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New Onset Diabetes in COVID-19 - What Does Evidence Tell Us?

Diabetes "de Novo" na COVID-19 - O Que nos Dizem as Evidências?

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Abstract

This article reviews the link between COVID-19 and the new-onset of diabetes. Current evidence suggests a bidirectional relationship between COVID-19 and diabetes. Observational studies and case-reports raise the hypothesis of a diabetogenic effect of COVID-19 infection, due to the new onset of diabetes and severe metabolic complications in previously known diabetics patients. Although the existent evidence is scarce, attention should be raised to the physician, regarding the potential metabolic complications of COVID-19.

Keywords: coronavirus infection; severe acute respiratory syndrome; COVID-19; diabetes; hyperglycemia

Resumo

Este artigo analisa a ligação entre COVID-19 e diabetes "de novo". As evidências atuais sugerem uma relação bidirecional entre COVID-19 e diabetes. Estudos observacionais e relatos de casos levantam a hipótese de um efeito diabetogénico da infeção pela COVID-19, devido ao aparecimento de diabetes "de novo" e de graves complicações metabólicas em doentes com diagnóstico prévio de diabetes. Embora as evidências existentes sejam escassas, deve-se chamar a atenção do médico para as possíveis complicações metabólicas do COVID-19.

Palavras-chave: infeção por coronavírus; síndrome respiratória aguda grave; COVID-19; diabetes; hiperglicemia

> BACKGROUND

COVID-19 is a disease caused by SARS-CoV-2, a novel coronavirus that was primarily identified in Wuhan, China, and by the 11th of March 2020 the World Health Organization had declared a global pandemic. [1] Since the outbreak, some studies have been published regarding the link between diabetes and COVID-19. Diabetes is associated with increased risk of COVID-19 severity and mortality. [3] On the other hand, new-onset of diabetes and metabolic complications on patients previously diagnosed with diabetes, have been observed in people with COVID-19. [4,5]

In this article, we do a narrative review regarding the new-onset of diabetes in COVID-19 patients.

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> REVIEW

Similar to SARS-CoV which caused an epidemic in 2002-03, the novel coronavirus enters cell hosts through Angiotensin II Converting Enzyme receptor (ACE2). [6] This receptor is found throughout the body and its pulmonary distribution explains, not only the respiratory clinical features, but also the acute respiratory distress syndrome that leads to severity of the disease. [7]

ACE2 receptor is found in the pancreas, both on exocrine cells and in the endocrine cells, that constitute pancreatic islets. [8] Interestingly, its expression is also relevant in the endothelial cells of the microvasculature supplying beta-cells that produce insulin. [9]

As it has been postulated, [10] upon the 2003-SARS pandemic, coronavirus' spike protein enters the cells using the ACE2 receptor, initiating an inflammatory response that leads to apoptosis. [11] Previous studies attempting to understand the pathophysiology of the SARS-CoV-2 infection over different organs and systems, have suggested that, following viral entrance and cell infection, ACE2 receptor is downregulated in lung tissue, which subsequently may trigger an inflammatory response. [12]

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It has been shown, on follow-up, that several patients developed diabetes and/or had hyperglycemia with greater than usual doses of insulin needed to control its glycemia. [4,5,13] For instance, Chee *et al.* [5] reported a 37 year-old man who presented with history of fever, vomiting, polydipsia and polyuria. His body mass index was 22.6 kg/m^2 and there was no evidence of insulin resistance. He presented with hyperglycemia, high anion gap metabolic acidosis and ketonemia.

Supporting this ketogenic effect of COVID-19 infection, Li *et al.* [4] reported in an observational study of 568 hospitalized patients with confirmed COVID-19 that 6.4% presented ketosis without fever or diarrhea. These patients were younger, had greater prevalence of fatigue, diabetes and digestive disorders. Additionally, the presence of ketosis was associated with higher mortality. Ketosis was present in 5% (27 from 568 patients) of the sample population without diabetes. However, patients with previous diagnosis of diabetes were more prone to have ketosis - 36% with ketosis *vs.* 19% without ketosis. We should note that when analyzing absolute numbers, these are not markedly impressive, as from a total of 129 patients with diabetes only 15 developed ketosis and 3 acidosis. These three patients were a 26 years old male, a 54 years old male and a 44 years old female.

In a major multicentric French study with 1317 patients with diabetes admitted for COVID-19, in March 2020, 41 (3.1%) were diagnosed with diabetes upon admission (defined as HbA1c > 6.5%). The remaining patients presented type 2 diabetes (1166; 88.5%), type 1 diabetes (39; 3.0%) and other type of diabetes (71; 5.4%). This classification was based on the information available in medical files by the physician in charge of the patient. [3]

Although some of these findings could suggest the development of new onset type 1 diabetes, [4,5] Yuan *et al.* [14] has demonstrated impaired glucose tolerance only in a model of long term high fat diet in a model of mice with gene knockout for the ACE2 receptor. Nonetheless, their findings suggest that the deficiency of this receptor compromises the vasculature in pancreatic islets, thus decreasing its endocrine function.

Although SARS-CoV-2 could directly impair insulin production of beta-cells, diminishing its function and disturb glucose metabolism, would that be enough to compromise insulin production in a long-term manner and induce type 1 diabetes? Is there any immune mediated process? Or is ACE2 downregulation the factor at stake?

One hypothesis could be that the cytokine storm - caused by the severe inflammatory response taking place in the lungs - also targets the pancreas possibly causing diabetes and, according to several reports, pancreatitis. [15,16]

Other hypothesis is related to the role of the renin-angiotensin system (RAS) and its counterbalancing arm, the ACE2-Ang(1-7)-Mas axis on the development of diabetes. [17,18] It has been shown previously how ACE2 decreased activity is detrimental for the development of acute respiratory distress syndrome (ARDS), [19] verified both during the SARS-CoV epidemic as well during the current pandemic of COVID-19.

In recent years, it has also been proposed that stimulation of the ACE2-Ang(1-7)-Mas axis could be protective against deleterious effects of diabetic nephropathy, hypertension and diabetic retinopathy and that patients with diabetes have lower Angiotensin-(1-7) levels and lower activity of ACE2. [17,18] These findings are consistent with the clinical features of patients infected by SARS--CoV-2: that develop de novo hyperglycemia with difficult metabolic control, since there is downregulation of the ACE2 receptor which is internalized. [20] Figure 1 summarizes the causes and consequences of internalization of SARS-CoV-2 in host cells.

The findings during and after the 2002-03 SARS epidemic and the similarities with COVID-19 pandemic, have urged scientists and physicians to focus on the ACE2-Ang(1-7)-Mas axis for new therapeutic targets. These could potentially prevent disease progression to ARDS but also help better glycemic control and insulin management. [21,22]

There is still a lot to understand concerning the full spectrum of effects of SARS-CoV-2 in glucose metabolism, both in the development of new onset diabetes and in the decompensation of patients with prior diabetes diagnosis.

To address these issues, a group of leading diabetes researchers have established a global registry of patients with COVID-19–related diabetes (CoviDiab project). [2] The aim of the project is to understand the extent and the characteristics of the manifestations of diabetes in patients with COVID-19, and the best strategies for the treatment and monitoring of affected patients.

> CONCLUSION

In conclusion, some observational studies and case reports suggest an increased risk of new onset diabetes and/or a ketogenic effect of COVID-19 infection. However, the current evidence is not enough to draw definitive conclusions. In the future, more evidence will be released which hopefully will help answer these questions. Meanwhile, physicians need to be aware of the potential increased risk of metabolic complications in COVID-19 patients. <

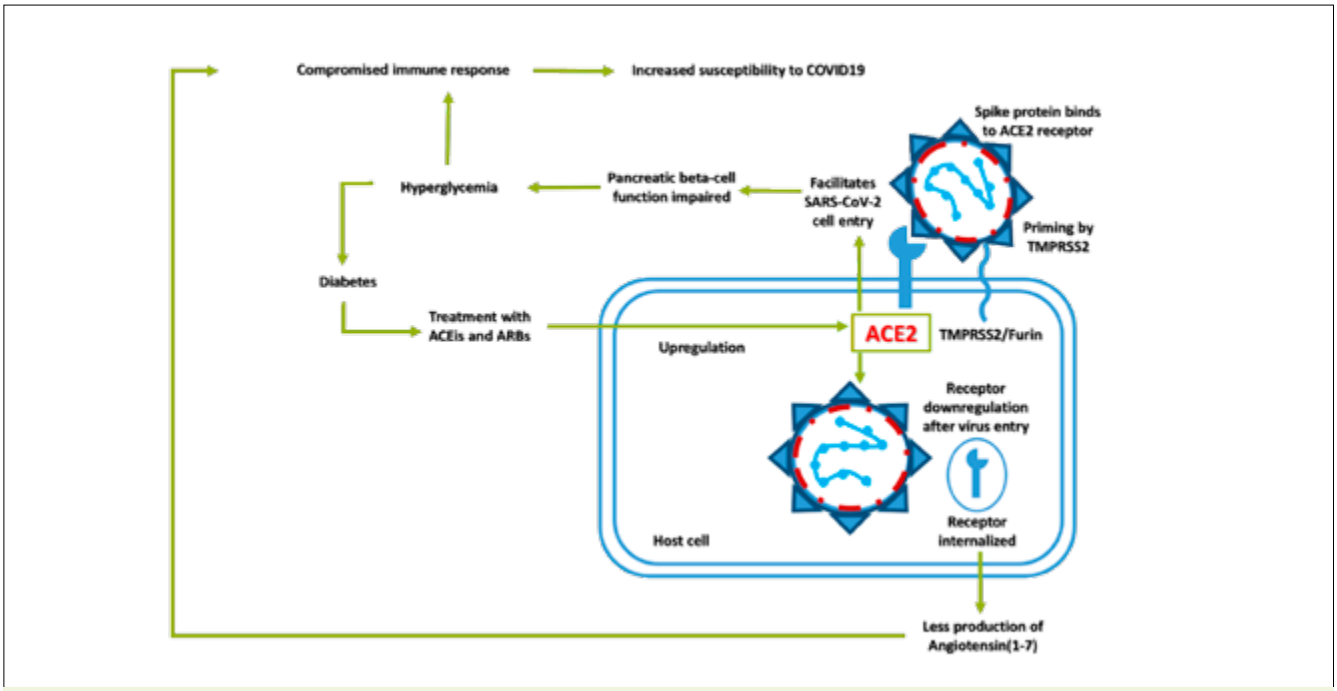

Figure 1 - Representation of SARS-CoV-2 internalization in the host cell and possible causes and consequences of uncontrolled glycemia (adapted from Cristelo *et al.* [20]).

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