



## COVID-19 and the Oral-Systemic Link

- by Kelly Rehan
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Emerging research is strengthening the oral-systemic link, but how much do we really know? Explore the latest evidence, including implications related to COVID-19, and get expert perspectives on how these findings may shape your patient interactions.

On March 11, 2020, the World Health Organization (WHO) announced a global pandemic in response to the rapid spread of COVID-19.<sup>1</sup> The research community raced to understand the disease that was, quite literally, taking over the world.

“Having little to no experience with any pandemic forced many researchers to start at square one,” said Richard H. Nagelberg, DDS, of East Norriton, Pennsylvania-based Plymouth Meeting Family Dental and oral medicine member of the *General Dentistry* Advisory Board. “Many investigations were undertaken rapidly as information started coming in regarding the route and course of infection, all amid conflicting public health information due to the meteoric pace of infection and a panic-stricken global population.”

COVID-19 has ramped up the pace of research significantly, and initial studies suggest poor oral health plays a role in the severity of the illness. The idea that oral health can affect whole-body health is the foundation of the oral-systemic link — that “oral infection, especially periodontitis, may affect the course and pathogenesis of a number of systemic diseases.”<sup>2</sup>

Although the scientific community still has much to learn about COVID-19, studies on the relationship between oral health and overall health have been ongoing for decades.

### **RESEARCH REFRESHER: PERIODONTAL DISEASE LINKS TO DIABETES AND HEART DISEASE**

Several oral-systemic links exist to various degrees, from correlational to causal. Susan G. Estep,

DMD, FAGD, of Atlanta-based Intown Smile Studio and current president of the American Academy for Oral Systemic Health (AAOSH), maps the oral systemic connection in three categories: oral pathogens, oral inflammation and airway problems.

Starting with oral pathogens, Estep said that strong evidence points to causal and correlative connections between bacteria in the oral cavity and cardiovascular diseases, metabolic diseases, Alzheimer's disease, pregnancy complications, and certain cancers, as well as autoimmune and inflammatory diseases and disorders.<sup>3-7</sup>

Estep said that oral inflammation (e.g., gingivitis, periodontitis, dental abscess) is not localized to the mouth; rather, it contributes to chronic systemic inflammation, which is known to be a root cause for Western diseases (cardiovascular disease, type 2 diabetes, diabetes, cancers, autoimmune and inflammatory diseases).

Out of the many conditions implicated in the oral-systemic link, the relationship between periodontal disease and diabetes is the most well established in literature, Nagelberg said. "Numerous studies have demonstrated a variety of effects among individuals with both periodontitis and diabetes, including worsening glycemic control, increased incidence and severity of diabetic complications, and a higher mortality rate compared to individuals with only diabetes," he said.<sup>8-10</sup>

Broadly, two mechanisms for oral-systemic associations have been advanced by research: the contribution of periodontal disease to the total inflammatory burden and direct effects of oral bacteria on the vasculature.<sup>4,11</sup> Speaking to the associations of poor oral health and heart disease, Nagelberg said research on whether oral bacteria actually leads to heart disease is somewhat mixed.

"Some of these studies conclude that periodontal pathogens, including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola* and *Fusobacterium nucleatum*, are causative, while others indicate that the risk for atherosclerosis is enhanced by the activity of these bacteria," he said.<sup>4,12</sup> "Many studies have demonstrated the presence of periodontal pathogens in the endothelium of coronary arteries and the gingival sulci of the same individuals, but with no conclusion of causality."<sup>13-15</sup>

Although some diseases implicated in the oral-systemic connection have deep research backing, others — such as COVID-19 and Alzheimer's disease — are less understood.

### **COVID-19 AND THE ORAL-SYSTEMIC LINK: WHAT WE KNOW**

After nearly 18 months of studying COVID-19, researchers have not found a direct causal relationship between periodontal disease and COVID-19. However, there is substantial evidence of a relationship between the two, Estep said.

The center of this relationship, she explained, is inflammation.

"Oral inflammation is not localized to the mouth; rather, it activates chronic systemic

inflammation, which wreaks havoc on the body's immune system," Estep said. "Bad COVID-19 outcomes appear to be related to a chaotic dysregulation in the body's immune system, and we believe that chronic systemic inflammation could be a root cause for this deadly shift in immune function."

Further explaining COVID-19's potentially deadly inflammatory response, Nagelberg explained that the virus enters cells by attaching to an angiotensin converting enzyme-2 (ACE-2) receptor. The virus then hijacks the cell's genetic material and rapidly replicates. The body elicits an immune response, which can lead to an uncontrolled release of pro-inflammatory mediators — such as certain cytokines — in severe cases of the disease.<sup>16,17</sup>

"The rapid viral replication causes death of the host cell, which is accompanied by the release of massive amounts of inflammatory mediators," Nagelberg said. "It brings to mind a perpetual motion machine, in which the increased release of cytokines causes continuous infection of immune cells, macrophages and other white blood cells, which in turn causes the release of additional inflammatory mediators, resulting in a 'cytokine storm,' which can cause multiorgan failure and death."<sup>18</sup>

Nagelberg said it appears that periodontitis, along with other systemic conditions, contributes to an enhanced inflammatory response and the development of a cytokine storm. Research thus far has found that cytokine storms contribute to COVID-19 disease progression and increase pneumonia incidence, a leading cause of death in patients with COVID-19.<sup>19-21</sup>

Other areas of research are exploring the presence of ACE-2 receptors in the gingival lining epithelium and the presence of the SARS-CoV-2 virus in periodontal pockets in the same sites. Nagelberg explained that the presence of the ACE-2 receptors in the gingival epithelium provides the potential for the gingival sulcus to be a site of SARS-CoV-2 replication. Other researchers are investigating the periodontal pocket as a potential reservoir for SARS-CoV-2 viral particles.<sup>22</sup>

"A number of studies have demonstrated that SARS-CoV-2 and ACE-2 receptors are found in many structures in the oral cavity, including the tongue, buccal mucosa, gingival tissues, periodontal pockets and gingival crevices," said Nagelberg.<sup>19</sup> "Two recent studies suggest that the periodontal pocket epithelium may be a focal point of SARS-CoV-2 infection and that periodontal therapy has the potential to help minimize the systemic spread of the virus."<sup>22,23</sup>

Although causal findings don't yet exist, Nagelberg said there's evidence that periodontal disease increases the likelihood of COVID-19 complications.

"The risk of complications was found to be significantly higher among patients with moderate to severe periodontitis as opposed to COVID-19 patients with no or mild periodontitis," he said. "Periodontitis was associated with a higher risk of ICU admissions, the need for ventilator usage and death."<sup>24,25</sup>

## **BRAIN-GINGIVAL CONNECTION**

In addition to COVID-19, Alzheimer's disease is another topic in the oral-systemic discussion. The latest findings suggest that the buildup of bacteria that causes periodontitis may play a role in dementia and Alzheimer's disease.

This evolving evidence is of particular interest to Charles Whitney, MD, an expert on the oral-systemic link and founder of Philadelphia-based Revolutionary Health Services, a medical practice dedicated to preserving long-term health.

Whitney explained that causation-level evidence already exists identifying the presence of certain periodontal bacteria species as some of the many causes of Alzheimer's disease, referencing a 2011 paper published in the *Journal of Neuroinflammation*.<sup>26</sup>

“Whenever there is any blood in the sink, this is an indication that the oral bacteria that cause periodontal disease and gingivitis have launched bloodborne [diseases],” Whitney said. “When they land in far-reaching locations, they drive the same inflammation that a dentist sees in the mouth. This includes crossing the blood-brain barrier to cause inflammation that leads to the formation of the amyloid plaques of Alzheimer's disease. Periodontal spirochetes have been found in disproportionately high levels in the brains of Alzheimer's patients.”<sup>26</sup>

Whitney also cited a 2019 study published in *Science Advances* that examined the effects of periodontal disease-causing bacteria *Porphyromonas gingivalis* on Alzheimer's disease.<sup>27</sup>

“*P. gingivalis* was found in the brain of Alzheimer's patients, along with a neurotoxic protein that *P. gingivalis* produces called gingipain,” Whitney said. “This toxic protein drives the production of tau and ubiquitin. Tau is a protein required for normal neuronal function that is impeded by gingipains, and ubiquitin is a component of plaques found in Alzheimer's patients. When researchers blocked the production of gingipain in mice, it blocked the production of amyloid plaque. This strongly implicated *P. gingivalis* as a cause of Alzheimer's.”<sup>27</sup>

Even more recently, research published in April 2021 in *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* that examined the cerebrospinal fluid of elderly patients with normal cognition showed a link between Alzheimer's and poor oral health.<sup>28</sup>

“[The authors] found that those with oral dysbiosis — a high ratio of bad to good oral bacteria — had cerebrospinal fluid beta-amyloid findings that place them at risk for Alzheimer's disease,” Whitney said.<sup>28</sup>

Whitney said physicians are recognizing the mounting levels of evidence supporting the oral-Alzheimer's connection, especially since the research is beginning to be discussed in medical and mainstream media.

“Doors are opening for dental teams to speak to patients and collaborate with medical providers more than ever before,” he said. Whitney referenced the work of Dale E. Bredesen, MD, author of “The End of Alzheimer's Program: The First Protocol to Enhance Cognition and Reverse Decline at Any Age,” which features a chapter on oral health contributors to Alzheimer's disease. As a trainer of medical providers, Bredesen suggests that all clinicians include a dental

provider in their cognitive decline care team.

Bredesen developed a systematic approach called Reverse COgnitive DEcline (ReCODE), certifying thousands of medical professionals in his method, Whitney said. Recently, Bredesen included dentists and dental hygienists in his certification program.<sup>29</sup>

“Certification offers continuing education and is tailored to the needs of dental professionals,” Whitney said. “It gives dental professionals the credibility as true partners in healthcare in the eyes of both medical teams and patients. Following certification, dental teams are introduced to ReCODE-certified medical providers and health coaches in their regions to begin collaboration and referrals. By speaking to patients with more confidence, there is significantly improved case acceptance and recare.”

Collaboration between dentists and physicians to enhance patient health needs to be a priority, according to Timothy Donley, DDS, a periodontist based in Bowling Green, Kentucky.

“Many of the risk factors for systemic diseases are also risk factors for chronic inflammatory periodontal disease,” Donley said. “Since there is now overwhelming evidence that inflammation of oral origin can contribute to the systemic burden of inflammation, managing the common risk factors that affect oral and systemic diseases can help better manage the inflammatory-driven systemic conditions. Behavior management is certainly an important component of the lifestyle changes necessary to reduce the contributing risk factors to both oral and systemic diseases, and partnering with medicine to modify a patient’s risk profile can only improve overall patient outcomes.”

## **DOES POOR MOUTH HEALTH CAUSE SYSTEMIC DISEASE? THE STATE OF ORAL-SYSTEMIC RESEARCH TODAY**

Thanks to continued research, the relationship between oral health and overall health is coming into focus. But the issue of causality between the two is not currently universally accepted among the scientific community, Nagelberg said.

“The consensus among dental and medical professionals is that the relationship between the mouth and the body is well established at this point in time,” Nagelberg said. “But opinions on the strength of the association vary, and there is no consensus on the issue of causality.”

Nagelberg explained that determining causality requires interventional trials over varying periods of time. For example, studying adverse effects of periodontal disease on pregnancy has a short study timeframe of nine months compared to the study period for cardiovascular events, which would take decades.

Alternatively, Nagelberg said causality may be found if researchers can determine the quantitative contribution of periodontal disease to the total inflammatory burden at some point in the future. “If it is determined to be considerable for specific systemic diseases and conditions, causality may be determined in that manner,” he said. Looking to the future of oral-systemic research, Estep said that in addition to the bidirectional medical links associated with oral

infection and inflammation, airway health plays a significant role in patients' complete health.

“It turns out that how a person breathes — mouth breathing versus nasal breathing — can improve or destroy their health,” Estep said. “Dentists and hygienists have known for a long time that mouth breathing causes chronic gingival inflammation, but it goes further than that. Chronic mouth breathing and associated sleep-disordered breathing contributes to systemic inflammation and increases systemic health risks.”

Estep explained that in infants and children, mouth breathing can lead to physical deformation and dysfunction of the developing dental arches and other oral structures. Mouth breathing also interferes with sleep cycles, and evidence suggests that mouth breathing and sleep-disordered breathing in children can affect brain health and development.<sup>30-33</sup>

“This is not the old sleep apnea science,” Estep said. “This is a massive arena in systemic health where dental teams serve as the frontline to educate our patients and help them improve their overall health.” Cause versus correlation aside, Estep said dentists shouldn't wait to act on the research.

“Every day, new and valid scientific evidence reveals more about these links,” Estep said. “In my opinion, at this point and with the mountain of evidence we now have, it would be harder to prove there is no link.”

## **TRANSLATING THE ORAL-SYSTEMIC LINK TO PATIENT EDUCATION**

What does this research mean to the daily work of general dentists? How can they put it to use in their daily practice and patient interactions?

Helping patients understand the connection between oral health and overall health should be part of every patient conversation because, as Estep explained, patients are smarter than you think.

“By now, dentists and hygienists should be educating their patients about the medical risks associated with oral health conditions,” Estep said. “We should be encouraging patients to properly treat these conditions to help reduce their medical risks for bad health outcomes now and in the future. At this point, the public is actually quite aware of the oral-systemic connection. If the patient is knowledgeable, and the dental team is not highlighting its importance, this could become a point of concern for patients.”

Estep said the ultimate role of each dentist is to reduce risk for patients in order to improve their overall health.

“When we take the time to educate our patients about their individual health risks, we might motivate them to take action for the benefit of their health,” Estep said. “Today, dental professionals are in a position to have a positive impact when it comes to our nation's health crisis. Organizations like AAOSH help educate dental and medical teams, making it easy to communicate the oral-systemic links to our patients.”

Speaking specifically to emerging oral-Alzheimer's links, Whitney offered several takeaways for general dentists that they can implement in their offices relatively quickly.

“Patients are far more likely to follow up for recare and accept treatment plans if they are doing it to benefit their brains, not just because their dentist says they should,” Whitney said.

First, Whitney suggested that dentists train their hygienists to ask questions during patient exams or include them on the medical history form to springboard conversations about the association between poor oral health and brain health.

These questions may include:

- Did you know that science is strongly suggesting that periodontal inflammation is one of the causes of Alzheimer's disease?
- Do you have a family history of dementia?
- Do you have the APOE ε4 gene variant, a variant of the apolipoprotein E gene, which increases your risk of Alzheimer's disease? If you don't know, talk to your primary care physician about this genetic test.
- Have you noticed any memory difficulties or slowing of mental processing speed?

Secondly, Whitney said dentists may consider offering in-office bacterial pathogen saliva testing or solutions that may be used in the office or at home to eliminate all blood in the sink.

Despite the varying opinions on the strength of the oral-systemic link, one fact not in dispute is the ability to reduce oral inflammation through control of oral biofilm levels by both the dental team and the patient, Nagelberg noted.

“An underappreciated fact about patient homecare is that brushing, flossing and rinsing are only therapeutic for gingivitis and typically have only a minimal effect on periodontitis,” Nagelberg said. “Hence the admonition to patients by dentists that gum disease cannot be brushed away. The importance of professional therapy cannot be overstated.”

The authors of a 2020 study on the effects of periodontal disease on diabetes put it plainly: “Patients should be aware that proper periodontal treatment may have beneficial effects on their glycemic control and diabetes complications. Patients should be advised that the cycle linking periodontal disease and diabetes can be managed for better oral and general health.”<sup>8</sup>

Dentists may apply this concept to other systemic diseases — including the one dominating many minds since March 2020.

“Dental professionals should encourage patients to present for treatment of periodontitis without delay,” Nagelberg said. “Similarly, dental clinicians should understand the effects of gum disease beyond the oral cavity and not wait until causality is proven and accepted by the profession and the public. The evidence is overwhelming that a variety of associations exist, regardless of a lack of causality.”

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