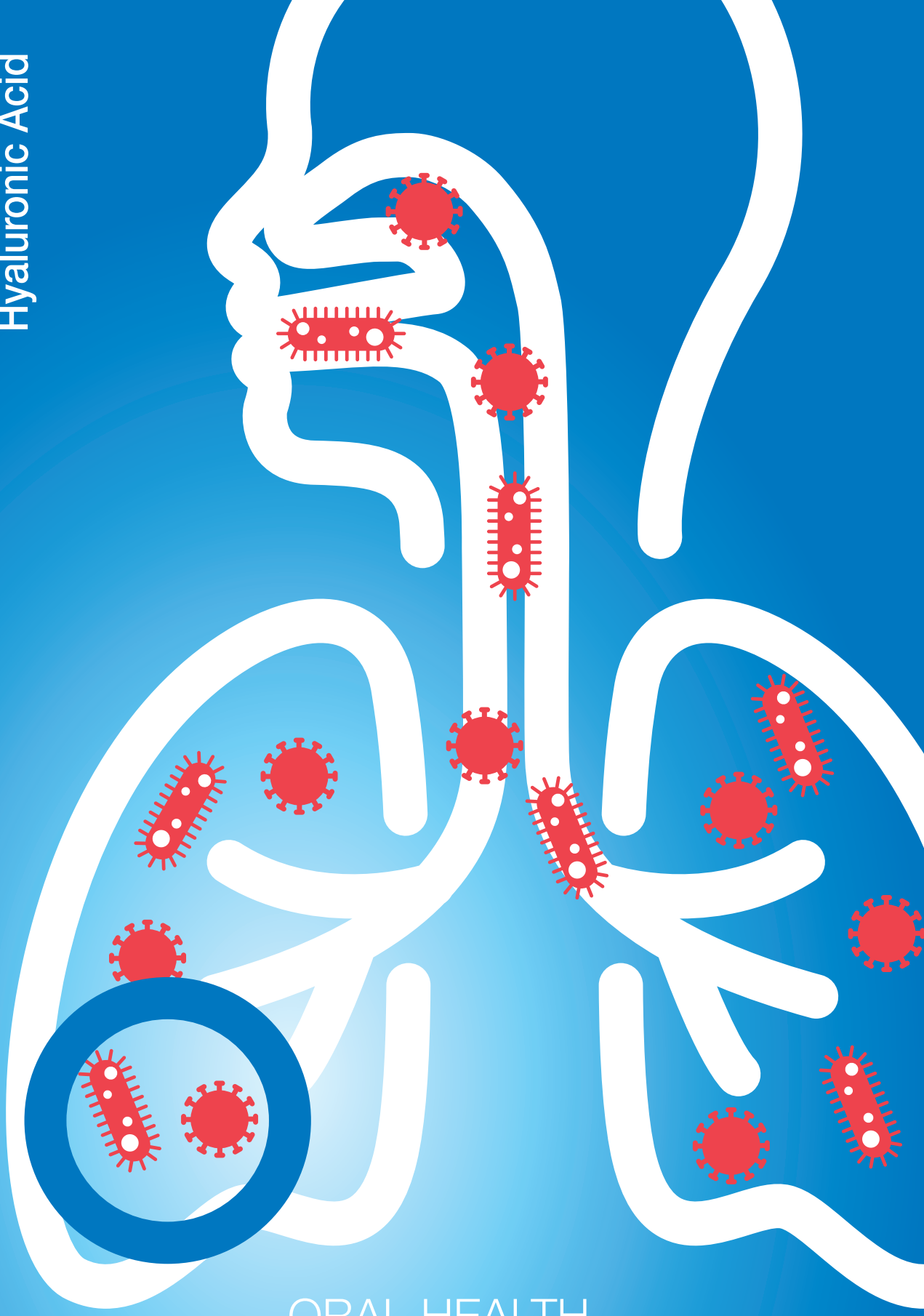
GENGIGEL®
Hyaluronic Acid



ORAL HEALTH & SARS-COV-2

FACT FILE

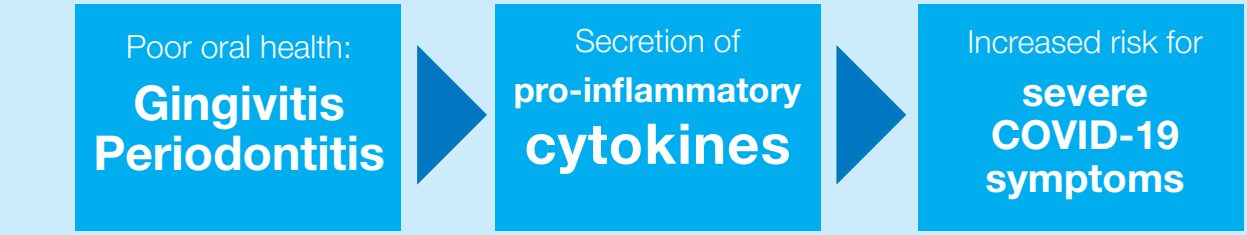
HOW CAN ORAL HEALTH AFFECT CORONAVIRUS 2 (SARS-COV-2) INFECTION?

The disease caused by the virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), COVID-19 disease, started at the end of 2019 in Wuhan, China. It spread throughout the globe at an alarming pace and became the first pandemic of the twenty-first century (Elibol 2021). Since the outbreak in December 2019, COVID-19 has affected >170,000,000 people (World Health Organization 2021a, data updated to June 2021, 1st). It is well-established that the disease can be asymptomatic or range from mild to very severe symptoms (Elibol 2021). Most patients with COVID-19 have a milder disease course; however, 20% of the patients develop severe disease with a mortality rate of 6% mostly associated with older age, systemic diseases, and immunosuppression (Kara et al. 2020). The oral cavity has been touted as one of the most significant points of entry of the novel coronavirus; its location in the confluence with the respiratory tract as well as the discharge of saliva predisposes it to be a major focus of attention with regard to SARS-CoV-2 (Gupta et al. 2021). In recent years, oral health has been shown to have a major impact on overall health. Several studies suggest that cytokines or microbial products released systemically in response to oral infection cause inflammation in distant organs, promoting the development of systemic diseases such as Alzheimer's disease, diabetes, atherosclerotic heart disease and cerebrovascular disease (Botros et al. 2020). Periodontitis, one of the most prevalent diseases worldwide that affects almost 10% of the global population (World Health Organization 2021b), is a polymicrobial infection and multifactorial disease and is characterized by chronic inflammation of the periodontium. If left untreated, it can lead to alveolar bone destruction and subsequent tooth loss, with periodontopathic bacteria inducing the production of pro-inflammatory cytokines (Takahashi et al. 2021). Periodontopathic bacteria are implicated in systemic inflammation, bacteraemia, pneumonia and even death. It is clear that bacterial superinfections are common in patients suffering from severe COVID-19, with more than 50% of deaths exhibiting bacterial superinfections (Sampson et al. 2020). A higher risk of mortality has been found in COVID-19 affected individuals with bleeding gums leading to the conclusion that mortality risk was higher in patients with periodontal disease (Larvin et al. 2020).

170 mln people has been affected by **COVID-19**

10% world population has periodontitis

HOW DOES PERIODONTITIS FAVOUR CORONAVIRUS 2 (SARS-COV-2) INFECTION?



During the initial phases of infection, the throat is a crucial region for viral replication (Sukumar and Tadepalli 2021). The entry is induced by the binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) as a host cellular receptor and is triggered by host cell proteases, such as transmembrane protease serine 2 (TMPRSS2) (Takahashi et al. 2021). Oral epithelial cells show higher expression of ACE2 and TMPRSS2. Periodontopathogens can also produce such proteases that may help activate the S-protein and further increase SARS-CoV-2 infectivity. Researchers hy-

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pothesized that the virus could enter the systemic circulation from periodontal pockets via gingival crevicular fluid (GCF) and then mix with saliva, or the systemic circulation via periodontal capillaries (Sukumar and Tadepalli 2021). Indeed, in a recent clinical trial, Gupta et al. assessed the presence of SARS-CoV-2 in GCF samples from patients with COVID-19 establishing GCF as a possible mode of transmission of SARS-CoV-2, also providing the first quantifiable evidence pointing toward a link between the COVID-19 infection and oral health (Gupta et al. 2021; Sukumar and Tadepalli 2021). Although severe respiratory disorders, such as acute respiratory distress syndrome (ARDS), are the leading cause of death in patients with COVID-19, cytokine storm rather than direct lung injury by SARS-CoV-2 is the major cause of ARDS (Takahashi et al. 2021). Earlier studies showed that serum pro-inflammatory cytokine levels in patients infected with SARS-CoV-2 were elevated, especially IFN-γ, IFNγ -induced protein 10, IL-1β, IL-6, IL-12, and MCP-1 (Sukumar and Tadepalli 2021). Periodontitis and poor oral hygiene disrupt the symbiotic relationships between oral microbes and can promote pro-inflammatory cytokine release. Bacteria in dysbiotic biofilms further stimulate cytokine release; these cytokines in GCF mix with saliva, and upon aspiration, may induce inflammation or infection within the lungs (Sukumar and Tadepalli 2021). A growing number of studies speculates that an increase in periodontopathic bacteria aggravates COVID-19 in relation to the mechanisms shown below:

- Periodontopathic bacteria promote SARS-CoV-2 infection by increasing the expression of ACE2.
- Promoted secretion of pro-inflammatory cytokines in the lower respiratory tract by stimulation with aspirated periodontopathic bacteria lead to COVID-19 aggravation.
- The protease of periodontopathic bacteria promotes SARS-CoV-2 infection by degrading the S protein of SARS-CoV-2 (Takahashi et al. 2021).

WHY RESORTING TO NON-DRUG TREATMENTS?

Over the past few years, it has become clear that oral health has a wide impact on overall health. Current studies suggest that the periodontal pocket epithelium may be a focal point of infection for SARS-CoV-2, and thus periodontal therapy could help minimize the systemic spread of viral pathogens (Bertolini et al. 2020; Fernandes Matuck et al. 2021). Improving oral hygiene may thus reduce oropharyngeal colonization and the risk of respiratory complications particularly in the elderly population and those in intensive care units (Botros et al. 2020). First-line treatments for periodontal diseases include non-pharmacological interventions such as effective daily oral hygiene with mouthwashes, fluoride-containing toothpastes and even plaque biofilm and tartar deposit removal through scaling and root planing (Wilder et al. 2016). Topical treatment of non-keratinized sulcular epithelium was found to deliver high concentrations of pharmacological agents to the periodontal tissue, gingiva, periodontal ligament, alveolar bone, and cementum (Casale et al. 2016). Recently, Sánchez-Fernández et al. showed that the topical application of High molecular weight hyaluronic acid (HMWHA) in patients with peri-implantitis reduced inflammation and peri-implant crevicular fluid concentrations of the pro-inflammatory cytokine IL-1β suggesting that HMWHA may be an effective therapeutic option to control the progression of this disease (Sánchez-Fernández et al. 2021). Hence, resorting to non-drug treatments might be a first line protection also against COVID-19 exacerbation.

WHY HIGH MOLECULAR WEIGHT HYALURONIC ACID?

HA is a natural and unbranched polymer belonging to a group of heteropolysaccharides called glycosaminoglycans (GAGs) diffused in the epithelial, connective and nervous tissues of vertebrates (Fraser et al. 1997). HA is major component of the ECM, particularly abundant during embryogenesis, in tissues undergoing rapid growth and development, during repair and regeneration, and in association with aggressive malignancies (Erickson and Stern 2012). HA has many different functions, including maintenance of tissue homeostasis and cell surface protection, but it is also involved in many physiological processes, such as cell attachment, migration and proliferation, wound healing, and regulation of immune response and inflammation (Kavasi et al. 2017). High molecular weight hyaluronic acid is deposited in normal tissues and interacts with other components of the ECM to control its structural organization and signaling. In addition, endogenous HMWHA possesses enhanced anti-angiogenic, anti-inflammatory and immunosuppressive properties (Kavasi et al. 2017). The amphophilic nature of HMWHA allows this molecule to trap large amounts of water while binding to hydrophobic molecules such as cell membrane lipids. This property is relevant to the control of hydration and helps to delay the passage of viruses and bacteria through the hyaluronan-rich pericellular zone, as well as during inflammatory processes (Chen and Abatangelo 1999). Clinical studies have shown that HA accelerates the healing of various types of wounds, including burns, epithelial surgical wounds, and chronic wounds (Shaharudin and Aziz 2016).

Why Gengigel®?

Gengigel® is a specific and innovative treatment for gingivitis and periodontitis that relies on the action of its main component, HMWHA to make the product strongly bioadhesive, an effect that may be enhanced by using a calibrated mixture of additional glycopolymers. Because of its adhesive properties, Gengigel® sticks to the oral mucosa long enough to promote the activation of physiological tissue repair processes which improve the healing response and reduce healing time. In addition, the presence of high molecular weight hyaluronic acid helps Gengigel® maintain the balance of extracellular fluids and promotes the resorption of oedema in inflammatory conditions, rapidly reducing the associated pain. Last but not least, it protects the oral mucosa by preserving the micro-environment of the mucosal surface and by regularizing the growth of bacterial flora. The evidence on Gengigel® includes clinical data from high-quality prospective, comparative studies (Polepalle et al. 2015; Gupta 2017; Al-Shammari et al. 2018). The studies covered different Gengigel® indications, including treatment of clinical signs associated with periodontal disease or gingival inflammation following surgical periodontal therapy. In all cases, patients were treated with the gel formulation, either in a single application at the time of surgery, or with multiple applications following periodontal surgery/treatment. Gengigel® proved to be an effective treatment in controlling the inflammatory process and gingival bleeding at various stages of periodontal disease.

REFERENCES

Al-Shammari NM, Shafshak SM, Ali MS. Effect of 0.8% Hyaluronic Acid in Conventional Treatment of Moderate to Severe Chronic Periodontitis. J Contemp Dent Pract 2018;19:527–534.

Bertolini M, Pita A, Koo S, et al. Periodontal Disease in the COVID-19 Era: Potential Reservoir and Increased Risk for SARS-CoV-2. Pesqui Bras Odontopediatria Clín Integr 2020;20:e0134.

Botros N, Iyer P, Ojcius DM. Is there an association between oral health and severity of COVID-19 complications? Biomedical Journal 2020;43:325–327.

Casale M, Moffa A, Vella P, et al. Hyaluronic acid: Perspectives in dentistry. A systematic review. Int J Immunopathol Pharmacol 2016;29:572–582.

Chen WYJ, Abatangelo G. Functions of hyaluronan in wound repair. Wound Repair and Regeneration 1999;7:79–89.

Elibol E. Otolaryngological symptoms in COVID-19. Eur Arch Otorhinolaryngol 2021;278:1233–1236.

Erickson M, Stern R. Chain Gangs: New Aspects of Hyaluronan Metabolism. Biochemistry Research International 2012;2012:1–9.

Fernandes Matuck B, Dolhnikoff M, Maia GVA, et al. Periodontal tissues are targets for Sars-Cov-2: a post-mortem study. Journal of Oral Microbiology 2021;13:1848135.

Fraser JRE, Laurent TC, Laurent UBG. Hyaluronan: its nature, distribution, functions and turnover. Journal of Internal Medicine 1997;242:27–33.

Gupta S, Kediege SD, Gupta A, Jain K. Evaluation of Gengigel® Application in the Management of Furcation with Coronally Advanced Flap through Surgical Re-Entry-A Split Mouth Clinical Study. J Clin Diagn Res. 2017;11:ZC27-ZC32.

Gupta S, Mohindra R, Chauhan PK, et al. SARS-CoV-2 Detection in Gingival Crevicular Fluid. J Dent Res 2021;100:187–193.

Kara C, Çelen K, Dede FÖ, et al. Is periodontal disease a risk factor for developing severe Covid-19 infection? The potential role of Galectin-3. Exp Biol Med (Maywood) 2020:245:1425–1427.

Kavasi R-M, Berdiaki A, Spyridaki I, et al. HA metabolism in skin homeostasis and inflammatory disease. Food and Chemical Toxicology 2017;101:128–138.

Larvin H, Wilmott S, Wu J, Kang J. The Impact of Periodontal Disease on Hospital Admission and Mortality During COVID-19 Pandemic. Front Med 2020;7:604980.

Polepalle T, Srinivas M, Swamy N, et al. Local delivery of hyaluronan 0.8% as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A clinical and microbiological study. J Indian Soc Periodontol 2015;19:37.

Sampson V, Kamona N, Sampson A. Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? Br Dent J 2020;228:971–975.

Sánchez-Fernández E, Magán-Fernández A, O'Valle F, et al. Hyaluronic acid reduces inflammation and crevicular fluid IL-1β concentrations in peri-implantitis: a randomized controlled clinical trial. J Periodontal Implant Sci 2021;51:63.

Shaharudin A, Aziz Z. Effectiveness of hyaluronic acid and its derivatives on chronic wounds: a systematic review. Journal of Wound Care 2016;25:585–592.

Sukumar K, Tadepalli A. Nexus between COVID-19 and periodontal disease. J Int Med Res 2021;49:030006052110026.

Takahashi Y, Watanabe N, Kamio N, et al. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. J Oral Sci 2021;63:1–3.

World Health Organization (2021a) Health emergency dashboard WHO (COVID-19) homepage. https://covid19.who.int/. Checked on June 1st, 2021.

World Health Organization (2021b) Oral health. https://www.who.int/news-room/fact-sheets/detail/oral-health. Checked on June 1st, 2021.

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