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PERSPECTIVE

COVID-19 and Diabetes Mellitus: Potential Metabolic Associations

Pedro Henrique Abreu da Silva[1,2], Andressa Santos Garcia[1,2], Fábio Aguiar Alves[3], André Luis Souza dos Santos[4,5,*] and Cátia Lacerda Sodré[1,*]

[1]*Departamento de Biologia Celular e Molecular (GCM), Instituto de Biologia (IB), Universidade Federal Fluminense (UFF), Niterói-RJ, Brazil;* [2]*Faculdade de Medicina, Universidade Federal Fluminense (UFF), Niterói-RJ, Brazil;* [3]*Laboratório de Epidemiologia Molecular e Biotecnologia (LEMB), Programa de Pós-Graduação em Patologia, Programa de Pós-Graduação em Microbiologia e Parasitologia, Universidade Federal Fluminense (UFF), Niterói-RJ, Brazil;* [4]*Laboratório de Estudos Avançados de Microrganismos Emergentes e Resistentes (LEAMER), Departamento de Microbiologia Geral, Instituto de Microbiologia Paulo de Góes (IMPG), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil;* [5]*Programa de Pós-Graduação em Bioquímica, Instituto de Química, UFRJ, Rio de Janeiro, Brazil*

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Abstract: The COVID-19 pandemic turned the SARS-CoV-2 into the main target of scientific research all around the world. Many advances have already been made, but there is still a long way to go to solve the molecular mechanisms related to the process of the SARS-CoV-2 infection, as well as the particularities of the disease, its course and the complex host-pathogen relationships. However, a lot has been theorized and associated with COVID-19, like the worst prognosis of the disease among individuals with some comorbidities, like diabetes mellitus. In this perspective, diabetic patients are repeatedly associated with more severe cases of COVID-19 when compared to non-diabetic patients. Even though ACE2 (angiotensin-converting enzyme 2) was recognized as the host cell receptor for both binding and entering of SARS-CoV-2 particles, it was also pointed out that this enzyme plays an important protective role against pulmonary damage. Therefore, paradoxically as it may seem, the low baseline level of this receptor in diabetics is directly linked to a more expressive loss of ACE2 protective effect, which could be one of the possible factors for the worst prognosis of COVID-19. Still, COVID-19 may also have a diabetogenic effect. From this point of view, the main topics that will be highlighted are (i) the mechanism of the viral entry, with special attention to the cellular receptor (ACE2) and the viral binding protein (spike), (ii) the relationship among the renin-angiotensin system, the infection process and the patients' prognosis, (iii) the glucose control and the medicines used in this event, and (iv) a brief analysis on diabetes triggered by COVID-19.

Keywords: Covid-19, Diabetes mellitus, ACE2, Hyperglycemia, Glucose control, Medicines.

1. INTRODUCTION

In March 2020, the disease caused by the new coronavirus (SARS-CoV-2; severe acute respiratory syndrome coronavirus 2) was announced by the World Health Organization (WHO) as the coronavirus disease-2019 (COVID-19) pandemic. First registered in Wuhan city, China, the SARS-CoV-2 is a member of the *Coronaviridae* family and an enveloped positive-sense single-stranded RNA (ssRNA+) virus [1]. Due to its capacity of lodging and replication in the upper respiratory tract, it spreads very rapidly among humans, mainly in closed and crowded environments. From a global perspective, the COVID-19 already resulted in more than 185 million confirmed cases worldwide, including over 4,000,000 associated deaths (https://covid19.who.int/). Clinically, COVID-19 patients tend to present symptoms such as dry cough, fever, fatigue, shortness of breath, nasal congestion, anosmia and ageusia [2, 3]. While most of the population will present mild symptoms or be asymptomatic, the elderly and those with comorbidities seem to be more prone to present severe cases of the disease and consequent mortality [2-4]. Thus, amid these comorbidities, diabetes mellitus stands out as one of the most significant in the worsening of COVID-19 [1-5].

Also related to the worsening of other viral respiratory infections [6, 7], such as H1N1 and SARS-CoV, diabetes mellitus is directly linked to poor glycemic control, which can accentuate pro-inflammatory conditions and, according to *in vitro* experiments, increase viral replication [5]. Furthermore, studies show that in COVID-19 cases, the number of diabetes mellitus patients is bigger in severe cases of the disease than in non-severe cases and the mortality rate is more than 3 times bigger in diabetic patients [1, 4].

*Address correspondence to these authors at the Departamento de Biologia Celular e Molecular (GCM), Instituto de Biologia (IB), Universidade Federal Fluminense (UFF), Niterói-RJ, Brazil; E-mail: catiasodre@id.uff.br (C.L. Sodré) and Laboratório de Estudos Avançados de Microrganismos Emergentes e Resistentes (LEAMER), Departamento de Microbiologia Geral, Instituto de Microbiologia Paulo de Góes (IMPG), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil; Programa de Pós-Graduação em Bioquímica, Instituto de Química, UFRJ, Rio de Janeiro, Brazil;
E-mail: andre@micro.ufrj.br (A.L.S. Santos)

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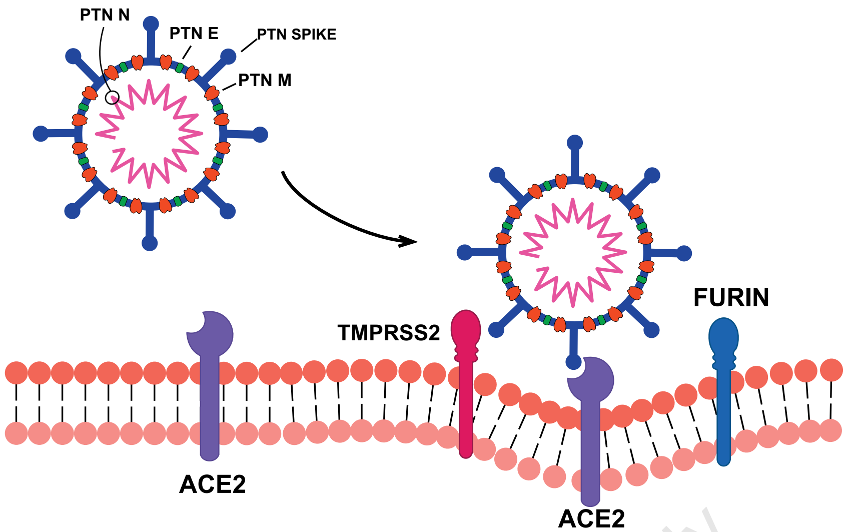

Fig. (1). SARS-CoV-2 entry mechanism in the host cell. The envelope protein (PTN E), the membrane protein (PTN M), the nucleocapsid protein (PTN N), and the spike protein (PTN SPIKE) are constitutional SARS-CoV-2 proteins. The cleavage of the *spike* protein, after its interaction with the ACE2 *N*-terminal region, is done by furin and TMPRSS proteases. This process allows the fusion between viral and cell membranes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Even though it is not clear that diabetes mellitus is a risk factor for COVID-19 severity, shreds of evidence shown in several reports [1-5] are enough to account for the relevance of studies and analysis that aim to point up and explain the specificities of the SARS-CoV-2 infection in diabetics. Hence, the knowledge of the viral entry mechanism in mammalian cells, the possible consequences of the infection, the metabolic predispositions/alterations that can worsen the patient condition and what to expect post-infection is crucial. Like any new disease, it is important to highlight that little is known about the theme in the discussion. However, all the published information on this subject is pivotal to the establishment of an effective approach for diabetic COVID-19 patients.

In this context, aspects of the virus and the COVID-19 will be discussed and related to diabetes mellitus according to the available literature, with an emphasis on the key points that associate these two diseases and their possible reasons: (i) the mechanism of the viral entry, with special attention to the cellular receptor (ACE2; angiotensin-converting enzyme 2) and the viral binding protein (*spike*), (ii) the relationship among the renin-angiotensin system and the infection process and the patients' prognosis, (iii) the glucose control, the medicines used in this event and perspectives of new therapeutic approaches based on molecular dynamics, and (iv) a brief analysis on diabetes triggered by COVID-19.

2. ACE2 AND VIRAL ENTRY

The origin of the SARS-CoV-2 is believed to be, as SARS-CoV and MERS, primarily developed in animals [8, 9]. The emergence of these kinds of viruses in the human population, at different moments, shows their capacity for adaptation, which means their ability to mutation and/or recombination, allowing cross-species transmission and the consequent productive infection of human cells [8].

The ACE2, also related to the SARS-CoV infection [9-11], was identified as the main receptor for SARS-CoV-2 particles entry into the human cells [10, 11]. Initially described in 2000, ACE2 is a zinc-dependent transmembrane mono-carboxypeptidase with 42% of the amino acid sequence in its only catalytic domain equal to each one of the two catalytic domains of ACE [12, 13]. Albeit it is mostly present in plasma membranes, it can also be blood soluble that indicates different renin-angiotensin system stages, mainly when there is an in-course disease associated with this system [14].

ACE2 can be found in many organs in the human body, such as the heart, testicles, kidneys, pancreas, bladder, stomach, ileum, adipocytes, liver [12, 15, 16] and in the alveolar epithelial cells of the lungs [17]. This variety of organs, which expresses ACE2, suggests that the virus has the potential to infect human cells forming various distinct tissues, corroborating the plethora of infections and symptoms related to COVID-19 infection. SARS-CoV-2 is able to enter into human cells through its superficial glycoprotein *spike* (S), codified by all known CoVs [18-21]. In *Betacoronavirus*, the genus of SARS-CoV-2 [8, 9], the receptor-binding domain (RBD) of the *spike* protein interacts with the human cell receptor [18, 19], which enables the binding of the S1 domain of the SARS-CoV-2 *spike* protein with the ACE2 *N*-terminal region. After this interaction, furin and TMPRSS2 (transmembrane serine protease) are responsible for the cleavage of the S protein, which releases the *spike* fusion peptide [18], allowing the fusion of viral and plasma membrane of human cells (Fig. **1**) [20].

The discoveries on the SARS-CoV-2 entry mechanism have stimulated a great number of studies about possible strategies to interfere in this key process.Therefore, some specific inhibitors of the viral proteases involved in this event were tested. TMPRSS2 inhibition has been proven

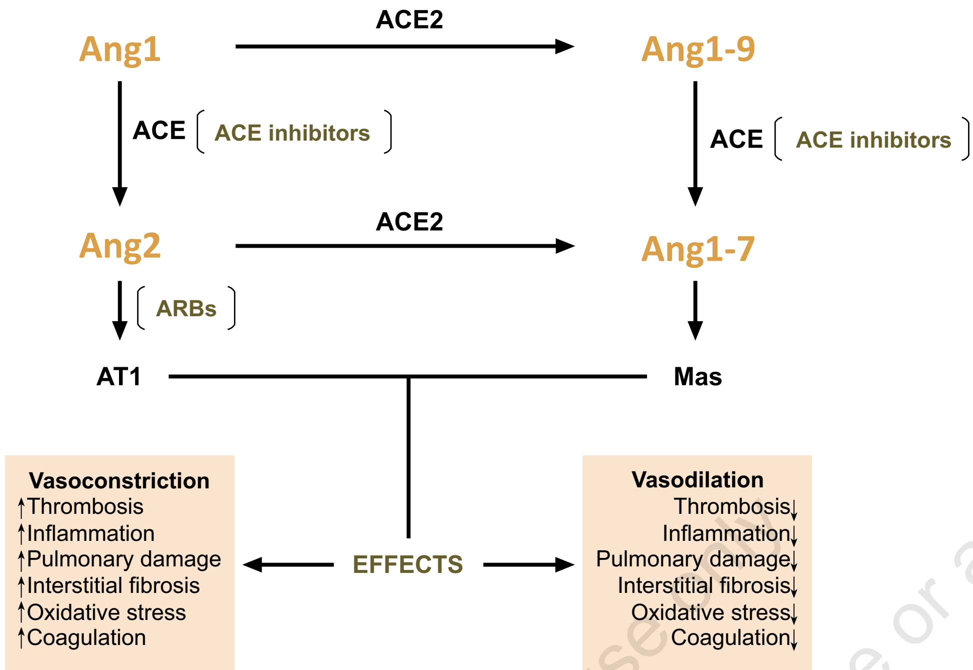

Fig. (2). Counterbalance of renin-angiotensin system. Angiotensin-converting enzyme (ACE) converts angiotensin 1 (Ang1) and angiotensin 1-9 (Ang1-9) to angiotensin 2 (Ang2) and angiotensin 1-7 (Ang1-7) respectively. Angiotensin-converting enzyme 2 (ACE2) converts Ang1 and Ang2 to Ang1-9 and Ang1-7 respectively. Ang2, when interacting with AT1 receptors, promotes systemic effects like vasoconstriction and increases susceptibility to thrombosis, inflammation, coagulation, pulmonary damage, interstitial fibrosis and oxidative stress. Ang1-7, when interacting with Mas receptors, promotes antagonistic effects to those of Ang2. Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit ACE activity and angiotensin receptor blockers (ARBs) block the interaction between Ang2 and AT1 receptors. The effects of these medications dislocate the system balance, increasing ACE2 expression and, consequently, of its products. Adapted from Verdecchia *et al.* [14]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

effective, since it prevented S protein cleavage and, ultimately, the viral fusion with the host cell [21]. It is also believed that it is more beneficial to develop antivirals that have TMPRSS2 as the target, since furin is physiologically more important [20, 21]. Furthermore, ACE inhibitors and angiotensin receptor blockers (ARBs), medications commonly prescribed to diabetics and hypertensives, aroused controversial arguments in the scientific community. Some researchers claimed that once these medications increase ACE2 expression, they could potentiate SARS-CoV-2 infection [22, 23]. However, other researchers stated that paradoxical as it may seem, the increased ACE2 expression could play a beneficial role through the infection course because ACE2 activity protects the lungs from acute damages [24-27]. In addition to that, diabetes mellitus has already been associated with lower ACE2 expression, a deficiency that aggravated other diseases [28].

Therefore, there is not enough evidence to make a categorical statement about the use of these medications and the worst COVID-19 prognosis. Still, these drugs are undoubtedly efficient to the patients to whom they are prescribed, so their use should not be altered or discontinued without the recommendation of a specialist. This is also recommended by the European Society of Cardiology [29], the Italian Society of Pharmacology [30] and the Heart Failure Society of America [31].

3. THE UNBALANCE OF THE RENIN-ANGIOTENSIN SYSTEM AND ITS SEVERITY IN DIABETICS

ACE2, the entry receptor of SARS-CoV-2, is essential for the regulation of the renin-angiotensin system, along with ACE. ACE is responsible for converting angiotensin 1 (Ang1) to angiotensin 2 (Ang2), which binds with angiotensin receptors type 1 (AT1) promoting vasoconstriction, aldosterone release and adverse effects, such as interstitial fibrosis, inflammation, thrombosis, oxidative stress, coagulation increase and hypertension associated with obesity [32]. ACE2 is responsible for converting Ang2 to angiotensin 1-7 (Ang1-7) and Ang1 to angiotensin 1-9 (Ang1-9), an Ang1-7 precursor. Ang1-7 binds with Mas receptors and has antagonistic effects to those of ACE → Ang2 → AT1 receptors, since it promotes vasodilation and reduces the adverse effects related to AT1 receptors [32] (Fig. **2**).

Due to these effects, it has been observed that the ACE2 → Ang1-7 → Mas receptors play a protective role against pulmonary damage [25-27, 33] and other chronic diseases associated with lower ACE2 expression, like diabetes and hypertension [28, 33, 34]. Beyond that, SARS-CoV-2, in its pathogenesis, reduces ACE2 expression in the plasma membrane [35, 36]. In this regard, the infected patient is more susceptible to the adverse effects of Ang2, since the lower

expression of ACE2 induced by SARS-CoV-2 reduces the protective role of this enzyme [35]. Studies conducted on rats showed that higher levels of ACE2 did not aggravate the clinical outcome of the animals tested; however, lower levels of ACE2 were determinant to the worsening of pulmonary symptoms [35]. This may be a representative observation of a possible beneficial role of ACE2, overlapping with the fact that this protein is the receptor responsible for viral entry. In this sense, ACE2 is indirectly responsible for viral infection. On the other hand, it could also be stated that ACE2 plays a fundamental role in the COVID-19 clinical chart, since a significant number of studies have shown that lower expression of this enzyme is, in some way, related to the severity in cases of this disease [26-28, 32, 33, 35]. Thus, it is possible to argue that diabetics comprise a risky group for COVID-19 as these subjects present a deficient basal level of ACE2 when compared to non-diabetics [28]. Moreover, apart from the loss of ACE2 protective effects, diabetes itself is associated with higher platelet aggregation and cytokine storm [5, 37]. These conditions are also identified in severe COVID-19 patients [37-39] and promote more extensive pro-inflammatory states. Once these innate characteristics are also associated with severe cases of the disease, diabetics could be more susceptible to a faster progression and worse prognosis of COVID-19 [5, 37, 40].

4. HYPERGLYCEMIA, DISEASE PROGRESSION AND SURVIVAL OF A DIABETIC PATIENT WITH COVID-19

As a new disease, little is known about what actually determines different outcomes of COVID-19. However, hyperglycemia has been associated with several factors related to prognosis severity in both diabetic and non-diabetic patients [41, 42].

As a multifactor metabolic condition, there are many consequences of diabetes that impact the organism systems in several ways. When poorly controlled, the diabetic patient tends to present high glycemic levels, which can accentuate endothelial dysfunction; platelet activation and antithrombin 3 glycosylation [41], conditions directly linked to thrombosis and multi-organ damage [41]. These symptoms are also related to severe cases of COVID-19 [42-44]. According to Li *et al.* [45], it was observed that COVID-19 patients recently diagnosed with diabetes presented higher mortality risk when compared to non-diabetic patients, to those with good glucose control and with the hyperglycemic ones [45]. This data could suggest an additional risk factor due to the lack of monitoring of glycemic levels. A cohort study by Zhu *et al.* [46] analyzed the clinical chart of 500 COVID-19 patients previously diagnosed with type 2 diabetes (250 patients with good glucose control and 250 patients with poor glucose control). The research indicated that pharmacological treatments were crucial for controlling the symptoms of patients with poor glucose control and the mortality rate of these patients in-hospital was 10 times bigger than the mortality rate of the other group [46]. In this sense, Codo *et al.* [47] showed that elevated activity of glycolytic path and higher glycemic levels promote an increase of SARS-CoV-2 replication and stimulate cytokines production. It is good to highlight that once inside the cell, glucose molecules can be partially oxidized in the glycolytic path, generating energy as well as other metabolites [47, 48]. Interestingly, an overexpression of several genes that are responsible for the codification of proteins classically associated with the glycolytic path was also observed in monocytes of COVID-19 patients [47].

Treatment wise, the medication used needs to be monitored closely. Some studies recommended that diabetics diagnosed with COVID-19 should stop the use of anti-hyperglycemic agents that can cause volume depletion or hypoglycemia [49] and that hospitalized patients with severe cases of the disease need to stop the use of oral agents like thiazolidinedione [50-52], sodium glucose cotransporter-2 inhibitors (SGLT2i) and particularly metformin [49-53]. Metformin is the most commonly prescribed drug for diabetes mellitus type 2 worldwide [54]. It is shown that this drug improves insulin sensitivity and inhibits hepatic production of glucose by inhibiting the mitochondrial shuttle [54]. However, this medication is associated with lactic acidosis, which is why the discontinuation of the drug is advised in severe cases of COVID-19 [49-53]. Insulin should be given preference as an agent for hyperglycemia control [49-53]. Also, it is said that it might be prudent to withhold the use of ACE inhibitors and ARBs only during the acute phase of COVID-19, because of the increased risk of acute kidney injury in some diabetic patients [53]. As stated before, the general discontinuation of ACE inhibitors and ARBs is not recommended [29-31, 53].

Meanwhile, there is great effort regarding the effective development and production of vaccines and more efficient and innovative therapeutics. Previous studies have already suggested that exploration of chemical structures and molecular dynamics could make a robust approach to present reaction paths and conformer research [55]. Allec *et al.* [55] also pointed out the contrast between conventional molecular dynamics methods and more accurate approaches, such as CPU+GPU-enhanced density functional tight binding (DFTB), which can highlight important conformations that could be missed by classical strategies. In this sense, new molecular dynamics studies proposed simulations of the glycosylated full-length model of the SARS-CoV-2 spike protein [56]. Experimental mutations directly in the *N*-glycan content of the RBD showed that the stability of this domain became disrupted, which triggered a reduction in the process of binding between ACE2 and RBD [56]. Moreover, through computational research concerning molecular dynamics and inhibition assays, Loschwitz *et al.* [57] pointed out eight chemical compounds with apparent inhibitory effects on the main protease (M^{pro} or $3CL^{pro}$) of SARS-CoV-2, which is a key enzyme for viral replication. The possible inhibitors include (i) natural products (*e.g.*, corilagin, ZINC000011865175 and rhoifolin), (ii) approved drugs by the Food and Drug Administration (FDA – USA) such as lurasidone, cilostazol, apixaban and dasatinib and (iii) promising compounds under experimental investigation (*e.g.*, telcagepant) [57]. Still, it has been suggested that hormonal steroids could also affect this process. However, while testosterone was shown to have sig-

nificant inhibitory activity against viral replication, estradiol did not reveal such potential [57]. These findings may represent an effective approach on the development and discovery of new therapeutic strategies, as well as repositioning of potential drugs. This line of research requires further and deeper analysis to establish their practical implications.

In light of these pieces of evidence, it can be discussed that hyperglycemia may be associated with severe cases of COVID-19 and because of that, it is essential to monitor blood glucose and ketone body frequently in every hyperglycemic patient diagnosed with COVID-19 [52]. It is also advised that diabetics are oriented to take extra care of their metabolic condition [49], being more aware of the regularity/quality of glycemic control, previously and during the SARS-CoV-2 infection. Furthermore, studies on new therapeutic approaches might contribute to improving the management of COVID-19-infected patients.

5. DIABETES: CATALYST AND/OR CONSEQUENCE?

Even though it is not possible to state categorically the details of the association between diabetes and COVID-19 severity, the available evidence is consistent and supported by several epidemiological data.

In China, data from 1099 COVID-19 patients indicated that diabetics represented 5.7% of non-severe cases and 16.2% of severe cases, which shows that they were almost 3 times more likely to develop to more critical cases [58]. Moreover, among patients admitted to the intensive care unit (ICU), 26.9% patients who needed mechanical ventilation or died were diabetic, while among the patients who did not have such critical cases, only 6.1% were diabetic [58]. A retrospective analysis with 320 patients, who died from COVID-19 in Piacenza, Italy, pointed out diabetes as the third most common comorbidity associated with the disease, present in 22.5% of these cases [59]. In Metro Manila, Philippines, in a study with 100 possible COVID-19 patients, diabetes was the second most common comorbidity (17%) among the 42 confirmed cases [60]. In New York, United States of America, in a study with 1000 COVID-19 patients in a medical center, among the 236 patients who were admitted in ICUs, 101 (42.8%) were diabetic, while among the 150 patients who remained in the emergency department 39 (26%) were diabetic [61].

The constant report of data that points out diabetes as one of the main comorbidities associated with a worse prognosis of COVID-19 [58-61] and the systemic effects of the disease previously related to diabetes justifies the need for a deeper understanding of this subject.

Furthermore, besides the evidence that suggests that preexisting diabetes may be a risk factor for COVID-19, there are signs that the COVID-19 pathogenesis may trigger hyperglycemic states associated with pancreatic infection. Some studies have shown that SARS-CoV-2 may infect pancreatic tissues through ACE2 expressed in cells of these tissues, leading to organ damage in 1-2% of non-severe cases and in 17% of severe cases of COVID-19 [62]. Because of the presence of ACE2 in pancreas' endocrine sites, evidence related to SARS-CoV-2 indicated that this virus has infected pancreatic islet cells and caused acute insulin-dependent diabetes [63]. Since type 1 diabetes mellitus has already been associated with other respiratory viral infections [64, 65], there are signs that the COVID-19 pandemic could cause an abnormal increase in diabetes cases, which highlights this metabolic condition not only as a possible catalyst but also as a product of COVID-19 pathophysiology [66].

Caruso *et al.* [67] pointed out that pancreatic beta cells damage caused by viral infection can induce the release of antigen sequestered from pancreatic islets. During chronic infections, these antigens could be presented to the immune system for a longer period than usual, increasing the risk of the development of autoantibodies for insulin productive cells [67]. Epidemiologically, a United Kingdom study suggested that previous exposure to SARS-CoV-2 may have caused an increase of type 1 diabetes mellitus cases in children [68]. According to this evidence, an international group of researchers specialized in diabetes had the initiative to build a global registry of diabetes-associated with COVID-19, the COVIDIAB, that aims to explain the diabetogenic phenomenon and its characteristics [69].

Therefore, until evidence is enough to establish a concrete association between COVID-19 and diabetes, concerning the diabetes role as a catalyst of the disease and its development from the viral infection, it is imperative that healthcare workers pay extra attention to the metabolic conditions of COVID-19 patients in order to provide thorough care. Moreover, these measures are also extremely relevant to assemble more solid epidemiologic data, to support future research more efficiently.

CONCLUSION

The emergence of the new coronavirus in a pandemic context demands a continuous search for clearer knowledge about the pathogenic evolution of SARS-CoV-2 in individuals grouped as a population under risk. In this sense, in view of the higher incidence of severe cases of the disease and a higher mortality rate, diabetes mellitus can be listed as one of the most relevant comorbidities associated with the worsening of COVID-19. This finding can be explained because diabetic individuals have a low baseline level of ACE2 compared to the general population, which is directly linked to a more expressive loss of the protective effect of this enzyme when its deregulation occurs after cell infection by the virus. In addition, diabetes is associated with conditions that provide longer pro-inflammatory states and a worse prognosis in the case of SARS-CoV-2 infection. Furthermore, there are indications that diabetes mellitus can also be seen as a possible product of the pathophysiology of COVID-19, which requires further evidence. So, although there is still no scientific evidence of the relationship between COVID-19 and diabetes mellitus, data shown by several studies, many referenced in this article, are robust enough to alert about the importance of monitoring diabetic individuals

infected by SARS-CoV-2 and controlling their blood glucose levels, to perform a more efficient clinical conduct and provide better prognosis to patients.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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