Article published online: 2023-06-19

Potential Impact of Long COVID-19 on Orthodontic Treatment

Thikriat Al-Jewair[1] Dimitrios Michelogiannakis[2] Edmund Khoo[2,3,4] Ryan Prevost[1]

[1] Department of Orthodontics, School of Dental Medicine, University at Buffalo, Buffalo, New York, United States
[2] Department of Orthodontics and Dentofacial Orthopedics, Eastman Institute for Oral Health, University of Rochester, New York, United States
[3] Department of Orthodontics and Oral Facial Genetics, Indiana University School of Dentistry, United States
[4] Department of General Dentistry, Eastman Institute for Oral Health, University of Rochester, New York, United States

Address for correspondence Thikriat Al-Jewair, DDS, MSc, MS, FRCD(C), 140 Squire Hall, Department of Orthodontics, School of Dental Medicine, University at Buffalo, 3435 Main Street, Buffalo NY 14214, United States (e-mail: thikriat@buffalo.edu).

Eur J Dent 2024;18:387–391.

Abstract

Pooled estimates indicate about 226 million individuals are currently experiencing or have experienced persistent symptoms from COVID-19. Long COVID-19 (LC) has been associated with a prolonged inflammatory and stress responses in affected individuals. Due to common pathways, LC could impact the biological mechanisms of orthodontic tooth movement, orthodontically-induced inflammatory root resorption and periodontal tissue response of patients undergoing orthodontic treatment. The authors of the present report discussed potential biological mechanisms through which LC may influence orthodontic treatment highlighting the need for further research in this area.

Keywords
- long COVID-19
- orthodontic tooth movement
- orthodontically-induced inflammatory root resorption

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) identified in 2019.[1] The global number of people infected by COVID-19 surpassed 526 million with a prevalence of 43%.[2] The COVID-19 infection leads to a variety of symptoms such as headache, fatigue, cough, shortness of breath, muscle and joint pain, altered taste and smell, cognitive impairment, and diarrhea; and may even lead to severe pneumonia and death especially in patients with underlying medical conditions.[3] The average recovery time from acute COVID-19 infection ranges between 2 and 3 weeks.[4] This is generally followed by a subacute phase that deals with symptoms that last between 4 and 12 weeks after the onset of illness.[5,6] Symptoms that persist after the acute and subacute infection phases (beyond 12 weeks up to an undefined period) lead to what is currently known as post-COVID-19 syndrome or long COVID-19 (LC).[7]

Symptoms of LC include anxiety, fatigue, myalgia, cognitive impairment, sleep disturbances, among others.[3,8] Fatigue and cognitive impairment have a lower incidence in children than adults.[9] Risk factors of LC include being female, older age, high body mass index, history of chronic respiratory disease, and having a severe reaction to COVID-19 during the acute phase.[10] In addition, the presence of more than five symptoms in the first week of acute infection was shown to be significantly associated with the development of LC, independent of the patient's age or sex.[11]

Pooled estimates indicate about 226 million individuals are currently experiencing or have experienced persistent symptoms from COVID-19.[2] A recent meta-analysis reported that 80% of people who suffered from COVID-19 experienced one or more long-term symptoms.[12] However, accurate reporting of the epidemiology of LC is restricted by several factors including inconsistencies in the diagnostic criteria, reporting systems, follow-up durations, and demographic

article published online
June 19, 2023

DOI https://doi.org/10.1055/s-0043-1768467.
ISSN 1305-7456.

© 2023. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

characteristics of the examined populations.[7] Nonetheless, the incidence of LC has been reported to range between 30 and 96% depending on the examination times after the acute infection.[7,13,14]

The pathophysiological mechanism for LC is poorly understood. However, a potential reason for persistent symptoms could be an overall hyperinflammatory response.[6] In particular, when a patient experiences fatigue due to LC it may persist because of direct viral encephalitis, neurological inflammation, hypoxia, and cerebral vascular disease.[9] From a mental health perspective, animal models and brain analyses of COVID-19 patients postmortem provided evidence that SARS-CoV-2 can also penetrate the blood–brain barrier.[15] This can then result in the brain triggering an immune response that releases interleukins (IL), tumor necrosis factor α (TNF-α), and nitric oxide.[15] In addition, hyperinflammatory state, oxidative stress, cytokine storm, and DNA damage have been hypothesized.[16] The LC can also be a sequalae of harboring the virus in tissue reservoirs across the body, leading to reactivation; there may be cross reactivity of COVID-19 antibodies with host proteins, leading to autoimmune problems; and there could be delayed viral clearance due to immune system exhaustion, an overall mitochondrial dysfunction, and alterations in the microbiome leading to long term health consequences.[6]

Various methods have been suggested for the diagnosis/detection of COVID-19 including routine clinical screening for the detection of symptoms and clinical manifestations, and confirmation with laboratory detection methods such as nucleic acid amplification test, real-time reverse transcription-polymerase chain reaction test, rapid antigen detection tests, serological techniques, and computed tomography scan.[17,18] However, accurate and early detection and identification of LC remain problematic, which highlights the need for developing new validated screening questionnaires and interviewing methods to identify persisting symptoms such as fatigue, mood and stress disorders, and other mental health conditions associated with LC.[19]

It can be a challenge to manage persistent LC symptoms; this is partly due to the overlap of persistent symptoms that could be a result of mental health problems from the pandemic socially or emotionally leading to fatigue, headache, and other symptoms.[20] Also, it can be a challenge to distinguish between the populations' baseline and their actual LC symptoms, especially for symptoms that present with relatively low prevalence.[21] Thus, it will be very important to consider patients' pre-COVID-19/baseline state.

LC in Orthodontic Populations

Orthodontic treatment (OT) is commonly performed in children, adolescents, and adults for the improvement of dentofacial esthetics, oral function, and occlusion.[22,23] Since OT and LC are prevalent in the general population (including both growing patients and adults), it is reasonable to assume that a growing number of individuals with LC are currently undergoing or will undergo OT. It has been reported that patients who experience mild or even asymptomatic COVID-19 infection exhibit a prolonged inflammatory and stress response even after 40 days postinfection.[24] In this regard, the authors of the present editorial speculate that the biology and outcomes of orthodontic tooth movement (OTM) might be altered in patients with LC compared with nonpreviously infected or fully recovered individuals. Several studies have assessed the disruption of OT during the COVID-19 pandemic and related lockdown.[25–27] These included the disruption of regular patient visits and management of orthodontic emergencies, extended treatment durations, and patient distress and decreased satisfaction with OT during the pandemic. Since it is likely that COVID-19 will continue to have an impact on patients' general and oral health in the foreseeable future, the next section aims to discuss the potential impact of LC on the biological mechanisms of OTM, orthodontically-induced inflammatory root resorption (OIIRR), and periodontal tissue response of patients undergoing OT.

Potential Impact of LC on OTM

Orthodontically applied forces on teeth create tensile and compressive strains on the surrounding periodontal tissues through a mechanism of mechanotransduction.[28] Specifically, force induced strains at the compression site of the periodontal ligament (PDL) lead to a constriction of the microvasculature (focal necrosis), which manifests histologically as an area of tissue hyalinization.[29] This results in the release of various proinflammatory cytokines including the receptor activator of nuclear factor kappa B ligand (RANKL), TNF-α, IL-1, IL-6, and other prostaglandins and lysosomal enzymes,[28,30] which mediate tissue resorption at the compression site of the PDL. On the other hand, strains at the tension side of the PDL increase blood flow and stimulate alveolar bone apposition by inducing osteoblast progenitor proliferation, reducing RANK signaling, and inhibiting osteoclast activity and formation.[31] In other words, OTM depends on coordinated bone and periodontal tissue remodeling, which is regulated by various biological processes including loading-induced fluid flow, induced hypoxia, and chemical and electrical signaling within the PDL.[31,32] This aseptic inflammatory cascade induced by orthodontic force application is regulated by cytokines, prostaglandins, osteoprotegerin, and other key factors,[31] which enables movement of teeth into the orthodontically-planned positions in patients with malocclusion who undergo OT. Control of the inflammatory process is crucial in patients undergoing OT as unregulated inflammation might lead to side effects including OIIRR, alveolar bone loss, and damage to the dental and paradental tissues.[31] Various factors such as systemic diseases, medications, nicotine, obesity, and stress may influence the inflammatory response to orthodontic force application,[33–37] indicating the need of potential patient counselling, close monitoring, and orthodontic plan/mechanotherapy adaptation in susceptible patient populations.

There has been no substantive research on the impact of LC on OTM. One of the possible routes on how it could affect OTM is via the use of medications to reduce inflammation. Patients with LC are often prescribed long-term anti-

inflammatory medications to counter the systemic inflammation. Corticosteroids may also be prescribed in varying durations and strengths.[38,39] The tooth movement pathway is reliant on inflammation, and multiple studies have shown that reducing or blocking inflammation either genetically or through pharmaceutical means can have a profound negative effect on the rate of OTM.[40,41] As such, patients who are on long-term anti-inflammatory drugs have a significant risk of reduced OTM,[42] and this would be an important factor for the orthodontist to take into consideration when formulating the appropriate treatment plan and creating realistic objectives and end-goals for the patient. Furthermore, LC has been associated with a prolonged inflammatory and stress response,[24] and it might affect periodontal tissue remodeling during OT altering the rate of OTM and increasing the risk of periodontal tissue destruction. The above-mentioned hypotheses focused on indirect relationships between LC and OTM. Direct association must not be excluded either. Due to common pathways, LC could impact the biological mechanisms of OTM. Further research is needed to validate these hypotheses.

Potential Impact of LC on OIIRR and Alveolar Bone Loss

OIIRR and alveolar bone loss are some possible side effects of OT. It has been shown that root resorption can be affected by the amount of orthodontic force, direction of force, and duration of OT.[43] It has also been reported that obesity, respiratory disease, infections, and chronic inflammation can increase the risk of root resorption.[44,45] For these reasons, patients suffering from LC may be at greater risk of OIIRR. At a cellular level, clastic cells such as osteoclasts and cementoclasts have both been implicated in the resorption of the external root surface. It has been demonstrated that there is a possible link between COVID-19 and inflammatory cytokines, especially IL-1, IL-6, and TNF-α which stimulate osteoclast activity, favoring bone resorption through the RANK/RANKL system. It has also been postulated that the COVID-19 virus may also act directly on bone resorptive units.[39] Whether these create a direct risk to OTM and related OIIRR is still not clear; however, the implications still need to be acknowledged.

Through these inflammatory and bone resorptive mechanisms, the risk of bone loss during OTM in patients with LC may potentially be higher. In addition, a dysfunction and alteration of the oral microbiome has been reported in patients with LC.[46] These patients had significantly increased populations of microbiota that induced inflammation, such as members of the genera Prevotella and Veillonella, which are bacterial species that produce lipopolysaccharides. This may also contribute to a greater risk of bone loss and periodontal disease.

Challenges and Future Research

Undoubtedly, the long-term impact of COVID-19 in the form of LC is still being studied in many fields of medicine and it is pertinent to understand its implications in dentistry and orthodontics. Potential research may include but not limited to retrospective data from orthodontic patients who have had COVID-19 infections and are still suffering from its prolonged state as LC including radiographs or other forms of imaging that may demonstrate impact on OIIRR and bone loss. Similar retrospective research may also be conducted to see if patients with LC who had undergone OT were subjected to longer treatment durations, poorer treatment outcomes, and poor oral hygiene. Furthermore, developing validated screening methods of LC and implementing them in the clinical orthodontic setting would be beneficial for the development of prospective clinical studies that assess the impact of LC on clinical orthodontic outcomes in patients undergoing OT. Such studies will help develop clinical protocols for the orthodontic management of patients with LC to ensure successful orthodontic outcomes while managing the risk of possible side effects.

Conclusion

The impact of LC on OTM and related parameters remains unclear. The authors of the present review discussed potential biological mechanisms through which LC may influence OTM, OIIRR, and periodontal tissue response to orthodontic force application highlighting the need of further research in this respect.

Funding
None.

Conflict of Interest
T. A.-J. reported the following roles: Chair role in ADEA Council of Advanced Education Programs. Site visitor role in Commission on Dental Accreditation. Scientific committee member role in American Academy of Dental Sleep Medicine and examiner for the American Board of Orthodontics. E. K. reported Consulting fees received from Verywell.com. E. K. also reported following roles: Committee member and partners in research sub-committee member role in American Association of Orthodontists, Council on Orthodontic Education (COE). Councilor role in ADEA Council on Sections. Site Visitor role in Commission on Dental Accreditation. R. P. reported following roles: Chair role in Wellness taskforce. President role in Orthodontics Interest Group. All other authors declare that they have no conflict of interest.

Acknowledgment
None.

References

1 Baig AM. Chronic COVID syndrome: need for an appropriate medical terminology for long-COVID and COVID long-haulers. J Med Virol 2021;93(05):2555–2556
2 Chen C, Haupert SR, Zimmermann L, et al. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. J Infect Dis 2022;226(09):1593–1607

3 Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med 2021;114(09):428–442
4 Burn E, Tebé C, Fernandez-Bertolin S, et al. The natural history of symptomatic COVID-19 during the first wave in Catalonia. Nat Commun 2021;12(01):777
5 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(04):601–615
6 Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. Clin Microbiol Infect 2022;28(05):657–666
7 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ 2021;374 (1648):n1648
8 Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: what is long-COVID and how should we manage it? Lung 2021;199(02):113–119
9 Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. Brain Behav Immun 2022;101:93–135
10 Nguyen NN, Hoang VT, Dao TL, Dudouet P, Eldin C, Gautret P. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review. Eur J Clin Microbiol Infect Dis 2022;41(04):515–545
11 Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med 2021;27(04):626–631
12 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-termeffects of COVID-19: a systematic review and meta-analysis. medRxiv 2021;2021.01.27.21250617
13 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270):220–232
14 Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2021;174(04):576–578
15 Bourmistrova NW, Solomon T, Braude P, Strawbridge R, Carter B. Long-term effects of COVID-19 on mental health: a systematic review. J Affect Disord 2022;299:118–125
16 Bektas A, Schurman SH, Franceschi C, Ferrucci L. A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? Immun Ageing 2020;17:23
17 Rai P, Kumar BK, Deekshit VK, Karunasagar I, Karunasagar I. Detection technologies and recent developments in the diagnosis of COVID-19 infection. Appl Microbiol Biotechnol 2021;105(02): 441–455
18 Chaimayo C, Kaewnaphan B, Tanlieng N, et al. Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand. Virol J 2020;17(01):177
19 Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and post-infective fatigue syndrome: a review. Open Forum Infect Dis 2021;8(10):ofab440
20 Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. J Infect 2022;84(02):158–170
21 Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens 2022;11 (02):269
22 Vulugundam S, Abreu LG, Bernabé E Is orthodontic treatment associated with changes in self-esteem during adolescence? A longitudinal study. J Orthod 2021;48(04):352–359
23 Horani S, El-Bialy T, Barmak AB, Rossouw PE, Michelogiannakis D. Changes in airway dimensions following non-extraction clear aligner therapy in adult patients with mild-to-moderate crowding. J Contemp Dent Pract 2021;22(03):224–230
24 Doykov I, Hällqvist J, Gilmour KC, Grandjean L, Mills K, Heywood WE. 'The long tail of Covid-19' - the detection of a prolonged inflammatory response after a SARS-CoV-2 infection in asymptomatic and mildly affected patients. F1000 Res 2020;9:1349
25 Suri S, Vandersluis YR, Kochhar AS, Bhasin R, Abdallah MN. Clinical orthodontic management during the COVID-19 pandemic. Angle Orthod 2020;90(04):473–484
26 Quan S, Guo Y, Zhou J, et al. Orthodontic emergencies and mental state of Chinese orthodontic patients during the COVID-19 pandemic. BMC Oral Health 2021;21(01):477
27 Dhanasekaran M, Shaga IB, Ponniah H, Sankaranarayanan P, Nagappan N, Parameswaran TM. The pandemic impact of COVID 19 on orthodontic practice: a cross sectional study. J Pharm Bioallied Sci 2021;13(Suppl 2):S1024–S1028
28 Wise GE, King GJ. Mechanisms of tooth eruption and orthodontic tooth movement. J Dent Res 2008;87(05):414–434
29 Murrell EF, Yen EH, Johnson RB. Vascular changes in the periodontal ligament after removal of orthodontic forces. Am J Orthod Dentofacial Orthop 1996;110(03):280–286
30 Yamaguchi M, Kasai K. Inflammation in periodontal tissues in response to mechanical forces. Arch Immunol Ther Exp (Warsz) 2005;53(05):388–398
31 Li Y, Jacox LA, Little SH, Ko CC. Orthodontic tooth movement: the biology and clinical implications. Kaohsiung J Med Sci 2018;34 (04):207–214
32 Meikle MC. The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt. Eur J Orthod 2006;28(03):221–240
33 Berry S, Javed F, Rossouw PE, Barmak AB, Kalogirou EM, Michelogiannakis D. Influence of thyroxine supplementation on orthodontically induced tooth movement and/or inflammatory root resorption: a systematic review. Orthod Craniofac Res 2021;24 (02):206–213
34 Michelogiannakis D, Rossouw PE, Al-Shammery D, et al. Influence of nicotine on orthodontic tooth movement: a systematic review of experimental studies in rats. Arch Oral Biol 2018; 93:66–73
35 Michelogiannakis D, Rossouw PE, Khan J, Akram Z, Menenakos E, Javed F. Influence of increased body mass index on orthodontic tooth movement and related parameters in children and adolescents: a systematic review of longitudinal controlled clinical studies. J Orthod 2019;46(04):323–334
36 Al-Shammery D, Michelogiannakis D, Rossouw E, Romanos GE, Javed F. Influence of psychological stress exposure on orthodontic therapy: a comprehensive review. J Investig Clin Dent 2019;10 (02):e12388
37 Almadih A, Al-Zayer M, Dabel S, et al. Orthodontic treatment consideration in diabetic patients. J Clin Med Res 2018;10(02): 77–81
38 Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med 2021;9(01): e8
39 Salvio G, Gianfelice C, Firmani F, Lunetti S, Balercia G, Giacchetti G. Bone metabolism in SARS-CoV-2 disease: possible osteoimmunology and gender implications. Clin Rev Bone Miner Metab 2020; 18(04):51–57
40 Chaushu S, Klein Y, Mandelboim O, Barenholz Y, Fleissig O. Immune changes induced by orthodontic forces: a critical review. J Dent Res 2022;101(01):11–20
41 Yamaguchi M, Fukasawa S. Is inflammation a friend or foe for orthodontic treatment?: inflammation in orthodontically induced inflammatory root resorption and accelerating tooth movement Int J Mol Sci 2021;22(05):2388
42 Arias OR, Marquez-Orozco MC. Aspirin, acetaminophen, and ibuprofen: their effects on orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2006;130(03):364–370

43 Weltman B, Vig KW, Fields HW, Shanker S, Kaizar EE. Root resorption associated with orthodontic tooth movement: a systematic review. Am J Orthod Dentofacial Orthop 2010;137(04): 462–476, discussion 12A
44 Saloom HF, Papageorgiou SN, Carpenter GH, Cobourne MT. Impact of obesity on orthodontic tooth movement in adolescents: a prospective clinical cohort study. J Dent Res 2017;96(05):547–554
45 McNab S, Battistutta D, Taverne A, Symons AL. External apical root resorption of posterior teeth in asthmatics after orthodontic treatment. Am J Orthod Dentofacial Orthop 1999;116(05): 545–551
46 Haran JP, Bradley E, Zeamer AL, et al. Inflammation-type dysbiosis of the oral microbiome associates with the duration of COVID-19 symptoms and long COVID. JCI Insight 2021;6(20):e152346