COVID-19 and diabetes mellitus: Unraveling the hypotheses that worsen the prognosis (Review)

RADU ALBULESCU[1,2*], SIMONA OLIMPIA DIMA[1,3*], IOANA RALUCA FLOREA[1,4],
DANIELA LIXANDRU[3,5], ANDREEA MADALINA SERBAN[1,3], VERONICA MADALINA ASPRITOIU[1,4],
CRISTIANA TANASE[1,6], IRINEL POPESCU[1,3*] and SARAH FERBER[1,7-9]

[1]'Nicolae Cajal' Institute, 'Titu Maiorescu' University, 004051 Bucharest; [2]National Institute
for Chemical-Pharmaceutical R&D, 031299 Bucharest; [3]Fundeni Clinical Institute, 022328 Bucharest;
[4]Department of Biochemistry and Molecular Biology, Faculty of Biology, University of Bucharest, 050095 Bucharest;
[5]Department of Biochemistry, 'Carol Davila' University of Medicine and Pharmacy, 050047 Bucharest;
[6]Department of Biochemistry-Proteomics, 'Victor Babes' National Institute of Pathology, 050096 Bucharest,
Romania; [7]Center for Stem Cells and Regenerative Medicine, Sheba Medical Center,
5262000 Tel Hashomer; [8]Orgenesis Ltd.; [9]Department of Human Genetics, Tel Aviv University,
Sackler School of Medicine, 6997801 Tel Aviv, Israel

Abstract. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the caused disease - coronavirus disease 2019 (COVID-19), has affected so far >6,000,000 people worldwide, with variable grades of severity, and has already inflicted >350,000 deaths. SARS-CoV-2 infection seems severely affected by background diseases such as diabetes mellitus and its related complications, that seem to be favoring the most severe manifestations of SARS-CoV-2 and, therefore, require special attention in clinical care units. The present literature review focus on addressing several hypotheses explaining why diabetic patients could develop multi-organ failure in severe acute respiratory syndrome coronavirus (SARS-CoV) infections. Undoubtedly, as diabetes related complications are present it is expected to emphasize the severity of the COVID-19. Dermatological complications can occur and worsen in diabetic patients, and diseases such as acanthosis nigricans and psoriasis are prone to more severe manifestations of COVID-19. Approaches to treat SARS-CoV-2 infected patients, based on different solutions i.e. plasma therapy, use of antiviral compounds, development of vaccines or new therapeutic agents are ongoing.

Correspondence to: Professor Cristiana Tanase, 'Nicolae Cajal' Institute, 'Titu Maiorescu' University, 185 Vacaresti Road, 004051 Bucharest, Romania
E-mail: cristianatp@yahoo.com

*Contributed equally

Contents

1. Introduction

Coronaviruses (CoV) are enveloped viruses with a single-stranded, positive-sense RNA genome 43 known to cause respiratory infections in humans (1). Given the phylogenetic similarity to the previously isolated severe acute respiratory syndrome coronavirus (SARS-CoV), the new virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes is called coronavirus disease 2019 (COVID-19) (2). SARS-CoV-2 was reported in people who had been exposed to a seafood market in Wuhan, China, where live animals were sold. Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19 (3).

The COVID-19 outbreak continues to cause severe morbidity worldwide and has now infected over 6 million people worldwide, with a death toll of >350,000 people (https://www.worldometers.info/coronavirus).

Worldwide data from 2020 have shown that COVID-19 is associated with different co-morbidities such as diabetes, hypertension, cardiovascular and lung diseases. Moreover, risk factors including age, male gender were associated with worse outcome in this disease (4). It is widely known that diabetes is associated with an increased risk of severe bacterial (5) and viral respiratory tract infections, including influenza and pneumonia (6). Diabetic patients with SARS-CoV-2 infection are at higher risk of experiencing a severe form of COVID-19 disease.

In the present review we are addressing several hypotheses that may explain why diabetic patients with SARS-CoV-2 infection are at higher risk of experiencing a severe form COVID-19 disease.

Diabetes by itself is unlikely to be a risk factor for SARS-CoV-2 infection. According to several studies, the prevalence of diabetes in people infected with the virus is about the same as in the general population, even slightly lower (2). However, poorly controlled blood sugar subjects are at increased risk for all infections and so there is no reason to think that this would be different for SARS-CoV-2. Moreover, any sickness that may pose a physiological stress could cause a difficult management of blood glucose levels in diabetics and especially type 1 diabetes mellitus (T1DM) patients.

Cell entry of CoV depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. Unravelling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets. SARS-CoV-2 uses the cell receptor for angiotensin converting enzyme 2 (ACE2) for cell entry and the serine protease TMPRSS2 for viral S (spike) protein priming (https://www.diabetesatlas.org/en) (7,8).

2. Interference of coronaviruses with diabetes

More than 463 million people worldwide have diabetes (https://www.diabetesatlas.org/en) (9). Recent studies demonstrate a high rate of mortality for people with diabetes compared to healthy subjects of similar age infected with SARS-CoV-2 (10).

The link between cell-mediated immunity, diabetes and SARS-CoV-2 infection. Diabetes is a disorder that appears after the accumulation of activated innate immune cells in metabolic tissues thus leading to a release of inflammatory cytokines, such as IL-1β and tumor necrosis factor (TNF)-α that promote insulin resistance and the β cell destruction (11).

SARS-CoV-2 infection associated with diabetes can trigger stress conditions with higher secretion of hyperglycemic hormones (glucocorticoid and catecholamines) that can result in insulin resistance, hyperglycemia and other complications (11-13). Pancreatic β cells, which are the only insulin producing cells in the body, could be also a target for infection and subsequent destruction as elaborated below, thus worsening the glucose homeostasis.

Respiratory viral infections including SARS-CoV-2 exhibit increased expression of interleukins (ILs), chemokines, interferon (IFN), tumor necrosis factors that were identified as cytokine storm in other studies (14). In this sense, obesity which is associated with diabetes mellitus may also worsen the outcome of SARS-CoV-2 infection, due to 'pre-activated' immune systems and resident cytokine signaling pathways such as TNF-α, IL-1 and IL-6 (15). IL-10 that acts as a negative regulator of inflammation process, could be at lower levels in diabetic patients (16). Thus, it is critical to maintain a balance between pro- and anti-inflammatory mechanisms in order to have a balanced lung homeostasis. Studies have shown that IL-6 can sustain the activation of several cytokine pathways for days after initial immune insult (17). Also, in initial studies of COVID-19, IL-6 was a strong predictor of mortality (18).

A link between SARS-CoV-2 cell entry and the endocrine pathway of diabetes. Angiotensin converting enzyme 2 (ACE2), transmembrane serine protease 2 (TMPRSS2) and DPP4 gained interest for the clinical relevance that they exert in CoV infection (2,3,8).

ACE22. ACE2, a transmembrane carboxypeptidase enzyme is expressed within epithelial tissues and represents the functional receptor for S1 of SARS-CoV and SARS-CoV-2 (19,20). ACE2 is expressed in all tissues, with major activity in the ileum and kidney followed by respiratory system, type I and II alveolar epithelial cells in lungs, heart, endothelial cells, kidney tubular epithelium, enterocytes, and both endocrine and exocrine pancreas (19-21).

ACE2 is a key enzymatic component of the renin-angiotensin-aldosterone system (RAAS); ACE catalyzes the conversion of the prohormone, angiotensin I (AngI) to the octapeptide, angiotensin II (AngII), whereas ACE2 converts AngII to Ang 1-7. AngII, through activation of Ang II type 1a receptors induces vasoconstriction and proliferation, whereas angiotensin 1-7 stimulates vasodilatation and suppresses cell growth (13).

Low expression of ACE2 within the vasculature can promote endothelial dysfunction and inflammation and exacerbate existing atherosclerosis and diabetes (13,22,23).

Both type I and type II diabetic patients have increased urinary ACE2 protein, enzymatic activity (24,25) and values for urinary ACE2/Creatinine ratios that correlate positively with fasting glucose and hemoglobin A1C (17). Additionally, dysglycemia development is mechanistically linked to ACE2 and complications in subjects with diabetes remains uncertain. RNA and protein expression of ACE2 and Ang (https://www.worldometers.info/coronavirus) (1-6) is upregulated in jejunal enterocytes from the experiments with diabetic rats induced

with streptozotocin. Whether hyperglycemia and insulin deficiency regulate ACE2 expression in human tissues has not been studied yet (26).

A relevant question to be analyzed through clinical studies is whether the virus can induce diabetes, by direct infection of pancreatic beta cells (27). Some signs of acinar pancreatic assault in COVID-19 patients was documented by increased serum elastase. The hypothesis underlying these observations is based on the fact that ACE2 has been identified in the liver and in the endocrine pancreas and is involved the development of insulin resistance (28,29).

TMPRSS2. TMPRSS2, a transmembrane serine protease is highly expressed within the lung and gastrointestinal tissues, including stomach, bowel, pancreas and liver. TMPRSS2 is implicated in viral infection as it cleaves and activates influenza A and influenza B virus hemagglutinin envelope glycoproteins and also the spike protein of SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, enabling virus-membrane fusion (30,31).

TMPRSS2 after binding to ACE2 is involved in S protein priming and cleavage of the spike. The viral pathogenicity importance of TMPRSS2 is analyzed in studies employing TMPRSS2 inhibitors, such as camostat mesylate, which attenuates SARS-CoV-2 infection of human lung cells cultured *ex vivo* (7,8).

Human dipeptidyl peptidase-4 (DPP4) in coronavirus infection and diabetes. DPP4 (also known as CD26) was identified as receptor for human coronavirus at Erasmus Medical Center (hCoV-EMC) (32). However, during the pandemic, specific clinical data regarding the influence of DPP4 inhibitors (DPP4i) on COVID-19 in people with diabetes are under investigation. In patients with type 2 diabetes, DPP4 is involved in insulin metabolism and inflammation by breaking the circulating glucagon-like peptide-1 (GLP1), upregulating the CD86 expression and lowering the infiltrate with macrophages (33). DPP4i, such as sitagliptin, vitagliptin, saxagliptin, alogliptin and linagliptin are currently used in therapy for patients with type 2 diabetes mellitus (T2DM). In addition to their glucose lowering effect they have been shown to decrease inflammation directly via GLP-1 dependent signaling.

A study from UK Clinical Practice Research Datalink based on a cohort study with diabetes mellitus patients found no increased risk of pneumonia in 22,435 subjects that were treated with DPP4i compared to 188,614 individuals treated with non-insulin glucose lowering agents (34). Another study had similar results also with no increased risk of infections detected in patients treated with DPP4i (35). A set of large clinical trials focused on the safety of saxagliptin, alogliptin, sitagliptin, and linagliptin in patients with diabetes mellitus at risk for cardiovascular or renal disease did not reveal clinically relevant safety issues in relation with immune or inflammatory disorders (36-39). However, in-depth investigation of the DPP4 role in SARS-CoV-2 infection is needed.

3. Could anti-diabetes drugs impact on disease progression?

To answer this question, we need to know if drugs, such as pioglitazone or rosiglitazone used for treatment of insulin

resistance or related inflammation could impact on prognosis of patients with diabetes and SARS-CoV-2 infection (40).

Administration of insulin diminishes ACE2 expression (41,42) while hypoglycemic agents such as GLP-1 agonists (liraglutide) and thiazolidinediones (pioglitazone), anti-hypertensives such as ACE inhibitors, and statins upregulate ACE2 (41,43-45).

In a study by Pfutzner *et al* (46), the anti-inflammatory effect induced by pioglitazone was assessed by highly sensitive C-reactive protein (CRP), level after starting therapy. It was also reported that pioglitazone induced the IL-6 and TNF-α increased expression in insulin resistant individuals without manifest hyperglycaemia, and inhibits the secretions of IL-1b, IL-6, and IL-8.

Another anti-inflammatory molecule that can be used in glucose-lowering therapies in subjects with diabetes mellitus and obesity is glucagon-like peptide-1 receptor (GLP-1R) agonist that reduces biomarkers of systemic inflammation in experimental studies (47). Other studies demonstrated that GLP-1R agonists attenuate pulmonary inflammation, reduces cytokine production and also preserve lung function in mice and rats with experimental lung injuries (48,49). It has also been observed that circulating GLP-1 levels are increased in human subjects with sepsis and critical illness and correlated with illness severity and mortality (50,51).

This effect is important for COVID-19 patients with advanced disease that had elevated levels of CRP at admission.

Metformin has anti-inflammatory proprieties and reduces circulating biomarkers of inflammation in people with diabetes mellitus (52). Metformin has also been used in patients with stable hepatitis or HIV infections and its immunomodulatory actions of metformin in the context of CoV infection are still to be studied (53,54).

4. Are diabetes related complications expected to worsen upon SARS-CoV-2 infection?

Diabetes can affect many different organ systems in the body and, over time, can lead to serious complications. Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy). Macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease. These complications of which many are related to damaged blood vessels are a significant cause of increased morbidity and mortality among people with diabetes (55). Many of the diabetes affected organs are also a target for SARS-CoV-2 infection, which may further augment the severity of the COVID-19 related disease. Moreover, all these complications are expected to worsen upon SARS-CoV-2 infection.

Effective onset of type 2 diabetes can precede clinical diagnosis by many years. In the first 10-15 years from the diagnosis of diabetes, the incidence of diabetic nephropathy in patients with diabetes mellitus is low, after which it increases rapidly to a maximum of approximately 18 years (56,57) which may explain the high prevalence of nephropathy in the diagnosis of diabetes when either a kidney transplant or a chronic dialysis treatment is needed (55). Special attention is needed on control of classic risk factors for kidney damage as recent studies show that in patients

confirmed with COVID-19 renal disturbances are common (58). Due to acute tubular necrosis induced by sepsis, hydration, cytokine storm syndrome, rhabdomyolysis and hypoxia, renal disorders caused by COVID-19 consist of acute renal damage, and have been detected direct invasion of the virus in renal tubular cells and interstitial or glomeruli (59). Moreover, acute renal damage in COVID-19 is strongly associated with a higher level mortality and morbidity, renal evolution being an indicator for survival with CoV infection (59). In a study on renal function of 59 infected SARS-CoV-2 patients, 63% of patients reported proteinuria. In addition, they recorded elevated serum values for creatinine (19%) and urea nitrogen (27%), respectively. In addition, all patients for whom a computerized tomography was performed to scan the kidneys, had inflammation and edema of the renal parenchyma.

Possible mechanisms may be due to dehydration, which may be related to fever or decreased fluid intake having various consequences on the kidneys, leading to a reduction in glomerular filtration rate and acute kidney damage (59). Other proposed mechanisms include COVID-19 sepsis, which leads to cytokine storm syndrome. In addition, direct invasion of the virus on the renal tubular and interstitial cells or glomeruli is possible due to direct cytopathic effects on different renal cells, and could be detected due to increased ACE2 in kidneys at much higher level than in the lung (19,60). The finding that SARS-CoV-2 uses ACE2 explains why the kidney cells are targeted and infected with COVID-19. This strengthens the hypothesis that renal dysfunction could accelerate the progression of inflammation started in the lungs, not just as a side effect of lung inflammation. Thus, inflammatory reactions through lung deficiencies can damage the kidney while the damage and death of renal tubular epithelial cells could also cause severe damage to the lungs and other organs through a large amount of inflammatory substances released. Above a certain critical point, the kidney-lung intersection could lead to an irreversible self-amplification storm of cytokines that quickly induces failure and death for multiple organs (61,62).

Neurologic injury has been confirmed in the infection of other CoV infections such as in SARS-CoV and MERS-CoV, the SARS-CoV nucleic acid has been found in the cerebrospinal fluid of these patients and also in their brain tissue on autopsy (63,64). One of the first reports centered on detailed neurologic manifestations of the hospitalized patients with COVID-19 had reported higher neutrophil counts, lower lymphocyte counts, higher CRP and D-dimer levels in patients with severe infection than that of patients with non-severe infection (65). In addition, multiorgan damage has been reported for patients with increased inflammation and blood coagulation. Of these patients, 14% had diabetes, 23.8% hypertension, 7% cardiac or cerebrovascular disease, and 6.1% malignancy, and 2.8% of diabetic patients had associated chronic kidney disease (65). Such aspects are illustrated in Fig. 1.

5. Platelet destruction in patients with diabetes and COVID-19

Higher platelet reactivity in diabetic patients is due to increased platelet functions, including an increased response to stimulation by platelet aggregation agonists, adhesion to thrombogenic surfaces and platelet aggregation (66). Oxidative stress and
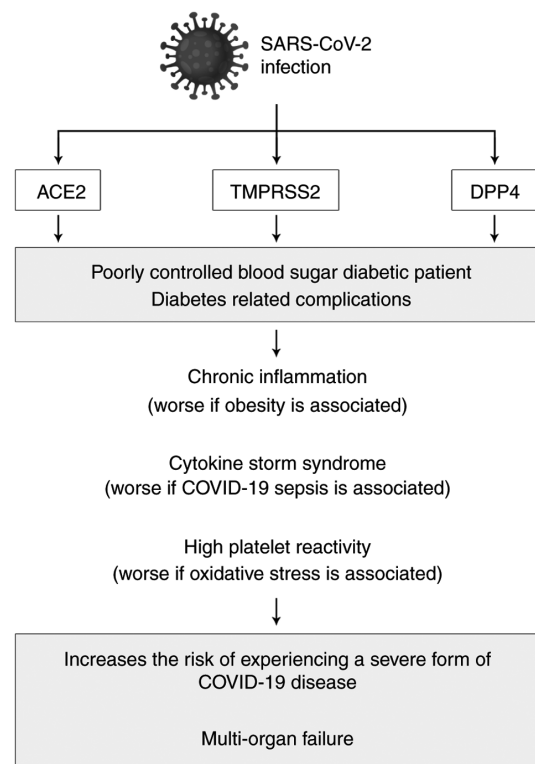

Figure 1. A hypothesis explaining severe forms of coronavirus disease 2019 (COVID-19) in diabetic patients. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin converting enzyme 2; TMPRRSS2, transmembrane serine protease 2; DPP4, dipeptidyl peptidase-4.

reduced antioxidant activity induced by hyperglycemia are significantly augmented in diabetic patients, subsequently leading to platelet activation and hyper-reactivity.

Increased blood coagulation could affect the severity of SARS-CoV-2 infection outcome on lung and additional critical organs function (67).

Diabetes mellitus patients have increased platelet reactivity, manifested by increased tendency to respond aggressively to particular stimuli (68). Consistent with this observation, hyperglycemia and hypertriglyceridemia contribute to increased platelet reactivity through direct effects and by promoting nonenzymatic glycation of proteins by decreasing membrane fluidity. Moreover, both decreased insulin production and insulin resistance have been shown to be a stimulator of platelet reactivity (69). Thus, both relative or absolute insulin deficiency is expected to increase platelet reactivity. If diabetes mellitus is associated with obesity, then increased oxidative stress and associated inflammation may promote the endothelial dysfunction. Oxidative stress exacerbates this effect by attenuating NO activity and promoting platelet activation. Inflammation favors the activation of platelets which, in turn, favors inflammation (70). Consequently, improved metabolic and glycemic control improves insulin sensitivity and maintains pancreatic β-cell function, and is likely to decrease platelet reactivity and increase the effects of antiplatelet agents. Thus, people treated with ACE2 and angiotensin 2 receptor type I (ARB) blockers, for high blood pressure that is associated with metabolic syndrome have been shown to display reduced inflammation in lungs (71). Previous pathogenic CoV, such as SARS-CoV, have been shown to bind to their target cells through ACE2, which is expressed by

the epithelial cells of the lungs, kidneys, intestines, pancreas and blood vessels (72). Hence, drugs that increase ACE2 expression including pioglitazone and liraglutide or ACE2 polymorphisms may further worsen virus infection prognosis (71).

Inflammatory state associated with metabolic syndrome, T2DM, and visceral obesity, plays a role also in imprinting the cluster of cardiovascular risk factors. These factors lead to an approximately 3-fold increase in the risk of coronary heart disease, stroke, and venous thromboembolism (73,74) that might be among the underlying pathophysiological mechanisms contributing to the increased morbidity and mortality of COVID-19 infected people that suffer from obesity-associated diseases.

The early hypothesis was that SARS is associated with cytokine dysregulation (75-81). Subjects with SARS have high levels of pro-inflammatory cytokines and chemokines associated with T cell depletion, lung inflammation, and extensive lung injury (80). Increased levels of IL-6 are associated with severe disease and are found in patients with respiratory syncytial virus (RSV) infection (79). Circulating levels of IL-8, IL-1β, and IL-6 undergo modifications in chronic inflammatory conditions, and are critically involved in abnormal clot formation, erythrocyte pathology and platelet hyperactivation (82). Decreased cytokine levels cause an increased hypercoagulability of whole blood and affect both erythrocytes and platelets. If there was an association of the three cytokines then it caused hyperactivation and platelet spread resulted in the largest changes (73,83-85).

6. Skin complications of diabetes mellitus - relevance for SARS-CoV-2 infection

The most recognized cutaneous manifestation in diabetes, present in 74% of obese patients with diabetes mellitus is *Acanthosis nigricans* (AN), a hyperpigmented velvety thickening of skin folds (86). Moreover, the presence of AN could be a good prognostic indicator for development of hyperinsulinemia in newly diagnosed diabetes mellitus with a possible genetic predisposition or increased sensitivity of the skin to increased plasma insulin levels (87,88). Benign AN type 2 is linked to T2DM, initially starting insidiously with hyperpigmentation while pseudo-AN type 3 is associated with metabolic syndrome. Both underlying conditions are associated with insulin resistance (86). Among other skin manifestations that accompany diabetes is chronic psoriasis, commonly in areas of the scalp, elbows and nails, a complex interplay between an inflammatory process, polygenic skin disorders with environmental triggers such as infections (89). Recent research shows that psoriasis can increase the predisposition for the development of diabetes, strong arguments being brought in a study of 52,000 participants, which concluded that people with psoriasis have a 49-56% higher risk of development diabetes mellitus later in life (90). Furthermore, being partly immune-depressed the psoriatic patients have an increased risk for infections, and there is no data for the beneficial effect of treatment with drugs such as cyclosporine, methotrexate and anti-TNF-α for COVID-19 (91).

Malum perforans pedis is a long-lasting trauma accompanied by various metabolic and infectious pathologies with a chronic ulceration in the sole of the foot (92). *Malum perforans pedi*s is a neurovascular disease for the most part on the skin with abnormal innervations with damage infusion, the development of ulceration in the accompanied foot, loss of sensation of pain having a predominance of the appearance in the elderly and with a severe form in diabetic neuropathies (93). Some findings indicate that a common cause of morbidity and mortality in diabetic patients could be changes in the healing of skin wounds. The effects of hyperglycemia on skin keratinocytes have been proved to enhance the proliferation-differentiation balance in an *in vitro* model of wound healing. Indeed, a decrease in the basal glucose update rate is associated with the induction of keratinocyte differentiation. These changes have been associated with enhanced GLUT1 expression, changes in cells morphology, as well as with a low proliferation and improving Ca^{2+}-induced keratinocyte differentiation, and it has been demonstrated that hyperglycemia and disruption of the insulin signaling pathway could be directly involved in the development of chronic complications of diabetes by affecting the use of glucose by keratinocytes, as well as by proliferating and differentiating the skin (94). However, the molecular mechanisms by which diabetes changes the structure of the skin has not been elucidated.

Currently, data in the literature on skin manifestations in COVID-19 is limited. One of the first cases that have been reported with observed cutaneous manifestations, skin rashes manifestations related with the COVID-19 disease, involving mainly the trunk, is a case with no drug intake for the previous 10 days. The observed skin manifestations are similar to those found in common viral infection (95). All of these skin complications can worsen the prognosis of people with diabetes, increasing the need for intensive care depending on severity of SARS-CoV-2 infection.

7. Treatment of SARS-CoV-2 infection

Recent studies explored the feasibility of convalescent plasma therapy for SARS-CoV-2 infections.

Convalescent plasma contains neutralizing antibodies that are capable of neutralizing SARS-CoV-2 from blood circulation and pulmonary tissues (96). Also, studies on COVID-19 showed that lymphocyte levels in the peripheral blood were decreased and cytokines levels in the plasma from patients with severe complication, IL-6, IL-10, TNF-α, and granulocyte-macrophage colony-stimulating factor, were significantly higher than in those who had mild symptoms (58,97).

The results of Duan *et al* (98) suggested that antibodies contained in convalescent plasma lowered the inflammation and overreaction of the immune system. All analyzed patients reached serum SARS-CoV-2 RNA negativity after convalescent plasma transfusion, accompanied by an increase of oxygen saturation and lymphocyte counts, and the improvement of liver function and CRP, 10 severe patients showed that only one dose of 200 ml of convalescent plasma increased significantly or maintained the neutralizing antibodies at a high level, leading to disappearance of viremia in one week. Convalescent plasma shows a potential therapeutic effect reducing the viral load and lowering risk in the treatment of severe COVID-19 patients. Combined with other treatments, such as antiviral therapy and other supportive care, convalescent plasma improved clinical outcomes. Certain strategies used for vaccines development

stimulate neutralizing antibodies for S proteins and T-cell responses which are together required in convalescence. The challenge for protective immunity against CoV at its start (99).

Use of 2019 nCoV receptor binding inhibitors with high affinity for ACE-2, and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor antagonists (ARA), drugs that inhibit the renin-angiotensin system (RAS) are gaining increasing popularity and could play a role in treating severe respiratory diseases (100,101). Efforts are being made to develop a vaccine, which will be a major tool in the fight against COVID-19 (https://www.who.int/blueprint/priority-diseases/key-action/list-of-candidate-vaccines-developed-against-ncov.pdf).

8. Conclusions

COVID-19 represents an unattended threat for health and life, having so far over 6,000,000 infected and about 300.000 deaths. The present review brought hypotheses that should be clinically analyzed of why diabetic patients, represent a population of patients which is prone to be affected by a more severe disease manifestation of this viral infection. As the human endocrine pancreas expresses ACE-2, the coronavirus might enter islets and cause acute β-cell dysfunction, leading to acute hyperglycemia and transient T2DM. Moreover, ACE-2 activity levels could be enhanced in diabetic patients making the SARS-CoV infections more efficient also in peripheral, non-pancreatic tissues. This may explain why diabetes mellitus can contribute mechanistically to multi-organ failure in SARS-CoV infections. Some skin complications can worsen the prognosis of people with diabetes, increasing the need for intensive care depending on severity of SARS-CoV-2 infection. On the other hand, some of the drugs used to ameliorate diabetes mellitus and its complications, can also affect rate of SARS-CoV infections, such as GLP-1 analogs and others.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RA, SOD, IRF, DL, AMS, VMA, CT, IP and SF contributed to the data acquisition, manuscript drafting and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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