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## EDITORIAL

## Long-COVID and the practice of oral medicine



Once we are beyond the life and death concern, the scariest aspect to me of getting COVID-19 is the prospect of long-term consequences that create disability and affect quality of life. In particular, when facing the long-haul or long-COVID syndrome, there is possible prolonged duration of change in smell and taste, chronic fatigue, cognitive difficulties, and other unknown durable sequelae. Being surrounded by stories of taste changes, from my 13-year-old niece who reported her sudden loss of taste to her mother that precipitated SARS-CoV-2 testing, to my dental assistant who reported it was like a “taste switch” was turned off where her taste was fine at breakfast and acutely was altered by lunchtime, to my dental resident who initially experienced complete loss of taste and smell and still today, 11 months after acute COVID-19 recovery, has altered taste/smell sensations described as an unusual, not particularly pleasant, singular taste/smell for all foods. Those in the practice of dentistry and particularly oral medicine may be sought out as consultants and care providers for a growing population with lingering effects of COVID-19 infection. Cases are now being reported of persisting parosmia and dysgeusia phenomenon that are not fully recovered 15 months after onset.<sup>1</sup>

The terminology is still evolving to label those who have had COVID-19 and have persistent symptoms for longer than 3 to 4 weeks. Names for this condition were initially varied and termed post-acute COVID-19, post-acute sequelae of COVID-19, chronic post-COVID, long-haul COVID, and more recently, long-COVID. Our ability to understand this condition or any new disease starts with consensus around a case definition. For long-COVID, the definition is still fluid and may change as does our understanding of this condition. The US Centers for Disease Control and Prevention (CDC)<sup>2</sup> offers this current case definition: “**Post-COVID conditions** are a wide range of new, returning, or ongoing health problems people can experience **four or more weeks** after first being infected with the virus that causes COVID-19. Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions. These conditions can present as different types and combinations of health problems for different lengths of time.” The CDC post-COVID symptom list includes “change in smell or taste.”<sup>2</sup> In July 2021, the US government added long-COVID to the list of disabilities under the Americans with Disabilities Act, Section

504, and Section 1557 if a person’s long-COVID conditions or symptoms cause physical or mental impairments that substantially limits one or more major life activities.<sup>3</sup>

In October 2021, the World Health Organization (WHO)<sup>4</sup> offered its own, more detailed version of a clinical case definition with recognition of impact on daily function and the episodic nature of symptoms. WHO’s definition is as follows: “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”<sup>4</sup> WHO included altered taste/smell in their Delphi analyses used to create the definition and recognize component signs and symptoms. After fatigue, shortness of breath, and cognitive dysfunction, respondents were most likely to include the following, in this order, in the clinical case definition of post COVID-19 condition: memory issues, post-exertional malaise, muscle pain/spasms, sleep disorders, and altered smell/taste; all of which outranked tachycardia/palpitations, cough, and chest pain.<sup>4</sup>

Our understanding of COVID-19 and its chronic debilitating sequelae is rapidly increasing with identification of previously unknown longer-term risks as time passes since the initial cases were identified. We still do not fully understand who might develop long-COVID, how long each of the symptoms last, and whether COVID-19 prompts the presentation of chronic diseases. With so many unknowns remaining to be addressed by scientific discovery, Dr. Francis Collins, Director of the US National Institutes of Health (NIH), announced in February 2021 that the US Congress had appropriated \$1.15 billion in funding over 4 years to support NIH-funded research to help us better understand pathogenesis, natural history in various populations, methods for prevention, and treatment of conditions presenting as sequelae of SARS-CoV-2 infection.<sup>5</sup>

At my academic institution, the University of North Carolina (UNC) Medical Center, as is occurring in settings around the country and globe, special clinics are

being established to care for the expanding group of long-COVID patients. Further, these academic medical center-based long-COVID clinics often conduct research to help grow our understanding of this complex and complicated experience with the neurologic complications of this viral infection. As of October 2021, over 550 patients have been assessed in the UNC COVID Recovery Clinic, with referrals made to multiple specialty clinics for management.

In a large pragmatic primary care study from the United Kingdom (UK) using patient-reported outcomes and electronic health record data collected from August 2020 to January 2021, Jones and colleagues reported long-COVID (symptoms persisting beyond 4 weeks) to occur in about 10% of respondents who were self-diagnosed, clinician-diagnosed, and/or tested.<sup>6</sup> Risk predictors for long-COVID were age over 40 years, female sex, frailty, visit to hospital emergency department, and hospital admission for COVID-19 symptoms. The impact of persistent taste loss (reported by 44.5%) is a significant health burden, with almost every long-COVID sufferer (95.2%) reporting associated loss of appetite.<sup>6</sup> Appetite is essential to assure adequate nutritional intake. Taste is essential to preserve appetite and enjoyment of food and drink along with avoiding ingestion of spoiled or tainted unhealthy food items.

Age seems to matter, with older patients being more susceptible to long-COVID. In a University of Washington longitudinal prospective cohort study, which was conducted between August and November 2020, of 177 mostly outpatients with mild or no presenting symptoms, 32.7% of outpatients and 31.3% of hospitalized patients reported at least 1 persistent symptom between 3 and 9 months after illness onset.<sup>7</sup> Persistent symptoms were slightly more common in older patients, with reports by 26.6% aged 18 to 39 years, 30.1% aged 40 to 64 years, and 43.3% aged  $\geq 65$  years. Loss of sense of smell or taste and fatigue (both reported by 13.6% of patients) were the most common lingering symptoms.<sup>7</sup>

We are learning that reports of anosmia and dysgeusia can persist for months after acute COVID-19 resolves and serve as a marker of past infection. In a large retrospective Mass General Brigham electronic health record cohort study involving over 96,000 patients tested between March 2020 and June 2021 for SARS-CoV-2 but not hospitalized, Estiri et al. identified that 1 of the 5 phenotypes documented with high confidence in the 3 to 6 month temporal window after PCR testing indicating COVID-19 infection was anosmia and dysgeusia.<sup>8</sup> In a study of 1031 Egyptian patients with COVID-related olfactory and gustatory dysfunctions, Teaima et al. found that most improved in the first 2 weeks, and by the 6-month follow-up, 66% had completely recovered, 22% had partially

recovered, and 12% had persistent dysfunction.<sup>9</sup> These dysfunctions were subclassified as follows: 50% ageusia and anosmia, 23% hypogeusia and hyposmia, 18% anosmia alone, 18% phantosmia, and 28% parosmia.<sup>9</sup>

Sufficient primary data has now been published to support a systematic review of short- and long-term rates of post-acute sequelae of SARS-CoV-2 infection, giving us better estimates of disease burden. Groff et al. classified symptoms as short term (occurring 1 month after COVID-19 diagnosis or discharge), intermediate (2 to 5 months) and long term (6 months).<sup>10</sup> In their review of 57 studies published through March 2021, including over 250,000 COVID-19 survivors, researchers found that over half (54%) of survivors experienced at least 1 symptom 6 months after recovery, with the most common being pulmonary, neurologic (including anosmia and ageusia/dysgeusia), mental health, functional mobility impairments, and general and constitutional symptoms of chest imaging abnormality, difficulty concentrating, general anxiety disorder, general functional impairments, and fatigue or muscle weakness.<sup>10</sup> Investigators included loss of taste/smell under the neurologic category of symptoms due to assumed mechanism of loss being a consequence of the effect of the virus on cranial nerve I (olfactory nerve) for smell and cranial nerves VII (facial), IX (glossopharyngeal nerve), and X (vagal nerve) for taste. Anosmia and dysgeusia both appear to have been reported on average, including first to third quartiles, with frequency between 8% and 18% in the included studies.<sup>10</sup> There is also an ongoing living systematic review protocol out of the UK to keep scientists, patients, and policy makers updated on this rapidly developing condition.<sup>11</sup>

Overcoming vaccine hesitancy is a first step in preventing long-COVID. The importance of vaccination for decreasing risk of long-COVID was emphasized recently by a report of a large UK adult prospective, community-based, nested, case-control study of COVID-19 symptoms, test positivity, and vaccination status self-reported by over 1.5 million users in a mobile phone study app between March 2020 and July 2021.<sup>12</sup> Antonelli et al. found that, among those with COVID-19 infection, the odds of adults having symptom duration of 28 or more days was reduced by almost half among those who had received 2 vaccine doses compared with unvaccinated adults.<sup>12</sup> Oral medicine providers engaged in promoting and/or administering COVID-19 vaccinations can help in this disease prevention effort.

In general, research to date has failed to identify detailed causes of long-COVID symptoms, aspects that impact their severity, how long they will last, or the potential recovery trajectory. It is essential that we identify the mechanisms underlying the diverse

symptoms that can affect survivors so that the long-term health consequences of COVID-19 can be prevented and/or treated effectively. Several hypotheses around the cause of COVID-related anosmia have been proposed, with the angiotensin-converting enzyme 2 being a major player.<sup>13</sup> These hypotheses include olfactory cleft obstruction; local inflammation in the olfactory epithelium (sustentacular cells); interleukin-6 and other cytokine-mediated early apoptosis of olfactory cells; changes in olfactory cilia receptors and odor transmission; effect on olfactory bulbs; olfactory epithelium injury; and damage to olfactory neurons, microglial cells, and stem cells. Similarly, interaction of the virus with angiotensin-converting enzyme 2 receptors on cells in taste buds and salivary glands creating direct damage, viral invasion creating local inflammation, or binding to sialic acid receptors may underlie some taste changes.<sup>14</sup>

The COVID-19 pandemic years have resulted in significant societal and personal stresses. Is there potential overlap of anosmia/dysgeusia symptoms and bodily manifestations of stress responses and anxiety? Are there genetic and psychosocial factors predisposing COVID-19 patients and survivors to these sensory dysfunctions? The human brain and our senses have complex neural, neurohormonal, and neuroimmune axes adding to the challenge of unraveling the pathogenesis of the long-COVID sensory changes. Because oral medicine specialists often treat patient populations with oral neurologic manifestations such as post-herpetic neuralgia and burning mouth syndrome, do we have a role to support long-COVID patients with anosmia and dysgeusia/ageusia? Can we work alongside neurologists, otolaryngologists, and rehabilitation medicine physicians to care for long-COVID patients?

Can we develop and implement therapeutic approaches to improve or reset long-COVID taste/smell loss or dysfunction? Current treatment options being explored for anosmia include olfactory training exercises, intranasal or oral corticosteroids, and intranasal sodium citrate, with several promising novel therapeutic options including tissue engineering/gene therapy and stem cell therapy under development.<sup>13</sup> Other therapeutics suggested for management of smell and taste loss include neuroprotective (omega-3), anti-inflammatory, and depolarizing agents including corticosteroids (intranasal fluticasone; oral triamcinolone paste), phosphodiesterase inhibitors (pentoxifylline), and intranasal insulin.<sup>14</sup> Chabot and Huntwork propose ingestion of one 1000-mg dose of a (curcumin) turmeric supplement, which is thought to be beneficial for various oncologic and autoimmune ailments, may help restore long-COVID related taste and smell.<sup>15</sup>

As oral medicine specialists conducting research in other medically complex patient cohorts, such as

patients with head and neck cancer who experience qualitative changes in taste/smell because of chemotherapy and radiation therapy, we will need to account for possible long-COVID dysgeusia/anosmia confounding our qualitative outcomes. Unfortunately, we currently lack robust validated objective biomarkers and have limited tools to aid in diagnosis and to quantifiably measure the state and quality of anosmia and dysgeusia specific to long-COVID in clinical and research settings. More objective chemosensory (olfactory and taste) function testing tools are needed to provide more details about the changes of parosmia and dysgeusia throughout both the acute COVID-19 experience and long-COVID periods of recovery.

With 244 million global (45 million in the United States) COVID-19 infections reported to date by WHO<sup>16</sup> and an estimated 8% to 18% experiencing long-COVID related prolonged taste/smell dysfunction,<sup>10</sup> we can anticipate having more than 20 to 44 million survivors globally (3.6-8.1 million in the US) potentially seeking help to manage their possibly chronic taste/smell sensory disability. Has long-COVID created a gap in care that oral medicine specialists can help fill?

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