LETTER TO THE EDITOR

Related molecular mechanisms of COVID-19, hypertension, and diabetes

Erman Akkus[1] and Mustafa Sahin[2]

[1]*Department of Internal Medicine, Faculty of Medicine, Ankara University, Ankara, Turkey; and* [2]*Department of Endocrinology and Metabolism, Faculty of Medicine, Ankara University, Ankara, Turkey*

Submitted 20 April 2020; accepted in final form 27 April 2020

TO THE EDITOR: Since the coronavirus disease (COVID-19) became a pandemic and hypertension and diabetes are important co-morbidities in COVID-19, there is a big debate about continuing or discontinuing angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) during the pandemic. Previously, Fang et al. (3) suggested that ARB and ACEI drugs could theoretically increase the risk of lung disease and death, as the COVID-19 virus binds to ACE2 protein and these drugs increase ACE2 protein expression. However, de Simone and Mancusi (2) concluded that speculation about antihypertensive drugs did not provide evidence and the virus reduced ACE2 protein expression, leading to a heavier lung picture because ACE2 activity could increase conversion of angiotensin II to angiotensin-(1–7). There is still big debate about ACE2 and ACEI/ARB use in COVID-19, and the role of ACE2 in the pathogenesis of COVID-19 should be understood.

COVID-19 is associated with cytokine storm syndrome in which macrophages are major component (6). Moreover, IL-6 is found to be predictor of the mortality in COVID-19 patients (7). It is also shown that ACE2 is expressed in macrophages, and the virus infects the macrophages (1). ACE2-expressing $CD68^{+}CD169^{+}$ macrophages were detected in the splenic marginal zone and in marginal sinuses of lymph nodes, and these macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6 (1).

ACE2 activity is found to be increased in monocyte-derived macrophages from prehypertensive subjects (5). The blood pressure level was 128.3 ± 0.8/78.1 ± 1.2 mmHg in this group. In these levels of hypertension, ACE2 expression may be increased in macrophages and normally it is protective for many diseases, but when the COVID-19 uses it to enter cells, high expression of ACE2 may become a disadvantage. Thus, ACEI and ARBs may increase chance of cytokine storm.

Many patients with diabetes are using ACEI and ARBs. So these drugs may not only increase ACE2 expression on alveolar cells but also in beta cells in the pancreas and immune cells so may increase inflammation and glucose levels in this patients. İnflammation and increased glucose levels make vicious cycle. Same mechanism may be also exist for lung cells. The virus infects macrophages and causes IL-6 production. IL-6 causes inflammation, increases LPS, and increases glucose levels and produces insulin resistance.

Glucose metabolism and inflammation are related to each other and viruses may increase hexosamine biosynthesis pathway. *O*-GlcNAcylation of transcription factor IRF5 induce inflammatory cytokine production. *O*-GlcNAc transferase promotes influenza A virus-induced cytokine storm by targeting interferon regulatory factor-5 (8). Thus, COVID-19 may use this mechanism to increase inflammatory cytokine production. Moreover, viruses by this mechanism may increase especially vascular complications in patients with diabetes (8). This also may explain the sudden cardiac deaths in COVID-19 patients.

Metformin and AMPK activation reduce *O*-GlcAcylation (4). Thus, metformin may be used to reduce inflammation in COVID-19 patient and may be protective from cytokine storm risk. However, it must be kept in mind that metformin may be contraindicated in critically ill patients because of organ dysfunctions.

It is crucial to understand molecular mechanisms involving the virus, ACE2 and comorbidities. The hypotheses we discussed and proposed here may arise some future researches.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.A. and M.S. conceived and designed research; E.A. and M.S. edited and revised manuscript.

REFERENCES

1. **Chen y, Feng Z, Diao B, Wang R, Wang G, Wang C, Tan Y, Liu L, Wang C, Liu Y, Liu Y, Yuan Z, Ren L, Wu Y.** The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. (Preprint) *medxiv*: 2020.2003.2027.20045427, 2020. doi:10.1101/2020.03.27.20045427.
2. **de Simone G, Mancusi C.** Speculation is not evidence: antihypertensive therapy and COVID-19. (In press) *Eur Heart J Cardiovasc Pharmacother* pvaa021, 2020. doi:10.1093/ehjcvp/pvaa021.
3. **Fang L, Karakiulakis G, Roth M.** Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 8: e21, 2020. doi:10.1016/S2213-2600(20)30116-8.
4. **Gélinas R, Mailleux F, Dontaine J, Bultot L, Demeulder B, Ginion A, Daskalopoulos EP, Esfahani H, Dubois-Deruy E, Lauzier B, Gauthier C, Olson AK, Bouchard B, Des Rosiers C, Viollet B, Sakamoto K, Balligand JL, Vanoverschelde JL, Beauloye C, Horman S, Bertrand L.** AMPK activation counteracts cardiac hypertrophy by reducing O-GlcNAcylation. *Nat Commun* 9: 374, 2018. doi:10.1038/s41467-017-02795-4.
5. **Keidar S, Strizevsky A, Raz A, Gamliel-Lazarovich A.** ACE2 activity is increased in monocyte-derived macrophages from prehypertensive subjects. *Nephrol Dial Transplant* 22: 597–601, 2007. doi:10.1093/ndt/gfl632.
6. **Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK.** COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395: 1033–1034, 2020. doi:10.1016/S0140-6736(20)30628-0.
7. **Ruan Q, Yang K, Wang W, Jiang L, Song J.** Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China (In press). *Intensive Care Med*. doi:10.1007/s00134-020-05991-x.
8. **Wang Q, Fang P, He R, Li M, Yu H, Zhou L, Yi Y, Wang F, Rong Y, Zhang Y, Chen A, Peng N, Lin Y, Lu M, Zhu Y, Peng G, Rao L, Liu S.** O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5. *Science Advances* 6: eaaz7086, 2020.

Correspondence: E. Akkus (e-mail: eakkus@ankara.edu.tr).

 0193-1849/20 Copyright © 2020 the American Physiological Society

Downloaded from journals.physiology.org/journal/ajpendo at Ankara Universitesi Tip Fakultesi (080.251.045.167) on December 11, 2021.