

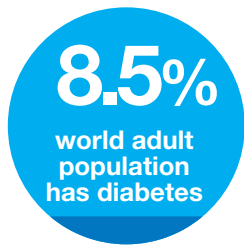
GENGIGEL[®]
Hyaluronic Acid



ORAL HEALTH & DIABETES

FACT FILE

FACTS & FIGURES ABOUT DIABETES



Diabetes is described as a serious, chronic disease that occurs either when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces (WHO Report, 2016).

HOW CAN DIABETES AFFECT ORAL HEALTH?

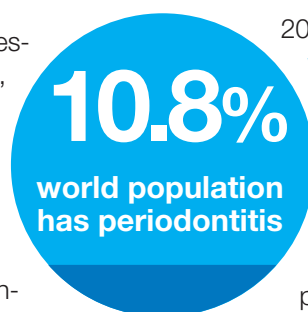
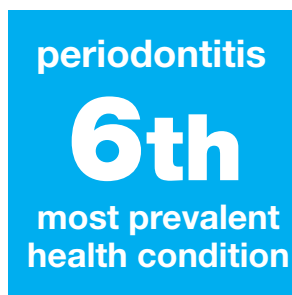
Diabetes is one of the major risk factors for periodontitis (Genco, 2013). Individuals with diabetes are more likely to have periodontitis of increased severity when their diabetes is uncontrolled or poorly controlled. In this sense, periodontitis is nowadays considered as a complication of diabetes (Loe, 1993).

If **prediabetes** and **early diabetes** were treated effectively, then the progression of hyperglycemia could be prevented or delayed, which may eventually lead to reduced progression of periodontitis (Phillips, 2014).

Aging is associated both with a progressive decline in glucose tolerance and coincidentally with increasing prevalence of periodontitis. Increasing life expectancy predicts an increasing burden of periodontal diseases worldwide, with considerable variations between different populations.

In 2010, severe periodontitis was the world's 6th most prevalent health condition, affecting approximately 10.8% (743 million) of people worldwide.

Between 1990 and 2010, the global age-standardized prevalence of severe periodontitis was estimated to be 11.2% (Kassebaum, 2014).



Both **periodontitis** and **diabetes** are **chronic, inflammation-driven diseases** that often occur in the same individuals and also mutually and adversely affect each other. In especially susceptible

individuals, bacterial challenge, particularly from the subgingival plaque, **induces breakdown of the periodontal soft and hard tissues** (Bartold, 2013), and these subgingival plaque bacteria are also associated with **inflammation and insulin resistance** (Borgnakke, 2014; Demmer, 2017).

Conversely, **hyperglycemia** may influence the subgingival microbiome with subsequent impact on the severity of **periodontitis** (Timonen, 2011). Both diabetes and periodontitis are associated with enhanced inflammation and impaired immunological responses (Calle, 2012; Knight, 2016).

Elevated levels of systemic inflammatory cytokines, such as interleukin-1beta and interleukin-6, and the acute-phase inflammatory marker, C-reactive protein, are consistently observed in type diabetes 2 as well as in periodontitis (Liu, 2016; Polepalle, 2015). In each case, a systemic inflammatory susceptibility is observed, eventually with an augmented, even though potentially subclinical, responsiveness

to inflammatory stimuli. The increase in systemic markers of inflammation in subjects with uncontrolled diabetes is accompanied by a local proinflammatory environment in the gingiva (Duarte, 2014).

Uncontrolled diabetes influences the expression of tissue-degrading enzymes in the inflamed gingiva, leading to up-regulation of the ratio between metalloproteinase and their inhibitors (Bastos, 2017; Gupta, 2016).

Chronicity of inflammation presents the strongest plausibility for detrimental effects of deteriorating inflammatory events that could also link periodontal disease to diabetes. In mechanisms underlying the relationship between chronic inflammation in diabetes and the link to chronic periodontitis, the cells and mediators of the immune system play a central role (Hasturk, 2015; Sonnenschein, 2015).

GOOD TO KNOW

For glycated hemoglobin, the thresholds for increased risk of diabetes, also known as prediabetes, are set at 5.7% and 6.4%, with diabetes defined to be present at a level of $\geq 6.5\%$ (47.5 mmol/mol) (ADA, 2017). The diabetes risk increases continuously with glycemic measures, such as glycated hemoglobin, and becomes disproportionately greater at the higher end of the range (Kocher, 2018).

WHY RESORTING TO NON-DRUG TREATMENTS?

In patients with chronic periodontitis and diabetes, scaling and root planing is an effective treatment for reducing periodontal probing depth and improving the clinical attachment level, irrespective of metabolic control during a short duration of follow-up. Resolution of pockets is independent of metabolic control in the short term. **Adjuvant systemic administration of antibiotic drugs improves pocket closure, but not attachment gain, in patients with diabetes.** Any decision to prescribe antibiotics depends upon the severity of periodontal destruction and the inflammatory status, rather than metabolic control. The prescription of adjunctive systemic antibiotics must take into consideration whether the clinical



benefit of marginally more periodontal probing depth reduction outweighs the potential side effects. **Adverse reactions can, in fact, occur in patients with sensitivity to a particular agent.** Furthermore, **antibiotics disrupt the normal flora in other parts of the body and are thus commonly associated with diarrhoea and vaginal candidiasis.** The decision of using antibiotics should therefore be based on individual periodontal destruction severity and be restricted to the most severe cases. This is in line with current recommendations for treatment of patients with chronic periodontitis (Keestra, 2015; Harks, 2015; Smiley, 2015).

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 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). High molecular weight hyaluronic acid (HMWHA) is a linear molecule with 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, **high molecular weight hyaluronic acid**, (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 high molecular weight hyaluronic acid, **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. Furthermore, several studies had a split-mouth design, which facilitated their interpretation by minimizing the effects of inter-patient variability. 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®.

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