Received: 22 August 2020 | Revised: 22 October 2020 | Accepted: 26 October 2020

DOI: 10.1111/odi.13711

ORAL DISEASES WILEY

LETTER TO THE EDITOR

Letter to the Editor: Diabetes, obesity and hypertension may promote oral SARS-CoV-2 infection—Salivary soluble ACE2 perspective

Patients with systemic diseases, such as hypertension and diabetes, are prone to severe disease when they acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Chen et al., 2020). A study on the viral load in the secretions from the oropharynx and oral cavity revealed that SARS-CoV-2 spreads faster among patients with underlying diseases, such as diabetes (Liu et al., 2020). We hypothesized that diabetes, obesity and hypertension may promote oral SARS-CoV-2 infection by affecting the ratio of membrane-bound and soluble forms of angiotensin-converting enzyme 2 (ACE2) in the oral cavity.

The critical SARS-CoV-2 entry receptor is the membrane-bound ACE2 (mbACE2), and transmembrane serine protease 2 induces intracellular cleavage of ACE2, leading to enhanced viral entry. Disintegrin and metalloproteinase 17 competitively participate in ACE2 processing by facilitating ACE2 ectodomain shedding as a soluble form of ACE2 (sACE2), which exists in extracellular fluids (Heurich et al., 2014) (Figure 1). In the human oral mucosal epithelial cells, the ACE2 receptor has been identified at the mRNA level (Xu et al., 2020), while ACE2 protein expression varies depending on the anatomical location and antibodies used for detection: staining of ACE2 in epithelial cells was obtained using polyclonal but not monoclonal antibodies (Descamps et al., 2020). As the location of the ACE2 extracellular cleavage site corresponds to an area targeted by the monoclonal antibody used, cleavage of the ACE2 ectodomain is a potential explanation for the lack of staining (Descamps et al., 2020). Recently, mbACE2 was found in exfoliated epithelial cells in saliva and the presence of sACE2 in the saliva is suggested as result of their shedding (Srinivasan et al., 2020). In contrast to mbACE2, inversely correlated sACE2 offers protection against viruses (Yang et al., 2014). A human recombinant sACE2 protein has been shown to inhibit SARS-CoV-2 infection of human organoids by intercepting the virus from binding to mbACE2 (Monteil et al., 2020). Since the development of sACE2 from mbACE2 is induced by angiotensin II acting via angiotensin II receptor type 1 (AT-1 receptors) (Patel et al., 2014), blockade of AT-1 receptors by angiotensin receptor blockers or inhibition of angiotensin II generation by ACE inhibitors, commonly prescribed for hypertension and diabetes, inhibits this process and leads to higher mbACE2 and lower sACE2 expression. Other drugs for diabetes and obesity, such as metformin, pioglitazone and liraglutide, may also increase mbACE2 (Pal & Bhadada, 2020; Zhang et al., 2018). Furthermore, drugs used in the treatment of diabetes, obesity, hypertension and diabetes per se induce hyposalivation, which could limit the effectiveness of sACE2 and promote oral SARS-CoV-2 infection (Figure 1). Noteworthy, SARS-CoV-2 infection is associated with xerostomia, likely due to the virus occupancy of ACE2 and consequent angiotensin II increase and aldosterone release that induce sodium and water retention in the salivary glands (Sunavala-Dossabhoy, 2020).

Regarding diagnostic impact, the greater involvement of sACE2 in saliva as a virus "decoy," which may reduce the bonding of SARS-CoV-2 to mbACE2 further in the respiratory tract, could help explain cases of patients exhibiting SARS-CoV-2-positive results in whole saliva or sputum and negative pharyngeal or bronchoalveolar swabs. Likewise, salivary sACE2 may be an important ally and advantage in asymptomatic SARS-CoV-2-positive patients. Further analyses of salivary ACE2 are required to confirm the present hypothesis and understand the nature of the ACE2 species.

CONFLICT OF INTEREST

The authors received no financial support and declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

Jelena Roganović: Conceptualization; Investigation; Visualization; Writing-original draft. **Miroslav Radenković:** Data curation; Investigation; Writing-review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.13711.

Jelena Roganović[1]
Miroslav Radenković[2]

[1]*Department of Pharmacology in Dentistry, School of Dental Medicine, University of Belgrade, Belgrade, Serbia*
[2]*Department of Pharmacology, Clinical Pharmacology and*

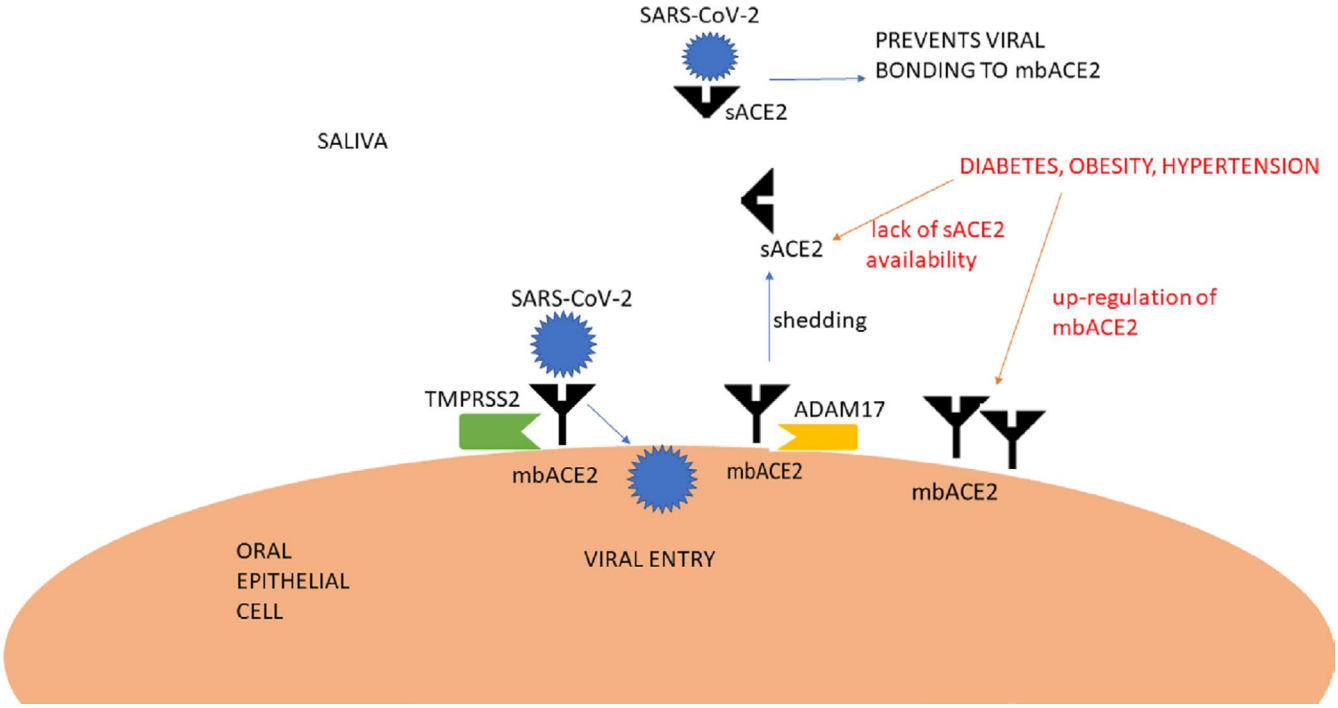

FIGURE 1 Hypothesis of diabetes, obesity and hypertension promotion of oral SARS-CoV-2 infection by affecting the ratio of membrane-bound and soluble forms of angiotensin-converting enzyme 2 (ACE2) in the oral cavity. Oral epithelial cell-membrane-bound ACE2 (mbACE2) serves as the main SARS-CoV-2 entry receptor, allowing viral entry. Cleavage by transmembrane serine protease 2 (TMPRSS2), enzyme moderately expressed in the salivary glands, enhances viral entry. Cleavage of mbACE2 by disintegrin and metalloproteinase 17 (ADAM17), enzyme which shows significant mRNA and protein expression in oral mucosa and salivary glands, does not relate to viral entry, and results in mbACE2 shedding and forming of soluble ACE2 form (sACE2) which could act virus-protective in saliva. Lack of salivary sACE2 availability and/or up-regulation of mbACE2 in diabetes, obesity and hypertension may underly promotion of SARS-CoV-2 oral infection observed in patients with these underlying diseases

Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Correspondence
Jelena Roganović, Department of Pharmacology in Dentistry, Faculty of Dental Medicine, University of Belgrade, Dr Subotica 1, Belgrade 11000, Serbia.
Email: jelena.roganovic@stomf.bg.ac.rs

ORCID

Jelena Roganović https://orcid.org/0000-0002-2950-4056

REFERENCES

Chen, T., Dai, Z., Mo, P., Li, X., Ma, Z., Song, S., Chen, X., Luo, M., Liang, K., Gao, S., Zhang, Y., Deng, L., & Xiong, Y. (2020). Clinical characteristics and outcomes of older patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: A single-centered, retrospective study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *75*(9), 1788–1795. https://doi.org/10.1093/gerona/glaa089

Descamps, G., Verset, L., Trelcat, A., Hopkins, C., Lechien, J. R., Journe, F., & Saussez, S. (2020). ACE2 protein landscape in the head and neck region: The Conundrum of SARS-CoV-2 infection. *Biology*, *9*(8), 235. https://doi.org/10.3390/biology9080235

Heurich, A., Hofmann-Winkler, H., Gierer, S., Liepold, T., Jahn, O., & Pöhlmann, S. (2014). TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. *Journal of Virology*, *88*(2), 1293–1307. https://doi.org/10.1128/JVI.02202-13

Liu, R., Yi, S., Zhang, J., Lv, Z., Zhu, C., & Zhang, Y. (2020). Viral load dynamics in sputum and nasopharyngeal swab in patients with COVID-19. *Journal of Dental Research*, *99*(11), 1239–1244. https://doi.org/10.1177/0022034520946251

Monteil, V., Kwon, H., Prado, P., Hagelkrüys, A., Wimmer, R. A., Stahl, M., Leopoldi, A., Garreta, E., Hurtado Del Pozo, C., Prosper, F., Romero, J. P., Wirnsberger, G., Zhang, H., Slutsky, A. S., Conder, R., Montserrat, N., Mirazimi, A., & Penninger, J. M. (2020). Inhibition of SARS-CoV-2 Infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*, *181*(4), 905–913.e7. https://doi.org/10.1016/j.cell.2020.04.004

Pal, R., & Bhadada, S. K. (2020). Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? *Diabetes Research and Clinical Practice*, *163*, e108146. https://doi.org/10.1016/j.diabres.2020.108146

Patel, V. B., Clarke, N., Wang, Z., Fan, D., Parajuli, N., Basu, R., Putko, B., Kassiri, Z., Turner, A. J., & Oudit, G. Y. (2014). Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: A positive feedback mechanism in the RAS. *Journal of Molecular and Cellular Cardiology*, *66*, 167–176. https://doi.org/10.1016/j.yjmcc.2013.11.017

Srinivasan, M., Zunt, S., & Goldblatt, L. (2020). Oral epithelial expression of angiotensin converting enzyme-2: Implications for COVID-19 diagnosis and prognosis. *bioRxiv*. 2020.06.22.165035. https://doi.org/10.1101/2020.06.22.165035

Sunavala-Dossabhoy, G. (2020). Renin-angiotensin II-aldosterone axis in SARS-CoV-2-associated xerostomia. *Oral Diseases*, https://doi.org/10.1111/odi.13594

Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., Li, T., & Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, *12*(1), 8. https://doi.org/10.1038/s41368-020-0074-x

Yang, P., Gu, H., Zhao, Z., Wang, W., Cao, B., Lai, C., Yang, X., Zhang, L. Y., Duan, Y., Zhang, S., Chen, W., Zhen, W., Cai, M., Penninger, J. M., Jiang, C., & Wang, X. (2014). Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Scientific Reports*, *4*, e07027, https://doi.org/10.1038/srep07027

Zhang, J., Dong, J., Martin, M., He, M., Gongol, B., Marin, T. L., Chen, L., Shi, X., Yin, Y., Shang, F., Wu, Y., Huang, H.-Y., Zhang, J., Zhang, Y. U., Kang, J., Moya, E. A., Huang, H.-D., Powell, F. L., Chen, Z., … Shyy, J.-J. (2018). AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*, *198*(4), 509–520. https://doi.org/10.1164/rccm.201712-2570OC

How to cite this article: Roganović J, Radenković M. Letter to the Editor: Diabetes, obesity and hypertension may promote oral SARS-CoV-2 infection—Salivary soluble ACE2 perspective. *Oral Dis*. 2020;00:1–3. https://doi.org/10.1111/odi.13711