

Manuscript Title

Tissue- and Cell-Specific Dysregulations of ACE2 may put Patients with Diabetes at Higher Risk for COVID-19

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Summary

The manuscript was received on August 03, 2020 and was peer reviewed by three reviewers and an editor.

The initial recommendation of Major Revision was made on September 11, 2020.

The first revision was submitted on October 06, 2020 and was re-evaluated by the editor.

The manuscript was accepted for publication on October 23, 2020.

Peer Review Comments

Reviewer 1:

In this review article the authors discuss how and to what extent the cell-specific expression of ACE2 in different tissues could explain the relationship of COVID-19 with hypertension and diabetes.

Comments:

1. When the authors discuss ‘... how diabetes is associated with severity and death in patients with COVID-19 has been improved considerably, for review see (2).’ They should also address two recently published important review articles (Nat Med. 2020 Jul;26(7):1017-1032.; Lancet Diabetes Endocrinol. 2020 Sep;8(9):782-792.), which have carefully addressed these points.
2. Furthermore, the authors should discuss that in several, particularly in the early published, studies, addressing the relationships of diabetes and hypertension with the severity of COVID-19, it was not accounted for obesity, which is both, associated with diabetes and hypertension and also independently predicts a more complicated course of COVID-19 (Nat Rev Endocrinol. 2020 Jul;16(7):341-342.).
3. When the authors state that ‘In a later phase of diabetes, however, the ACE2 might be downregulated [7], which causes several complications, e.g., diabetic nephropathy, oxidative stress in the pancreas and impaired insulin secretion [6,10].’, the should state that this ‘associates with’ not that it ‘causes’, complications, because causative effects are not well documented.
4. Considering the important role of body fat distribution and different properties of adipose tissue for metabolism (Lancet Diabetes Endocrinol. 2020 Jul;8(7):616-627.), the authors should also discuss the role of ACE2 expression in adipocytes and adipocyte-like cells for the course of COVID-19 (Obesity (Silver Spring). 2020 Jul;28(7):1187-1190; Front Immunol. 2020 Jul 21;11:1714.).

5. Furthermore, as an excessively activated immune response is thought to contribute to a severe COVID-19 (Nat Metab. 2020 Jul;2(7):572-585.) and an unduly immune response can result in adipocyte inflammation, fatty liver and type 2 diabetes (Ann Intern Med. 2020 Jun 16;172(12):836-837.) the authors should discuss this aspect in the present article.
6. The authors should also discuss that SARS coronaviruses can directly infect the pancreatic islets and, thereby, cause diabetes (Acta Diabetol. 2010 Sep;47(3):193-9.).
7. The authors should provide a schematic image summarizing their hypotheses.

Reviewer 2:

The title of the paper suggests that the authors are interested in exploring the impact of age, hypertension, and diabetes on the dysregulation of Angiotensin-converting enzyme 2 (ACE2) and the severity of COVID-19. At the start of the manuscript they outlined that they were particularly interested in investigating ACE2 because it serves as the cellular entry point for COVID-19. They reviewed how ACE2 expression could vary depending on the phases of diabetes, and they posited that the up- and down-regulation of ACE2 could impact individuals with diabetes who become infected with COVID-19. Also, they discussed how ACE2 expression could be affected by age depending on the organ and tissue type, before presenting a detailed discussion on investigating ACE2 expression at the cellular level in order to have a better understanding of the connection between COVID-19 and chronic diseases like diabetes. In the conclusion they suggest future work to investigate the role of sACE2 and ACE2 with regards to COVID-19.

Comments:

The theme of the brief is timely and worth investigation; however, the authors did not explicitly state an aim in the main body of the manuscript. The reader is left to infer whether the authors' objective was:

1) to investigate the impact of age, hypertension, and diabetes on ACE2 and COVID-19 (as stated in the manuscript title and most of the introduction) or

2) to discuss why the cellular level approach was better than the whole-body approach when investigating ACE2 expression (as stated in the abstract and most of the paper starting at line 58).

These objectives are related though they are not the same, and the authors' intent should be clear.

In addition, there are several instances where the flow of the manuscript and sentence structure needs some attention.

Reviewer 3:

This manuscript is well written, explored important aspect of COVID-19 pathophysiology and definitely is a valuable work , however to me was not clear how is research led to the conclusions was conducted. There was mention of data mining on PubMed, but not specify for which work

Although the title includes hypertension effect on the severity of the disease this not clearly illustrated, treatment with ACEi was mentioned in the context of treatment of diabetes and HF. Also soluble ACE2 role was in the conclusion, but not earlier explained.