementia could represent an important risk factor for COVID-19 severity and mortality and hence, a mutualistic relationship between SARS-CoV-2 infection and AD can be hypothesized [42].

Indeed, an early sign of being infected with COVID-19 is the loss of the sense of taste and smell. Moreover, the brain is also affected by organ failure elsewhere (e.g. heart or lung), and hypoxemia is a hallmark of severe infection, and can itself lead to cerebral edema and brain malfunction [43]. In this respect, and owing to these brain complications, it could be assumed that preexisting dementia, especially with involvement of the blood vessels in the brain (vascular dementia) renders dementia patients to increasing risk of adverse outcomes, leading to morbidity and mortality from COVID-19. In case of vascular dementia, cognitive impairment is attributable to cerebrovascular pathologies and alteration in cerebral blood vessels [44,45] with damage to the BBB [46]. Because the virus can attack the brain or its blood vessels directly, and receptors for the virus are found in the vicinity of brain vasculature [43], it can be postulated that impaired cerebral blood flow, or damaged endothelium, is a risk for SARS-CoV-2 entry. Consistently, it was previously reported that the odds of SARS-CoV-2 infection for patients with vascular dementia remained more than three times increased over patients without vascular dementia even after adjusting for different chronic diseases and other known risk factors. This suggests that while comorbidities and other COVID-19 risk factors increased the risk for COVID-19 in patients with vascular dementia, the brain vascular pathology itself could also be involved in SARS-CoV-2 infection or subsequent damage in the brain.

In addition, there is a bidirectional relationship between viral infections and dementia: people with dementia have an increased risk for SARS-CoV-2 infection because known COVID-19 risk factors (e.g. cardiovascular diseases, obesity, and type-2 diabetes) overlap with those for dementia, while a poor immune response to infection places individuals at increased risk for dementia [47]. The damaged BBB in patients with dementia predisposes them to bacterial and viral infections. It should be considered, however, whether a SARS-CoV-2 infection will accelerate cognitive decline in individuals suffering from dementia or lead to long-term cognitive impairments and trigger dementia in infected people. Neurological manifestations of COVID-19 range from headache, loss of smell, confusion, strokes, and brain hemorrhage to memory loss [43]. Increasing evidence shows that SARS-CoV-2 can infect neurons and affect brain function through chronic hypoxia, metabolic dysfunction, systemic inflammation, and immune dysregulation [48–50].

Following invasion of the virus into the CNS, subsequent interaction occurs between SARS-CoV-2 spike protein and the ACE2 [51,52]. As previously indicated, ACE2 expression is a key determinant of viral tropism and COVID-19 pathogenesis. In the brain, ACE2 is expressed both on neurons and glial cells, as well as on endothelial and arterial smooth muscle cells. ACE2 is also expressed on the temporal lobe and hippocampus, which represent cerebral regions involved in the pathogenesis of AD [51]. Additionally, genome-wide association studies showed that the expression of ACE2 gene is elevated in the brain tissue of AD patients with increased levels in severe forms [53]. Thus, enhanced ACE2 expression could represent a risk factor for COVID-19 transmission in AD patients. It has been reported that oxidative stress is a direct mediator between AD and *ACE2* expression. Since aging leads to the imbalance in the redox state, resulting in the generation of excess reactive oxygen species or the dysfunction of the antioxidant system, leading to oxidative stress [54], this makes aging correlated with AD a high-risk factor for

development of COVID-19. Interestingly, ACE2 inhibitors have recently been suggested as potential treatment for neurodegenerative diseases, including AD [55], which could help in reducing vulnerability to the virus infection.

Noteworthy, AD and COVID-19 share several risk factors and comorbidities, such as age, sex, hypertension, and diabetes and APOE ε4 expression. Such evidence could in part explain the increased prevalence of SARS-CoV-2 infection in AD patients. Furthermore, an interesting phenomena arise whether patients with COVID-19 could develop AD? Overall, coronaviruses can enter the CNS via different routes, including retrograde axonal transport via the olfactory and enteric neurons or infected lymphocytes, which cross the disrupted BBB [56]. Since aging is characterized by a gradual loss of the BBB integrity [57], therefore, the elderly could be more susceptible to neuroinvasion during SARS-CoV-2 infection. SARS-CoV-2 infects the olfactory neurons and, through the neuroepithelium of the olfactory mucosa, reaches the olfactory bulb in the hypothalamus [37,58] and in this stage, non-neuronal cells, such as mast cells, microglia, and astrocytes, are activated, and proinflammatory cytokines are released. SARS-CoV-2 uses the phospholipids of the infected cells to build its own envelope. This causes that the cells, in particular the innate immune cells, lose precursors for the synthesis of the autacoid local injury antagonist amides, which have a pivotal role for controlling the excessive reactivity [59]. Consequently, the resulting neuroinflammation could become uncontrollable, especially in the aged people, who have a weaker immune system response [60,61]. Neuroinflammation, associated with intense oxidative stress, could induce neurodegeneration, potentially favoring the development of neurodegenerative diseases, such as AD [58,62]. In addition, COVID-19 patients with advanced age and comorbidities with an inflammatory basis, such as in chronic diseases and subclinical dementia, could be at increased risk of developing AD. Several metabolic mechanisms may be involved in the potential increased risk of developing AD in COVID-19 patients. Neuroinflammation plays a vital role inducing the activation of microglia and astrocytes, which accordingly secrete proinflammatory cytokines, including IL-1β, IL-6, IL-12, and TNF-α. Such metabolic biomarkers take part in the synaptic dysfunction, inducing neurodegeneration, which could potentially lead to AD [63]. Hypoxic alterations and demyelinating lesions have been shown in COVID-19 patients [64,65]. Neuroradiological studies demonstrated alterations of functional brain integrity, especially in the hippocampus, in recovered COVID-19 patients at 3-month follow-up. Since the hippocampus is an area particularly vulnerable to respiratory viral infections [66], hippocampal atrophy is associated with cognitive decline and represents a common characteristic of AD patients [67]. Furthermore, the altered BBB could allow the infiltration of immune cells, leading to cognitive decline and dementia in COVID-19 patients. Moreover, endothelial dysfunction is a pathognomonic characteristic of COVID-19, and loss of pericytes could impair the clearance of cerebral metabolites, including Aβ peptides. The excess and accumulation of Aβ protein in senile plaques, especially in the hippocampus, represent the main pathophysiological mechanism underlying the AD. It was previously reported that common features of severe COVID-19 include ischemic white-matter damage due to the reduced perfusion secondary to hypercoagulability and disseminated intravascular coagulation. Previous studies showed that this damage also occurs at a very early stage of AD, which may accelerate the progression of AD and contribute to cognitive decline [68]. Moreover, cerebral hypoperfusion can increase the phosphorylation rate of tau protein [69]. In severe COVID-19, the systemic inflammation characterized by the so-called 'cytokine storm' leads to the disruption of the BBB and neural and glial-cell damage that could be involved in long-term sequelae. Systemic inflammation is recognized as a pathophysiological mechanism underlying AD [70]. Also, proinflammatory-released cytokines alter the capacity of the microglial cells to phagocyte β-amyloid, promoting the accumulation of amyloid plaques [71]. The virus-induced systemic inflammatory storm, associated with a massive release of mediators able to access the CNS due to the increased permeability of the BBB, could amplify neuroinflammation and contribute to the neurodegeneration process [72]. Another interesting postulation suggests that the potential expected increase of AD risk in COVID-19 patients could be attributed to amyloid β (Aβ), which can act as an antimicrobial peptide. Thus, it may be assumed that the SARS-CoV-2 neuroinvasion could induce Aβ generation, as part of the immune response, and the β-amyloid cascade, leading to β-amyloid deposition [73]. Specifically, mechanical ventilation, which is a standard therapy to maintain adequate gas exchange in severe COVID-19, could contribute to long-term cognitive impairment [74]. Experimental studies showed that short-term mechanical ventilation triggers the neuropathology of AD by promoting cerebral accumulation of the Aβ peptide, systemic

and neurologic inflammation, and BBB dysfunction [75,76].

In conclusion, the long-term complications of COVID-19 would be expected in the next 10–15 years. Nowadays, it is not possible to assess them because the pandemic started last year. However, in the future, it will be pivotal to evaluate the risk of long-term COVID-19 neurological sequelae, especially in the elderly and patients who developed severe forms.

Cancer

Viral infections are considered a great challenge for cancer patients and oncologists. COVID-19, caused by the SARS-CoV-2, is continuously spreading worldwide with subsequent waves. Cancer patients are reported three times more susceptible to SARS-CoV-2 infection with possibly poorer prognosis because they suffer a state of systemic immunosuppression caused by the case of illness or anticancer treatments. The continuously increasing numbers of cancer patients and increased COVID-19 infections in these patients undiagnosed, diagnosed, under treatment, or under remission, have made it a vital concern to understand the link and develop novel therapies to cotarget both viral infections and cancer [77].

The inability of the host immune system to differentiate between self and nonself, results in, and links, the pathogenesis of cancer and viral infections. Both viruses and cancers express proteins that are recognizable by host T cells and both prompt T-cell-mediated inflammation [78]. Viral infection-mediated chronic inflammation has long been associated with increased tumor growth and metastasis, and nonsteroidal anti-inflammatory drugs have been shown to reduce tumor growth and cancer development [79]. It was previously reported that lung cancer patients show lower immune response to influenza infection due to lower levels of interferon-beta. The latter are associated with the presence of tumor-derived exosomes that transfer epidermal growth factor receptor protein to immune cells such as macrophages. These cells could not produce enough interferon-beta in response to viral infection [80]. This suggests that the effects of the two diseases are defined by factors comprising the type of viral infection or cancer, and the immune system components involved.

Coronaviruses mainly target the human respiratory system. COVID-19 by itself is biologically novel and this makes its role in cancer not fully understood. Similar to other severe acute respiratory outbreaks (SARS-CoV, MERS-CoV), morbidities such as hypertension and malignancy predispose COVID-19-positive patients to adverse clinical outcomes [81]. According to the WHO, the case-fatality rate for COVID-19 patients with cancer as a comorbid condition was 7.6% versus a case-fatality rate of 3.8% in the entire COVID-19 population. Therefore, it becomes clear that cancer possibly affects COVID-19 pathogenesis. Despite of cancer patients being at high risk of developing severe complications following SARS-CoV-2 virus infection, data on COVID-19 infection in patients with cancer are still insufficient. Immune dysregulation and chronic inflammation may be potential drivers of severe outcomes in COVID-19-positive cancer patients. Therefore, it is important to better understand the underlying mechanistic link between COVID-19 and cancer, which may aid in reducing the negative effects of infection and may also help in designing novel therapies targeting both infections. The success in treatment of viral infections and cancer is unprecedented since the comorbidity of both conditions poses a major challenge in the management of these patients. It should be taken into consideration how to balance between chemotherapy and antiviral medication regimens and the optimum conditions for their administration. For some cancer patients, the antiviral treatment must be completed before chemotherapy, while others receiving cancer treatment cannot obtain the antiviral therapy [77].

It is worth inquiring: is SARS-CoV-2 infection involved in cancer either causing or increasing its risk and does COVID-19 induce tumor progression or impact patients' survival of cancer patients? Is there a different treatment for COVID-19-positive cancer patients? What are the metabolic strategies for interactions between COVID-19 and cancer?

There is no positive fact that SARS-CoV-2 is causative, but, is an infective agent in immunocompromised cancer patients, although it is not clarified whether all cancer patients are at a high risk of becoming infected with SARS-CoV-2 virus [82]. It is thus of prime importance that cancer patients receiving antitumor regimens should avoid in-person clinic visits to be kept safe from contacts, should be vigorously screened for COVID-19 infection, and their immunosuppressive treatments and the doses applied should be potentially decreased if COVID-19 co-infection is proved [83]. It is also necessary that cancer patients, especially the elderly, receive

stronger personal protection facilities and more intensive observation should also be considered for those bearing COVID-19. Therefore, cancer patients are prone to suffer from severity of infection but not for contracting the infection. Generally, the symptoms of COVID-19 are the same in cancer patients as in the general population (fever, coughing, and shortness of breath). However, steroids or other treatments in cancer patients may suppress the fever symptom of COVID-19. If a cancer patient is coinfected with COVID-19, the treatment strategy depends on the type of cancer, stage of treatment, and severity of the viral infection [84].

As stated earlier, ACE2 plays a vital role in the metabolic interactions, which is expressed in multiple organs, including respiratory, cardiovascular, digestive, and urinary systems. This enzyme is a carboxypeptidase that converts angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7. It is an important regulator of heart function and has a protective role in acute lung injury [85]. SARS-CoV-2 enters human cells through ACE2 [86]. The spike protein of the virus binds to this enzyme, and together enters the cell to replicate and expand. ACE2 expression level is high in cells and tissues of cancer patients and it may be assumed that these patients are more likely to be infected with SARS-CoV-2 than healthy individuals and have poor prognosis [87]. Renal tissue shows higher expression levels of ACE2, and this may be the reason that most COVID-19 patients develop renal dysfunction. Moreover, ACE2 is present on the X chromosome, meaning males have one copy and females two, however, the observed risk of infection is not lower in men compared with women, although the former patients exhibited more severe outcomes than the latter [88]. There is a possibility that the presence of ACE2 in multiple organs may be the reason that more deaths from COVID-19 have been caused by multiple-organ dysfunction syndrome rather than respiratory failure. However, more studies should be done to prove the mechanistic link between ACE2 expression and SARS-CoV-2 infection in cancer. Thus, it would be worthwhile to test whether levels of ACE2 increase or decrease in various tissues of cancer patients and COVID-19 patients and how this impacts COVID-19 infection in these patients.

During malignancy, alterations in both innate and adaptive immunity and in cytokine profiles are presented. Cytokine storm or cytokine release syndrome (CRS) is a systemic inflammatory response that can be triggered by factors such as pathogenic infections, chimeric antigen-receptor (CAR)-T-cell therapy, antibody treatments, and certain drugs [89]. The induction of a cytokine storm is the main cause of pathogenic inflammation, both in SARS-CoV and SARS-CoV-2 infection. Cao *et al.* [90] reported the presence of a lethal cytokine storm in the immune system of severe SARS-CoV-2-infected patients, with pneumonitis signatures in their lung computed tomography scans. COVID-19 patients are reported to have elevated levels of IL-6, IL-1β in serum, TNF-α, lactate dehydrogenase, and increased levels of circulating monocytes [90]. These extensive proinflammatory and interferon-antagonizing properties in COVID-19 patients mimic those observed in cancer patients receiving CAR-T-cell therapy or immunotherapy [91]. Although the cytokine levels in COVID-19 patients with ARDS are lower than those observed in CRS in cancer patients receiving CAR-T-cell or immunoglobulin therapies, the experience and understanding of cancer biologists and oncologists in modulating severe inflammatory response is greatly efficient. It is clear that cytokine release and macrophage activation results in the immunopathology in COVID-19 disease and thus, anti-inflammatory cancer drugs may be repurposed for decreasing the morbidity in COVID-19 patients.

The risk of cancer increases with increasing age. According to the National Cancer Institute, a quarter of new cancer diagnoses are in individuals aged between 65 and 74 years of age. This may be due to more accumulated mutations following prolonged exposure to carcinogens, or, increased chronic inflammation in the microenvironment, weaker immune system, and less effective DNA-damage-repair mechanisms [92]. Similarly, older individuals are at higher risk for developing more serious complications from COVID-19 and it is reasonable to suggest late that some of the underlying reasons for severe outcomes of SARS-CoV-2 virus infection in older individuals may be similar to those observed in cancer patients. Hence, a connection between age, cancer, and COVID-19 presumably exists.

Both cancer and COVID-19 are associated with coagulopathy in a complex manner. Thrombotic and bleeding complications are the leading causes of death in cancer patients and are often associated with the morbidities in COVID-19 patients. Various prothrombotic properties of tumor cells, such as release of cytokines, cysteine proteases, tumor microparticles, and other procoagulants, can cause an

imbalance in hemostasis [93]. Disseminated intravascular coagulation is associated with 71.4% of COVID-19 nonsurvivors and hence may be the cause of mortality in these patients. Increased levels of D-dimer and prothrombin and decrease in fibrinogen were reported in these patients at days 10–14 [94]. In this respect, the importance of frequently screening these factors in COVID-19 and cancer patients should be greatly considered with concise focusing on the molecular connections of these disease conditions to coagulopathy, which may thence help in reducing mortality in these patients.

Clearly, the most promising approach for preventing or fighting a viral infection is through vaccination. However, several vaccines have been lately developed against SARS-CoV-2 virus. Also, globally, pharmaceutical and research organizations are aggressively pursuing efforts to direct preexisting antiviral drugs as well as convalescent serum from COVID-19-recovered patients. However, in the meantime, the severe inflammatory response and respiratory complications that occur in severe COVID-19 patients should be addressed. Cocktails of different monoclonal antibodies (mAbs) that recognize the different epitopes on the viral surface may have better efficacy in neutralizing the SARS-CoV-2 virus. Cytokines may impose another promising target, especially IL-6, since higher levels are correlated with cytokine storm in COVID-19 patients. Oncologists have been using IL-6 inhibitors (e.g. tocilizumab and siltuximab mAbs) for the management of CRS in cancer patients receiving CAR-T-cell therapy. Another proinflammatory cytokine upstream of IL-6 is IL-1, which is also upregulated in CRS. IL-1-receptor antagonists such as anakinra have been frequently used to treat arthritis patients with CRS symptoms. Calcineurin inhibitors present another class of nontoxic immunosuppressants that impair T-cell function and thereby reduce cytokine levels. These may help to mitigate the severe COVID-19 symptoms in patients. Lung cancer patients undergoing immunotherapy and with immune-related severe adverse responses have benefitted from tocilizumab [48]. It is important to consider however that comorbidities from CRS symptoms due to cancer immunotherapies and SARS-CoV-2 infection could be fatal in patients.

The presence of viral gene components vital for the unchecked proliferation of viruses in host cancer cells may also provide targets for possible effective therapies [95] and may help in understanding the main differences between the biology of COVID-19-infected cancer versus normal host cells and the relevant constituents of the immune system may be successful in attaining new biological strategies to fight the serious comorbidity arising from viral infections in cancer patients. Furthermore, the recent insights into the roles of dendritic cells, T cells, and natural killer cells in the pathology and therapies of both cancer and viral infections are greatly promising for development of novel immunomodulatory therapeutic strategies to cotarget these diseases. As innate effectors, functional natural killer cells can orchestrate antiviral responses against influenza infection and they are also reported as potential host-directed anticancer agents due to their associated negligible graft-versus-host signature [96]. In this respect, they may provide a safer and faster alternative to cotarget COVID-19 and cancer. However, further studies should be directed toward the therapeutic benefit of these immunotherapies in COVID-19 infection since these immunomodulatory therapies may induce cytokine storm effects in these patients.

An interesting point of research arises on the application of nanotechnology as a safer delivery option for various antiviral drugs, including vaccine candidates. By increasing the bioavailability and effectiveness of the payload, nanoparticles decorated with recombinant human ACE2 protein on their surface may provide an effective therapeutic option for COVID-19 patients. ACE2-conjugated nanoparticles will bind to the spike protein of SARS-CoV-2 virus and may thus neutralize the virus and prevent it from binding the ACE2 receptor present on host cells [97].

In conclusion, studies are needed to understand how a normal cell versus cancerous cell interacts with the SARS-CoV-2 virus. This will provide knowledge on which cells are most susceptible to SARS-CoV-2, and how exactly we can target SARS-CoV-2 virus with immunotherapies, drugs, and vaccines to prevent or treat COVID-19 and cancer. Ziegler *et al.* [98] recently demonstrated the specific human cells that SARS-CoV-2 primarily targets for infection and that human ACE2 expression in epithelial cells is interferon dependent. This indicates that any potential use of interferon as a treatment to fight COVID-19 will require careful monitoring to determine if and when it might help patients. Identifying the relevant components of the immune system will likely lead to new biological strategies to fight the serious comorbidity arising from viral infections in cancer patients. It is likewise important for cancer patients

to maintain a healthy lifestyle and take steps to support their immune system.

Diabetes

Diabetes mellitus is a chronic metabolic disorder that poses a serious health problem affecting many millions of people worldwide. The disease is caused by either absolute insulin lack in type-1 diabetes or insulin resistance in type-2 diabetes and results in acute and chronic inflammation, which is a complication also associated with COVID-19. In this respect, it is clear that both diseases can impact each other, which triggers the need to understand the metabolic profile of diabetes coexisting with COVID-19.

COVID-19 primarily attacks the respiratory system causing pneumonic changes. For viral entry, the role of the ACE2 is again obvious through binding of the coronavirus S-glycoprotein to the enzyme receptor in the host followed by fusion with the cell membrane. The S-glycoprotein is composed of S1 and S2 subunits, which are situated on the surface spikes of the virus, which are cleaved with the help of furin, a protease that is also reported to be increased in diabetic patients. In the cytosol, viral replication occurs in the presence of proteases such as cathepsin in acidic medium [99].

The inflammatory conditions that happen first in the respiratory system result in the generation of multiple cytokines and chemokines, such as TNF-α; IL-1, 7–10; interferon gamma; granulocyte colony-stimulating factor; granulocyte–monocyte colony-stimulating factor; fibroblast growth factor 2; monocyte chemoattractant protein-1; and macrophage inflammatory protein-1 alpha. Interestingly, inflammatory markers, such as C-reactive proteins, IL-6, plasminogen activator inhibitor-1, TNF-α, leptin, and adiponectin, are also identified in diabetic patients [1].

Dipeptidyl peptidase-4 (DPP4) is an enzyme present in the intestinal tract that degrades incretins that are responsible for insulin secretion, and hence reduced levels of these incretins are a feature demonstrated in type-2 diabetes. This same enzyme has been described as an entry-receptor factor for the coronaviruses, such as MERS-CoV, and is referred to as CD26 [100]. Since MERS-CoV and SARS-CoV-2 belong to the same subfamily of Coronavirinae, it may be assumed that this mechanism in diabetes and viral infections may be similar. An interesting question arises whether DPP4 inhibitors may be efficient in treating diabetic patients bearing COVID-19.

As previously indicated, ACE2 receptor is important for entry of SARS-CoV-2 into the cells and it is expressed by the epithelial cells of the lungs, intestine, kidney, and vessels. In a previous study, it was shown that diabetic patients also express high levels of ACE2. The hypothesis that ACE2 polymorphisms are linked to some diseases, such as diabetes, hypertension, stroke, and genetic predisposition to developing SARS-CoV-2 infection, has been postulated [101].

ACEi and ARBs are antihypertensive drugs used by patients with hypertension and diabetes and are reported to elevate cardiac ACE2 [102]. Since ACE2 is involved in COVID-19 pathogenesis, it is necessary to consider the effects of these drugs on the severity of infection and further studies are needed to assess the clinical outcomes in diabetic patients with coexisting COVID-19 using ACEi or ARBs.

In addition, diabetic patients are more susceptible to viral and bacterial infections, including those affecting the respiratory system causing impaired leukocyte function of phagocytosis (impaired immunity). Thus, the possible increase in being infected with SARS-CoV-2 is greatly expected in diabetic patients [103].

Diabetes also impairs the lung and typically affects the gaseous exchange, which may result in the easy invasion of some respiratory pathogens, including SARS-CoV-2 [104]. Some possible mechanisms defining the role of diabetes in increasing SARS-CoV-2 morbidity and mortality include the increased cellular-binding affinity and successful viral entry, decreased T-cell function, and higher susceptibility to hyperinflammation and cytokine storm. In the present COVID-19 pandemic, a study performed in Italy revealed that diabetes mellitus ranks high among the comorbidities in COVID-19 patients [105]. In addition, another study done in Wuhan showed that 2–20% of COVID-19 patients were diabetes mellitus positive and comprised about 7.1% of ICU admissions [1]. Yang *et al.* [106] and Chen *et al.* [107] also reported a prevalence of 17 and 12.1%, respectively, among 52 and 99 coronavirus-positive cases in China.

An interesting study done in New York revealed that among 5700 hospitalized patients with COVID-19, 33.8% were diabetic, 56.6% had systemic hypertension, while 41.7% were obese [108], which evidences the influence of these diseases on COVID-19 infection.

Moreover, in diabetic patients with COVID-19 infection, hyperglycemia induces the process of

cytokine storm, endothelial dysfunction, and multiple-organ injuries, and causes deterioration in metabolic functions in the lungs, the primary target of COVID-19, and directly impacts innate immunity. On the other hand, hypoglycemia may arise during glycemic control and this may increase cardiovascular mortality by increasing proinflammatory monocytes that trigger platelet aggregation [109]. The disturbance in optimizing glycemic conditions in COVID-19 patients is correlated with higher mortality rate as previously reported by Bode *et al.* [110], who found that the mortality was 28.8% in diabetic patients compared with 6.2% in the nondiabetic ones.

Further, during COVID-19 infection, glucocorticoids and catecholamines are released into circulation, which have adverse effects on glycemic control and increase the formation of glycation end products in many organs and worsen prognosis [111].

Considering the interrelationship between COVID-19 and diabetes, the effect on or possible invasion of the virus into the pancreas was previously addressed since high levels of ACE2 in the pancreatic islet beta cells were found and this causes increased islet-cell injury and impaired insulin secretion. The above phenomena were supported by Wang *et al.* [112], who demonstrated that 17% of admitted patients in Wuhan with COVID-19 pneumonia developed pancreatic injury with the majority also revealing glucose intolerance. After viral entry into the beta cells, ACE2 is downregulated with elevated angiotensin level, which also impairs insulin secretion [113]. This pancreatic injury involves direct cytopathic effect of SARS-CoV-2 replication, systemic response to respiratory failure, and harmful immune response induced by SARS-CoV-2 infection [112,113].

It should be pointed out that corticosteroids, which are used to suppress inflammation and cytokine storm, may result in certain complications, such as worsening diabetes, avascular necrosis, and psychosis. The application of these drugs may raise blood glucose by 80% in diabetic patients with COVID-19 infection and to a lesser extent in those without diabetes [114]. Thus, mortality rates are increased in diabetic patients with coronavirus infection.

It should be pointed out that the policy of lockdown to control COVID-19 waves had an adverse impact on diabetic patients since the latter were apart from their routine clinic checkup and were not stuck to their control diets and medications, which resulted in worsening glycemic conditions and developing severe complications [115].

Concerning inflammatory markers, Zhu *et al.* [116] showed that type-2 diabetic patients had higher levels of C-reactive protein and procalcitonin (57.0 and 33.3%) than the nondiabetic individuals (42.4 and 20.3%), respectively. Elevated C-reactive protein may be a tool monitoring those with high risk of death from COVID-19. The D-dimer, which is a marker of coagulation status, was also elevated in the diabetic group compared with the nondiabetic group (50.5 vs. 33.3%). The levels of these inflammatory markers are directly related to the severity of COVID-19 infection [117]. It could thus be confirmed that the degree of inflammatory response to COVID-19 is more marked in diabetic patients than in nondiabetic cohorts.

For treatment of diabetic patients with coexisting COVID-19 infection, the applied medications should not only lower blood glucose but should also not worsen the prognosis of COVID-19 infection. In this respect, some antidiabetic drugs are discussed below with their efficiency during coinfection with COVID-19.

It was suggested that insulin increases the activity of ACE2 and increases the infectivity of SARS-CoV-2 in laboratory experiments, but is yet to be indicated in humans. Insulin acts by suppressing proinflammatory cytokines and enhancing immune mediators and thus possesses an anti-inflammatory effect [118]. Serdu *et al.* [119] showed that insulin efficiently resulted in better glycemic control in diabetic patients with COVID-19, and is hence recommended to be described to diabetic patients with COVID-19, especially hospitalized patients.

Conversely, Chen *et al.* [120] reported that COVID patients who take insulin compared with noninsulin users in the diabetic cohort were associated with poor prognosis.

Another drug used in diabetes is metformin, which acts by phosphorylating ACE2 receptor involved in SARS-CoV-2 entry into the cells, rendering it nonfunctional by activation of adenosine monophosphate kinase [121]. This results in lowering the binding capacity of the virus by incorporation of PO4–3 molecule. When the virus enters the cell, there is a downregulation of ACE2 receptor and a simultaneous activation of renin–angiotensin–aldosterone system, responsible for the cardiac and pulmonary complications of COVID-19

infection. Since metformin inhibits the viral entry into the cell by disruption of binding capacity, it may be considered beneficial in COVID-19 infection.

However, although metformin is efficient at the molecular levels, it is not recommended in the clinical management of COVID-19 infection because of the risk of lactic acidosis, which may ensue in diabetic patients with dehydration from acute viral infection, resulting in prerenal acute kidney injury [122].

Sulfonylureas, on the other hand, are not efficient in the control of hyperglycemia in COVID-19 as they may induce hypoglycemia owing to their poor caloric intake in acute infections. Thiazolidinediones such as Pioglitazone has the tendency to cause fluid retention and worsen heart failure and thus is not suitable for patients with both diabetes and COVID-19.

Moreover, the anti-inflammatory property of DPP4 inhibitors may mitigate the effect of COVID-19 on glycemic control and may be considered useful in diabetic patients with COVID-19. Bornstein *et al.* [122] recommended this class of drug in treating hyperglycemia in COVID-19 patients.

In conclusion, the knowledge of interaction between diabetes and COVID-19 is still under investigation. However, the role of ACE2 is implicated with increased severity of COVID-19 infection in patients with diabetes. Also, DPP4 is involved in MERS-CoV pathogenesis, so theoretically it may be implicated in SARS-CoV-2 also, as they belong to the same subfamily and family. Inflammation has been evident in both disease conditions.

Although some antidiabetic drugs have effects on the cellular-entry molecules, worsening of diabetes control with these drugs in COVID-19 infection is not clear. These drugs can reduce inflammatory processes and achieve good glycemic control. Insulin is of special importance in managing COVID-19 patients with diabetes, especially those who have hyperglycemic emergencies or in ICU admission. More elaborate research and randomized control trials are still required to elucidate some unclear postulates regarding the molecular and therapeutic interrelationship between diabetes and COVID-19 infection.

Liver and kidney diseases

Liver diseases nearly cause 2 million deaths each year, with one-half related to liver cirrhosis and the other-half to hepatocellular carcinoma and viral hepatitis. Viral infections induce hepatocellular necrosis and progressive fibrosis, and finally, cirrhosis is the end stage of chronic liver disease [123]. Despite the efforts undergone for management of chronic liver diseases, the global health burden of the disease increased between 1990 and 2017 and was attributed to aging and an overall increase in the global population [124].

According to Kidney Disease Improving Global Outcome (KDIGO), chronic kidney disease (CKD) is a dysfunction of the kidney arising as a complication to diabetes and hypertension. Some other factors may also contribute to CKD, such as cardiovascular diseases, obesity, age, or genetics [125]. These factors, being risk factors for COVID-19, constitute a metabolic link between CKD and the vulnerability to the virus infection. In 2017, the number of deaths associated with CKD-related or CDK-related complications amounted to 4.6% of global deaths [126].

COVID-19-induced liver and kidney injuries have been previously reported, and it is important to investigate whether patients with a history of liver or kidney injuries are at risk to be infected with COVID-19. Previous reports have documented that the prevalences of CKD and liver diseases in COVID-19 are 1 and 3%, respectively. In another statistical analysis, it was found that COVID-19 severity reached 83.93% and 57.33% in patients with CKD and liver diseases, respectively. In addition, the mortality rates amounted to 53.33 and 17.65%, respectively, in COVID-19 patients with CKD and liver diseases [127]. Biomarkers of liver injuries were shown to be elevated in patients with COVID-19, although no virus was detected in the liver tissue of patients who died from the disease. This can be explained by the fact that angiotensin-II-converting enzyme receptor, the major clue in SARS-CoV-2 virus replication, is not expressed in liver cells, but is present in cholangiocytes [128], and thus it may be assumed that the binding of SARS-CoV-2 to the epithelial cells of the biliary tree may induce biliary dysfunction. Zhang *et al.* [129] postulated that the transient liver injuries detected in COVID-19 patients may be related to drug toxicity, cytokine storm, or hypoxia. However, the mechanisms correlating liver dysfunction in COVID-19 still require further investigations. On the other hand, ACE2 receptor is overexpressed in the tubular cells of patients with CKD [37], with kidney-function disorders manifested by increased serum creatinine

and urea nitrogen in COVID-19 [130]. Taken together, the alterations in ACE2 receptor expression, dysregulation of immune function, together with inflammation in CKD patients, may explain the observed kidney dysfunction in COVID-19 patients and provide the answer to why patients with CKD are vulnerable to the SARS-CoV-2 virus with increasing severity and mortality.The most important clinical conclusion is that liver disease and CKD patients are potentially highly vulnerable to COVID-19 and should be accurately observed and checked with strict social isolation to prevent infection.

Smoking and cardiovascular disease

Tobacco is harmful to body systems, including the cardiovascular and respiratory systems [131], which may also be harmed by COVID-19. People who suffer from cardiovascular or respiratory problems by consuming tobacco or otherwise, are highly susceptible to develop severe COVID-19 symptoms [132]. Smoking is also associated with increased development of ARDS, a key complication for severe cases of COVID-19 [133].

Tobacco use has a huge impact on respiratory health and is the most common cause of lung cancer and chronic obstructive pulmonary disease, which affects the air sacs in the lungs, rendering the latter not capable to take in oxygen and expel carbon dioxide, and mucus is built, and the final case is painful coughing and breathing difficulties [134]. Since COVID-19 primarily affects the respiratory system causing mild-to-severe respiratory disorders, this could in turn suggest that COVID-19 may cause serious complications to smokers infected with the virus, which could result in fatality.

In addition, the virus that causes COVID-19 (SARS-CoV-2) is from the same family as MERS-CoV and SARS-CoV, both of which have been associated with cardiovascular damage [7]. This relationship between COVID-19 and cardiovascular health is important because tobacco use and exposure to second-hand smoke are the major causes of CVDs worldwide. Thus, patients with cardiovascular problems are subject to develop serious complications and severe symptoms if coinfected with COVID-19 [135].

An interesting interrelationship may be documented that hypertension and diabetes are the leading risk factors for CVD and kidney diseases, and it is also evidenced that COVID-19 damages these organs [136].

Pregnancy

The overall risk of COVID-19 to pregnant women is low. However, pregnancy increases the risk for severe illness and death with COVID-19. Pregnant women who have COVID-19 appear more likely to develop respiratory complications. Also, those who have underlying medical conditions, such as diabetes, also might be at even higher risk of severe illness due to COVID-19 [137].

Some research suggests that pregnant women with COVID-19 are also more likely to have a premature birth and cesarean delivery, and their babies are more likely to be admitted to a neonatal unit [137].

Roughly two-thirds of pregnant women with COVID-19 have no symptoms at all, and most pregnant women who do have symptoms only have mild cold or flu-like symptoms. However, a small number of pregnant women can become unwell with COVID-19. Pregnant women who catch COVID-19 may be at increased risk of becoming severely unwell, particularly in the third trimester. Pregnant women have been included in the list of people at moderate risk (clinically vulnerable) as a precaution and therefore should avoid crowded places and keep a safe distance, especially at 28 weeks and over [137].

Conclusion

Finally, many reports on COVID-19 are continuously evolving with the most recent outcomes from different research.

On the other hand, the present review has focused on the following: in-depth review of risk factors correlated to COVID-19, a clinical manifestation of severe COVID-19 effects on patients, the vulnerability of patients with chronic diseases to infection with COVID-19, and the impact of coexistence of chronic diseases and COVID-19 on those patients. In addition, some factors contributing to vulnerability to COVID-19 are addressed, such as age or smoking. Furthermore, our review suggests that hypertension, diabetes, obesity, cancer neurological, respiratory, and cardiovascular diseases are associated with severe COVID-19. These demographic and clinical factors can be informative for predicting the risk of severe COVID-19.

Current control strategies mainly depend on development of efficient vaccines to enable the host immune system to fight the virus upon invasion. Vaccination policy for most of the population will stop prevalence of the virus among individuals and in turn will weaken the pandemicity of the virus. However, further clinical trials are under investigation as to the efficiency of these vaccines on facing the successive waves of the virus, the emerging modified strains, the duration of the immune response in the host, and the long-term effects of these vaccines in the body.

In addition, many scientific research centers and drug companies are working on establishing a novel drug or modified preexisting drug for treatment of COVID-19.

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