

GENGIGEL[®]
Hyaluronic Acid



ORAL HEALTH &
HORMONAL GUM DISEASES
FACT FILE

HOW CAN HORMONES AFFECT ORAL HEALTH?

Oral conditions remain a major and growing global public health challenge. The Global Burden of Disease (GBD) 2015 study reported that the number of people with untreated oral conditions reached 3.5 billion in 2015 and this number is set to increase considerably due to the lifestyle and diet habits, furthermore in particular, it appears that **severe periodontal disease affected 538 million people** (Kassebaum, 2017). **The bulletin of the World Health Organization reported that most children and adolescents worldwide have signs of gingivitis and about 2% of youth is affected by aggressive periodon-**

**AGGRESSIVE
PERIODONTITIS
IN 2%
YOUTH**

titis (Petersen, 2005). Recently, a Finnish report showed that **among 15- to 16-year-old adolescents the prevalence of initial or early periodontitis is between 10% and 15%** (Heikkinen, 2019). Risk factors that have been suggested to periodontitis among children and adolescents include, for example, social and psychological factors, periodontopathic bacteria, diabetes mellitus, and smoking (Heikkinen, 2019). However, the accrual of a myriad of observations has been suggesting a connection between androgens, estrogens and progestins and

**UP TO
15%
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IN 15-16
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the functional milieu of the oral cavity. More specifically, research into the relationship between gonadal hormones and periodontal tissues has established a significant link to both normal function and pathophysiology of disease. Although research suggests that all four tissues of the periodontium are modulated by androgens, estrogens and progestins, the gingiva has been extensively studied and is indeed responsive to steroid sex hormones. It has been hypothesized that the incidence and severity of gingivitis in childhood is influenced by plaque levels, dental caries, mouth breathing, crowding of the teeth, tooth eruption and puberty (Mariotti, 2013).

HOW DOES HORMONES FAVOR THE ONSET OF PERIODONTITIS?

Several tissues, such as periodontal tissue, are hormone-sensitive for the presence of sex steroid hormone receptors, named estrophiles. Long ago studies brought evidence for the expression of specific steroid hormone receptors for estrogens (Vitek, 1982), androgens (Vitek, 1985) and progestins (Mohamed, 1974) in periodontal tissues (Elattar, 1974; Jafri, 2015). During periods of gingival inflammation, the number of gingival estrogen receptors is elevated approximately 10-fold (Staffolani 1989). To date, the specific relationship of sex steroid hormones with periodontal endocrinopathies are still debated. **The most prominent explanations for the significance of hormone action in the periodontium have dealt with the effect of hormones on microbial organisms, on the vasculature** (i.e. swelling of endothelial cells and pericytes of the venules, formation of microthrombi, enhanced vascular permeability and vascular proliferation), **on the immune system and on specific cells in the periodontium** (Marriotti, 2013; Krejci, 2002). Progesterone in particular has been shown to stimulate the production of the inflammatory mediator prostaglandin E2 and to enhance the accumulation and chemotaxis of polymorphonuclear leukocytes in the gingival sulcus, moreover, it downregulates IL-6 production in human gingival fibroblasts up to 50% compared to control values (Markou, 2009). The response of the periodontium in disease is probably not a single mechanism but rather multifactorial (Mariotti,

2013). Gingivitis is considered to be primarily a microbial disease that can be modulated by different systemic and environmental factors, however speculative interpretations support a transient increase in a specific microorganism during puberty or pregnancy. Clinical evidences showed that inflammatory variations observed during puberty in women have been also associated to the effect of progesterone on number and vascular permeability of the vessels. Specifically, **it is very likely that estrogens, and not progestins, are responsible for the changes occurring to periodontal blood vessels** (Mariotti, 1994; Kumar, 2013). In the periodontium, sex steroid hormones exert their effects in the endothelium, gingival epithelium and connective tissue cells found in the gingiva, periodontal ligament, bone and cementum, as well as in cells from the immune system. Generally, at times of significant hormone fluctuations, these periodontal cells become reactive. Hence, **during puberty, the protective nature of sex steroid hormones becomes an acute inflammatory process**. More specifically, the intensified inflammatory response in the periodontium is necessary to protect both the local (i.e. periodontal attachment) and systemic (i.e. toxic sepsis) environments by destroying, diluting or walling off the invading organisms. It is only when the inflammatory response becomes chronic in nature that elevated levels of sex steroid hormones may be harmful to the periodontium and to the individual (Mariotti, 2004).

WHY RESORTING TO NON-DRUG TREATMENTS?

Prevention, early diagnosis and early treatment of periodontal diseases in children and adolescents are important for many reasons: the prevalence of and severity of periodontal diseases are high; incipient periodontal diseases in children may develop into advanced periodontal diseases in adults; there is an association between periodontal and systemic diseases; patients, families, or populations at risk for periodontal diseases may be identified and included in special programs for the prevention, diagnosis, and treatment of oral diseases. Finally, prevention and treatment of most periodontal diseases are relatively simple and very effective, providing lifetime benefits (Bimstein, 1991; Hirschfeld, 2019; Jepsen, 2017; Chapple, 2017). Attention to plaque control and removal of local irritants is very important for the gingival health of the patients in puberty. Gingival overgrowth, an increase in gingival size, is a common feature of gingival diseases. Gingival overgrowth impedes proper dental hygiene and apart from the cosmetic disfigurement, causes painful chewing and eating. The studies about the pathogenesis and aetiological factors of gingival overgrowth show that it is related with systemic diseases, local factors and side effects produced by some medications. The drug-induced gingival overgrowth caused by drugs like phenytoin, nifedipine, cyclosporine causes an overgrowth of the connective tissue matrix. Studies have shown that it is more commonly seen in male



children and adolescents (Tungare, 2019). As far as periodontal treatment is concerned, current treatment options include nonsurgical interventions alone or a combination of nonsurgical and surgical interventions. Nonsurgical approaches include an oral hygiene program, a scaling and root planning, and also the elimination of local irritant factors that enhance plaque accumulation. This periodontal therapy is effective since it can reduce the volume of the gingival enlargement up to 40%. Besides, nonsurgical periodontal treatment allows a more significant reduction of the gingival overgrowth. It also avoids the need of surgical therapy even 12 months after nonsurgical treatment and maintenance (Malek, 2019). When gingival inflammation is severe, or unresponsive to periodontal therapy, systemic antibiotics are prescribed. Nevertheless, antibiotics alter and even disrupt the resident flora in the other body districts being thus associated with diarrhea and vaginal candidiasis particularly in when hormonal variations happens and in those patients with sensitivity to a particular agent. However, in those subjects with mild to moderate periodontitis that typically respond well to mechanical treatment, to control symptoms and alleviate pain, benefit can be gained by using products that provide stability and elasticity to the tissues and facilitate healing while inhibiting destructions of tissue.

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).



The wound healing during childhood, spanning from the age of 2 until the end of puberty, is associated with more hypertrophic scars, both in duration and in intensity. Consequently, wound healing and gingival disease should benefit from complementary treatments based on hydration of the tissues (Sanchez, 2016). HMWHA has a highly complex secondary and tertiary structure in aqueous solution; its amphiphilic 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 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 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 (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®.

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