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# Coronavirus Disease 2019 May Affect Dental Implant Integration



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This communication is preliminary to a manuscript being submitted to this journal. The author has observed implant failure during the integration period in patients who had coronavirus disease 2019 (COVID-19). From March through November 2020, a total of 5 implants failed among 122 implants placed; 4 of the failures were in patients with COVID-19 and 1 in a patient who was COVID naïve. The failures occurred during the period of implant integration. One had COVID-19 infection 6 weeks before implant placement and developed intense progressive pain within 6 days of implant placement, resulting in removal of the implant and immediate relief of pain. A second patient was COVID positive 4 weeks after implant placement and developed severe bone loss around the implant resulting in its removal. Two other patients lost implants early after placement. Both of these patients had prior COVID-19 but tested negative at the time of implant placement. These patients did have mild comorbidities suggesting additional implant risk. All had uneventful implant placement with excellent primary stability. Mechanisms to explain these observations are COVID-19 alterations in the ACE2 pathway, the inflammatory cytokine “storm,” and/or microvascular dysfunction.<sup>1</sup>

## The ACE2 Pathway

ACE2 is a receptor for the spike glycoprotein of the coronavirus.<sup>2</sup> ACE2 promotes cleavage of angiotensin into Ang-(1-7) and targets MasR. Both ACE2 and MasR are expressed by osteoblasts and osteoclasts. In vivo, Ang-(1-7) decreases alveolar bone loss through optimization the osteoblast/osteoclast ratio. ACE2/Ang-(1-7)/MasR is an active player in alveolar bone remodeling. One mechanism for inhibition of osteogenesis may

occur when coronavirus-19 combines on the receptor for ACE2, resulting in downregulation of the ACE2/Ang-(1-7)/MasR pathway. This would change the balance of osteoclast/osteoblast action. When the coronavirus interferes with the ACE2 receptor, the aforementioned actions are inhibited, and bone resorption and lack of bone apposition may occur.<sup>3</sup>

The role of inflammatory factors and the cytokine storm IL-1 $\beta$ , IL-6, TNF- $\alpha$ , G-CSF, IP-10, MCP-1, MIP-1 $\alpha$  have been detected in patients with COVID-19, especially those who required ICU admission.<sup>3</sup> These factors may enhance bone resorption through the RANKL signaling pathway. If not under control, the elevated levels of these cytokines may result in osteoclast recruitment, bone loss, and decreased bone formation. Immunosuppression may be important to consider for our implant patients whose implants have exposure to oral bacteria.

## MICROVASCULAR DYSFUNCTION

Evidence exists that the microvasculature is effected by COVID-19. In the study by Rovas et al,<sup>4</sup> 23 moderate to severely ill patients with COVID-19 were compared with healthy volunteers. Intravital microscopy, red cell velocity, and glycocalyx dimensions were used to evaluate perfusion boundaries. Patients with COVID-19 showed up to 90% reduction in vascular density. This was almost exclusively small capillaries with diameters ranging from 4 to 6 micrometers. Vascular velocity was also decreased. Their data clearly showed alterations of the microcirculation and the endothelial glycocalyx in patients with COVID-19.

SARS-CoV-2, the causative virus of COVID-19, binds to ACE2 in vascular endothelial cells and arterial smooth muscle cells. It is believed that COVID-19 can cause endothelial glycocalyx damage.<sup>5</sup>

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Fragmented vascular endothelial glycocalyx is elevated in patients with COVID-19 and may be useful as an indicator of the COVID-19 state.<sup>6</sup>

Lowenstein and Solomon<sup>7</sup> propose that severe COVID-19 is a microvascular disease resulting in microvascular inflammation and thrombosis. They claim that patients with COVID-19 are in a hyperinflammatory state with elevated cytokines and microvascular thromboses are prominent. They propose a pathway of pathogenesis that is triggered by microvascular inflammation with exocytosis caused by endothelial cell damage.

The aforementioned 3 pathways may result in decreased healing and decreased osteogenesis around dental implants. The following case reports illustrate unique implant failures. The first case may represent microcirculatory dysfunction and the second generalized alteration in bone remodeling bone formation and infection during the integration period.

The surgeon will need to identify patients with COVID-19 experience - either previous positive testing with subsequent negative testing before implant placement or a positive COVID-19 test after the implant is placed within the early time period of integration. A patient who has had recent positive testing for COVID-19 should be counseled as to possible risks that can adversely affect implant treatment, until the systemic effects of COVID-19 have passed.

One problem that clinicians have is that minimal information is available concerning the long-term effects of COVID-19, regarding the alterations in the ACE2 pathway, the inflammatory state, and microvascular dysfunction. If a patient tests positive during the period of integration soon after implant placement, they may be at an increased risk for implant failure and the patient must be informed of the possible risk.

Obviously, a larger patient sample is needed to confirm this observation.

## References

1. Zheng K, Zhang W-C, Xu Y-Z, Geng D-C: COVID-19 and the bone: Underestimated to consider. *Eur Rev Med Pharmacol Sci* 24: 10316, 2020
2. Queiroz-Junior CM, Santos ACPM, Galvão I, et al: The angiotensin converting enzyme 2/angiotensin-(1-7)/Mas Receptor axis as a key player in alveolar bone remodeling. *Bone* 128:115041, 2019
3. Huang C, Wang Y, Xi L, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395:497, 2020
4. Rovas A, Osiaevi I, Buscher K: Microvascular dysfunction in COVID-19: the MYSTIC study *Angiogenesis*. *Angiogenesis* 14:1-13, 2020 Online ahead of print
5. Tojo MY: Endothelial glycocalyx damage as a systemic inflammatory microvascular endotheliopathy in COVID-19 *Biomed. Biomed J* 43:399, 2020 Epub 2020 Aug 24
6. Minako YT: Vascular endothelial glycocalyx damage in COVID-19. *Int J Mol Sci* 21:9712, 2020
7. Lowenstein CJ, Solomon SD: Severe COVID-19 is a microvascular disease *Circulation*. *Circulation* 142:1609-1611, 2020