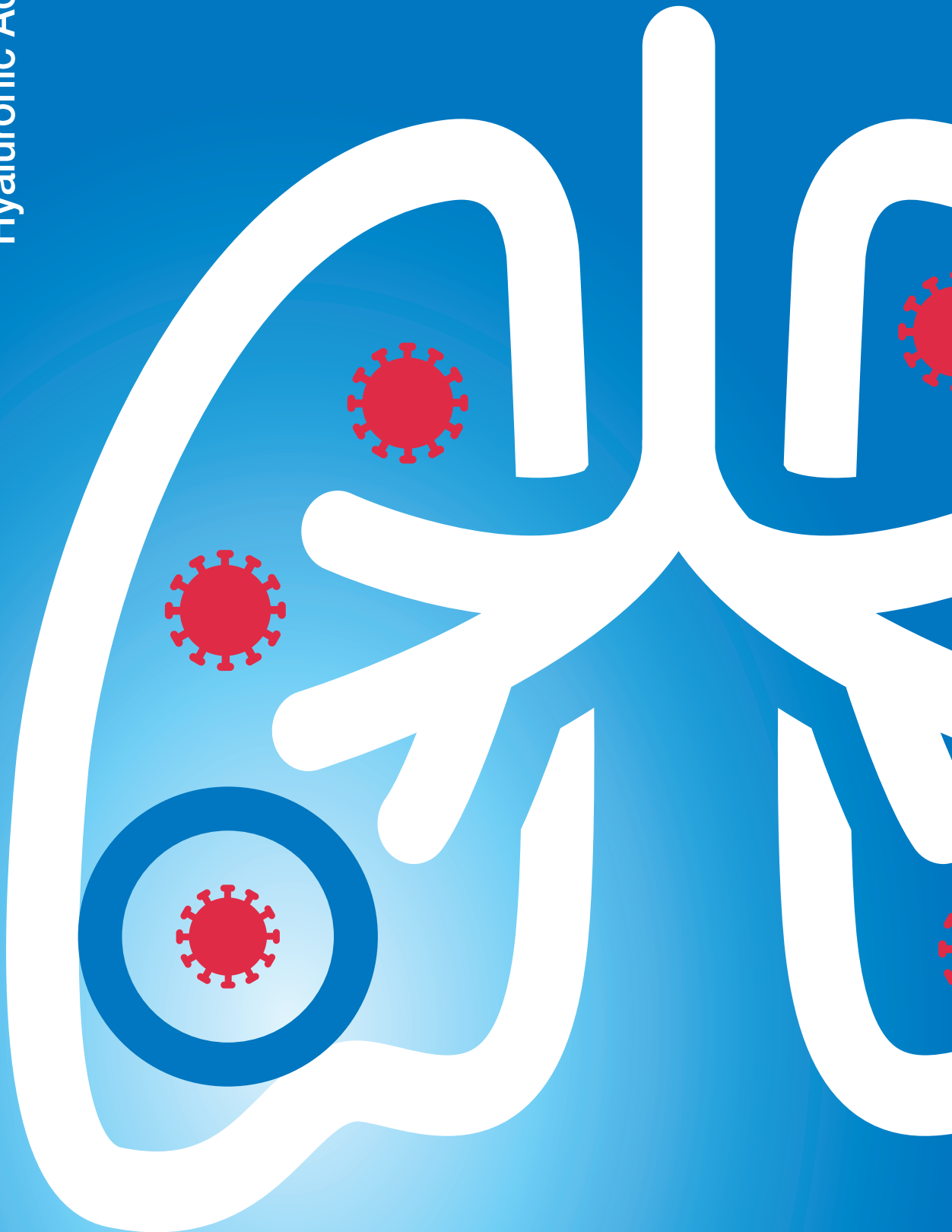


GENGIGEL[®]

Hyaluronic Acid



ORAL HEALTH
& SYSTEMIC DISEASES

FACT FILE

HOW CAN ORAL HEALTH AFFECT SYSTEMIC HEALTH?

Periodontal diseases are caused by pathogenic microbiota (pathobionts) in the dental plaque formed on the hard root surface adjacent to the supporting soft tissues and **are affecting millions of people worldwide** (Kassebaum, 2017). **A variety of microorganisms, including bacteria, archaea, protozoa, fungi and viruses is found in the oral cavity** (Wade, 2013; He, 2015). Dental plaque is a complex oral biofilm of a microbial community where bacteria are the main residents, with 700 different bacterial species inhabiting the oral cavity. The oral cavity hosts also many viruses thought to be disease-associated (such as herpes simplex or human papillomavirus).

Many of these viruses are bacteriophages that specifically infect bacteria and exploit these latter to be spread into the organism (Pinto, 2016). **Periodontitis not only has local effects on the dentition and tooth-supporting tissues, but also may impact a number of systemic conditions.**



While the very nature of multifactorial, chronic diseases has made it difficult to establish a definitive causal role for periodontal pathobionts in systemic infection, the body of literature supporting an aetiopathological role for these organisms is too substantial to be ignored as merely coincidental. **The focal infection theory posits that migration of microbial pathogens through the blood circulation expand their pathogenicity and affect in different manner the targeted tissues, as happens in severe sepsis** (Kumar, 2017). Some examples of diseases that have been attributed to focal sepsis are respiratory tract diseases such as **aspiration pneumonia and chronic obstructive pulmonary disease (COPD), herpes simplex, varicella zoster, mononucleosis, cytomegalovirus, enteroviruses, rubella, rubella, mumps, and human papillomavirus** (Borgnakke, 2015; Kumar, 2017; Clarkson, 2017; Bourgeois, 2019). **Aspiration pneumonia is an inflammatory condition of the lung paren-**

chyma, usually initiated by the introduction of bacteria or viruses into the lower airway. This disease is particularly prevalent in the elderly, especially those in institutions such as nursing homes, and in those with several important risk factors. Elderly may lack dexterity and vision to perform correct oral hygiene without assistance. Consequently, a substantial bacterial load in elder persons' mouths is often present and become a considerable risk for infections and periodontal diseases. **The incidence of community-acquired pneumonia requiring hospitalisation is 1.96 to 10 times higher amongst elderly nursing home residents than community-dwelling elderly people** (Liu, 2018). The chronic obstructive pulmonary disease is an inflammatory condition with progressive deterioration of pulmonary function and increasing airway obstruction (Moghadam, 2017). **Prevalence studies suggest that COPD affects upwards of 384 million people and is the third leading cause of death worldwide** (Burge, 2020).

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HOW DOES PERIODONTITIS FAVOR THE ONSET OF RESPIRATORY TRACT DISEASES?

The lower respiratory tract is protected from microorganisms by the cough reflex, ciliary movement of the lining cells, and innate immune mediators, however, impairment of these defences can result even in nosocomial systemic diseases. Periodontal pathogens, for example, *P. gingivalis*, *F. nucleatum*, *Prevotella oralis*, *Campylobacter gracilis*, *Fusobacterium necrophorum* and *Aggregatibacter actinomycetemcomitans*, have been identified in lung aspirates of subjects with pneumonia (Kumar,

2017). Aspiration pneumonia is caused by foreign material descending into the bronchial tree and the lung alveoli, which, when originating from the oral cavity, may most commonly consist of food debris, saliva, biofilm, or a combination of these. Healthy adults may also aspirate some oropharyngeal secretions during sleep, but with coughing and ciliary transport as well as intact immune mechanisms, the airways are protected. With age and functional decline, these defence mechanisms

>>> HOW DOES PERIODONTITIS FAVOR THE ONSET OF RESPIRATORY TRACT DISEASES?

become impaired, which renders fragile elders more vulnerable to developing aspiration pneumonia (Müller, 2015). A study of 80 year old Japanese adults found that the adjusted mortality due to aspiration pneumonia, was 3.9 times higher in persons with 10 or more teeth with a probing depth exceeding 4 mm (i.e. with periodontal pockets) than in those without periodontal pockets (Awano, 2008). A bench of studies have suggested that oral bacteria and viruses may cause respiratory diseases when are aspirated from oral reservoirs into the lower respiratory tract or when salivary enzymes released during chronic periodontal disease modify the oral mucosa and permit increased adhesion of respiratory pathogens and release of circulating pro-inflammatory cytokines (Paju, 2007; Linden, 2013). Periodontal pathogens

and inflammatory cytokines might therefore induce systemic inflammation that can take part in the pathogenesis of chronic obstructive pulmonary diseases. This process takes place already in the lungs, initiating pulmonary inflammation. Periodontal bacteria may also move into gingival vasculature through micro-ulcerations in the epithelium, permitting hematogenous dispersion of bacteria and inflammatory mediators (Hasegawa, 2014). Bacteremia of oral origin triggers and accelerates acute response and reactive oxygen species and cytokines released by systemic neutrophils (Usher, 2013). Hence, local cytokines and other active molecules produced by periodontal inflammation penetrate into the systemic circulation with ensuing inflammatory burden at distant sites.

WHY RESORTING TO NON-DRUG TREATMENTS?

Dealing with systemic diseases implies that many districts of the organism are involved and different treatment options might be necessary. The pharmacological treatments are held to attenuate symptoms and to reduce the progression of a specific disease thus, first-line treatments for systemic diseases are corticosteroids and non-steroidal anti-inflammatory drugs but may also include other immunosuppressive agents, intravenous immunoglobulin and plasmapheresis based on the variety of districts involved (Kasperkiewicz, 2017). Therefore, a crucial step in the systemic intervention is to recognize the aetiopathogenesis of the infection. A well established role in the onset of systemic diseases is given to the oral cavity microbiome, that can become a pathogen-rich ecosystem (Socransky, 2005). Hence, it is fundamental to maintain an



adequate oral hygiene and to promptly address periodontal diseases when occurring. The first-line treatments for periodontal diseases are non pharmacological interventions such as effective daily oral hygiene with mouthwashes, fluoride-containing toothpastes and even plaque biofilm and tartar deposits removal through scaling and root planing (Wilder, 2016). These activities increase clinical attachment levels, reduce probing depths and bleeding on probing, nevertheless, the effectiveness of the treatments is dependent on the successful eradication of bacteria residing in deep pockets. Hence, resorting to non drug treatments and rather creating a barrier to prevent the entrance of pathogens through the oral cavity might be the very first line treatment for systemic diseases.

WHY HIGH MOLECULAR WEIGHT HYALURONIC ACID?

Hyaluronic acid (HA), or hyaluronan, is a naturally occurring non-sulphated, linear polymer composed of repeating units of glucuronic acid and N-acetylglucosamine (Chen, 1999; Kavasi, 2017). HA levels are particularly high in the extracellular matrix (ECM) of tissues undergoing rapid turnover, where regeneration and repair are occurring, such as the oral mucosa (Valachová, 2016). HA has many different functions, including maintenance of tissue homeostasis and cell surface protection, but is also involved in many physiological processes, such as cell attachment, migration and proliferation, embryogenesis, wound healing, and regulation of immune response and inflammation (Kavasi, 2017). High molecular weight hyaluronic acid (HMWHA) is deposited in normal tissues and interacts with other components of the ECM to control the structural organization of ECM and signalling. In general, endogenous HMWHA possesses



enhanced anti-angiogenic, anti-inflammatory and immunosuppressive properties (Kavasi, 2017). HMWHA has a highly complex secondary and tertiary structure in aqueous solution; its amphophilic nature allows this molecule to trap large quantities of water and, at the same time, to bond to hydrophobic molecules such as the lipidic substances of cell membranes. **This property is relevant in controlling hydration and contributes to retardation of viral and bacterial passage through the hyaluronan-rich pericellular zone, as well as during periods of change when HA levels are elevated, during inflammatory processes** (Chen, 1999). Clinical studies have shown that HA accelerates the healing of various types of wounds, including burns, epithelial surgical wounds, and chronic wounds (Shaharudin, 2016).

Why Gengigel®?

The devices belonging to the Gengigel® family achieve their expected performance due to the action of its principal component HMWHA, which makes Gengigel® strongly bioadhesive, an effect that may be enhanced by using a calibrated mixture of some ancillary glycopolymers. **In this way Gengigel® adheres to the oral mucosa for long enough to promote the activation of the physiological tissue repair process, improving the healing response and reducing healing time.** Further, by maintaining the balance of extracellular fluids, again because of the presence of HMWHA, **it promotes resorption of oedema in inflammatory states, rapidly reducing the associated pain. Last but not least, it protects the oral mucosa from harmful agents, preserving the micro-environment of the mucosal surface, and regularizing the growth of bacterial flora.** Clinical evidence concerning

Gengigel® includes clinical data from prospective, comparative studies, which can thus be considered to be of high quality (Gupta, 2017; Al-Shammari, 2018; Polepalle, 2015). The studies covered different Gengigel® indications, including management of clinical signs associated with periodontal disease or gingival inflammation following surgical periodontal therapy. In all cases, the patients were treated with the gel formulation, either in a single application given at the time of surgery, or with multiple applications following the initial periodontal surgery/treatment. Depending on the study, the follow-up period varied between 7 days and 6 months, providing sound clinical data on the effectiveness of long-term treatment with Gengigel®.



REFERENCES

- Al-Shammari NM; Shafshak SM; Ali MS. Effect of 0.8% Hyaluronic Acid in Conventional Treatment of Moderate to Severe Chronic Periodontitis. *The journal of contemporary dental practice*. 2018;19:527-534.
- Awano S, Ansai T, Takata Y, et al. Oral health and mortality risk from pneumonia in the elderly. *J Dent Res*. 2008;87:334-339.
- Borgnakke WS. Does Treatment of Periodontal Disease Influence Systemic Disease?. *Dent Clin North Am*. 2015;59:885-917.
- Bourgeois D, Inquimbert C, Ottolenghi L, Carrouel F. Periodontal Pathogens as Risk Factors of Cardiovascular Diseases, Diabetes, Rheumatoid Arthritis, Cancer, and Chronic Obstructive Pulmonary Disease-Is There Cause for Consideration?. *Microorganisms*. 2019;7:424.
- Burge AT, Cox NS, Abramson MJ, Holland AE. Interventions for promoting physical activity in people with chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2020;4:CD012626.
- Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. *Wound Repair Regen*. 1999;7:79-89.
- Clarkson E, Mashkoor F, Abdulateef S. Oral Viral Infections: Diagnosis and Management. *Dent Clin North Am*. 2017;61:351-363.
- 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.
- Hasegawa A, Sato T, Hoshikawa Y, et al. Detection and identification of oral anaerobes in intraoperative bronchial fluids of patients with pulmonary carcinoma. *Microbiol Immunol*. 2014;58:375-381.
- He J, Li Y, Cao Y, Xue J, Zhou X. The oral microbiome diversity and its relation to human diseases. *Folia Microbiol (Praha)*. 2015;60:69-80.
- Kasperkiewicz M, Ellebrecht CT, Takahashi H, et al. Pemphigus. *Nat Rev Dis Primers*. 2017;3:17026.
- Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W; GBD 2015 Oral Health Collaborators. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. *J Dent Res*. 2017;96:380-387.
- Kavasi RM, Berdiaki A, Spyridaki I, Corsini E, Tsatsakis A, Tzanakakis G, Nikitovic D. HA metabolism in skin homeostasis and inflammatory disease. *Food Chem Toxicol*. 2017;101:128-138.
- Kumar PS. From focal sepsis to periodontal medicine: a century of exploring the role of the oral microbiome in systemic disease. *J Physiol*. 2017;595:465-476.
- Linden GJ, Herzberg MC; Working group 4 of joint EFP/AAP workshop. Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Clin Periodontol*. 2013;40 Suppl 14:S20-S23.
- Liu C, Cao Y, Lin J, Ng L, Needleman I, Walsh T, Li C. Oral care measures for preventing nursing home-acquired pneumonia. *Cochrane Database of Systematic Reviews* 2018, Issue 9.
- Moghadam SA, Shirzaiy M, Risbaf S. The Associations between Periodontitis and Respiratory Disease. *J Nepal Health Res Counc*. 2017;15:1-6.
- Müller F. Oral hygiene reduces the mortality from aspiration pneumonia in frail elders. *J Dent Res*. 2015;94:14S-16S.
- Paju S, Scannapieco FA. Oral biofilms, periodontitis, and pulmonary infections. *Oral Dis*. 2007;13:508-512.
- Pinto G, Silva MD, Peddey M, Sillankorva S, Azeredo J. The role of bacteriophages in periodontal health and disease. *Future Microbiol*. 2016;11:1359-1369.
- Polepalle, T; Srinivas, M; Swamy, N; Aluru, S; Chakrapani, S; Chowdary, BA. 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;19:37-42.
- Shaharudin A, Aziz Z. Effectiveness of hyaluronic acid and its derivatives on chronic wounds: a systematic review. *J Wound Care*. 2016;25:585-592.
- Socransky SS & Haffajee AD. Periodontal microbial ecology. *Periodontol 2000*. 2005;38: 135-187.
- Usher AK, Stockley RA. The link between chronic periodontitis and COPD: a common role for the neutrophil?. *BMC Med*. 2013;11:241.
- Valachová K, Volpi N, Stern R, Soltes L. Hyaluronan in Medical Practice. *Curr Med Chem*. 2016;23:3607-3617.
- Wade WG. The oral microbiome in health and disease. *Pharmacol Res*. 2013;69:137-143.
- Wilder RS, Bray KS. Improving periodontal outcomes: merging clinical and behavioral science. *Periodontol*. 2000. 2016;71:65-81.



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