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# Drugs of Today

## The Role of Hyaluronic Acid in the Management of Periodontal Disease



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## THE ROLE OF HYALURONIC ACID IN THE MANAGEMENT OF PERIODONTAL DISEASE

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### Summary

*Hyaluronic acid is an extracellular constituent of connective tissue that regulates the hydration and movement of macrocells in the tissue matrix. It plays an especially important role in post-inflammatory tissue regeneration, with a specific action on the migration of fibroblasts and on fibrogenesis. Hyaluronic acid has been widely used with good results in the treatment of a large number of inflammatory conditions of the knee and in the treatment of the temporomandibular joint. Endogenous hyaluronic acid is found in elevated concentrations in the gingival tissue where it takes part in its repair after odontological interventions and in the restoration of tissue structure after an episode of gingivitis. These findings have led to the study of the topical application of this acid in the treatment of periodontal disease. Clinical studies carried out to date have shown a good outcome with a high degree of tolerance and acceptability by patients, which is indicative of the clinical value of hyaluronic acid in the treatment and management of gingivitis, a highly prevalent disease in the general population. © 2000 Prous Science. All rights reserved.*

### Introduction

Periodontal disease affects the tissues that surround and support the teeth (1) and consists of their inflammation and degeneration. More than 300 million people world-wide are estimated to be affected by this disease. The pathogenic course of this condition usually starts

with a gingival inflammation caused by bacteria residing in the plaque which accumulate in the crevices between the teeth and the gums. In order of importance, these bacteria are *Streptococcus mutans* (the leading cause of caries), *Actinomyces viscosus* (the bacteria that most frequently initiate the formation of

plaque) and *Porphyromonas gingivalis* (the major cause of periodontitis).

### Anatomy of the Periodontal Region

The term periodontium means "around the tooth" and is used in the anatomical or pathological reference to the tissues that surround the tooth and its root, which are basically the gums, the membrane or periodontal ligament

and the alveolar bone (Fig. 1). The gum is the fibrous connective tissue in which the teeth are embedded and covers the coronary portion of the alveolar bone. It is subdivided into the free or marginal gingiva (which is the part of the gum that surrounds the tooth, the edge of which is called the gingival sulcus); the attached gingiva (which is the part of the gingival tissue that extends apically to the oral or alveolar mucosa with a variable thick-

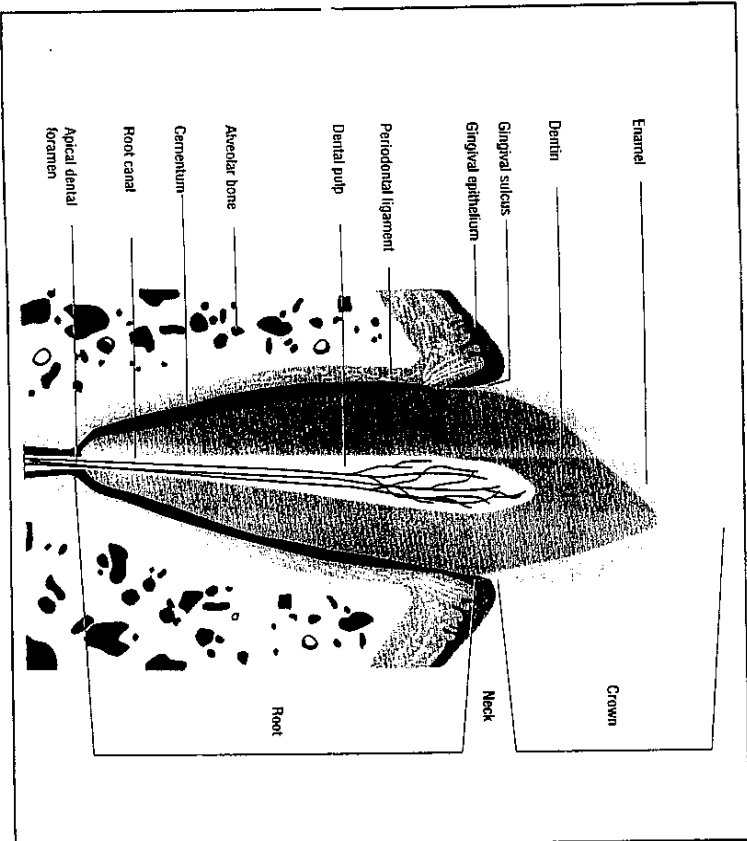


Fig. 1. General anatomy of a tooth and the periodontal tissue. The tooth (enamel, dentin and dental pulp) is attached to the alveolar bone of the maxillae and jaw by means of the cementum and the periodontal ligament (very fibrous connective tissue), which stems from the connective tissue of the gingival mucosa (soft connective tissue).

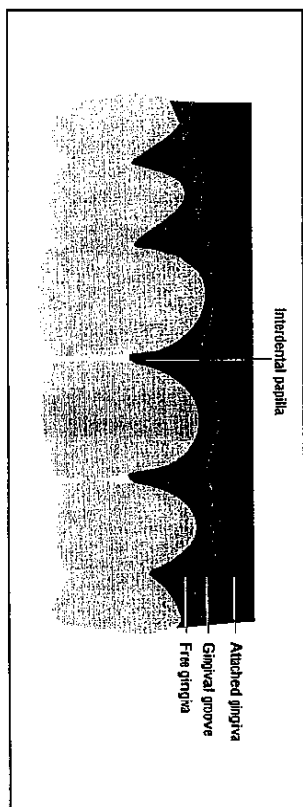


Fig. 2. Anatomy of the gums. The gum is divided into the free gingiva (which surrounds the teeth and is separated from them by the gingival sulcus), the attached gum (which is firmly anchored to the mandibula or maxillae) and the gingival groove (which separates the attached and free gums and can be identified as a slight lineal groove that connects the bases of the crowns). In the free gingiva, the portion of the gum around each tooth is called the gingival margin, where the facial aspect joins the wall of the gingival sulcus and the interdental gum occupying the interproximal area between the teeth, forming a protuberance or papilla.

ness that depends on the region of the mouth: it narrows distally from the cuspid, is narrowest at the bicuspids, and becomes wider in the anterior maxillary region); the gingival groove (which is the point where the free and the attached gingivae join at the level of the cementoenamel junction, where a longitudinal ridge can be seen); and the mucogingival junction (where the gum adjoins the oral mucosa) (Fig. 2). The epithelium of the outer gum is keratinised, squamous tissue with a stippled surface resembling the skin of an orange. This is more visible on the labial surface of the gum than on the lingual surface: it predominates in adults and tends to disappear with age and with gingival inflammation (oedema).

The periodontal ligament is a fibrous meshwork that attaches the teeth to the bony structure. It is a highly vascularised structure (anatomically it is not a ligament and thus, a more correct term would be periodontal membrane), while the alveolar bone corresponds to the cri-

brous layers of the mandible and the maxillae into which the teeth are inserted (2-4).

### Classification of Periodontal Disease

Gingivitis and periodontitis are the two classical periodontal diseases with the highest prevalence in the adult population. Gingivitis is an inflammation of the gums without detachment of connective osseous tissue from the dental base, whereas periodontitis causes a detachment from the alveolar bone that can result in tooth loss (Figs. 3, 4). Both these conditions are subdivided into several different types, depending on the age at which they first appear, the clinical picture, the progression or rate of evolution, the pathogenic microbial flora and systemic influences. In order to establish a differential diagnosis it is necessary to take a thorough dental history and to perform an extensive periodontal examination, together with ad-

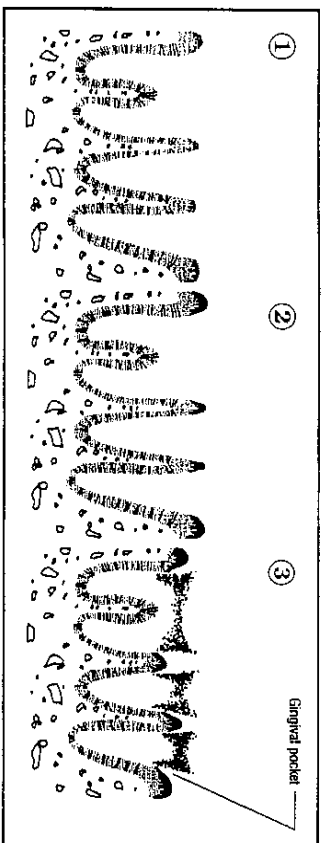


Fig. 3. Outline of the progression of a healthy gum (1) into gingivitis (2) and into periodontitis (3). Gingivitis is an inflammation of the gums which does not affect the teeth; in periodontitis the gum is seriously damaged and the base of the tooth is affected, which can result in tooth loss. The formation of the gingival pocket favours the formation of an area which is difficult to get to during daily oral hygiene and can be the starting point for gingivitis or periodontitis.

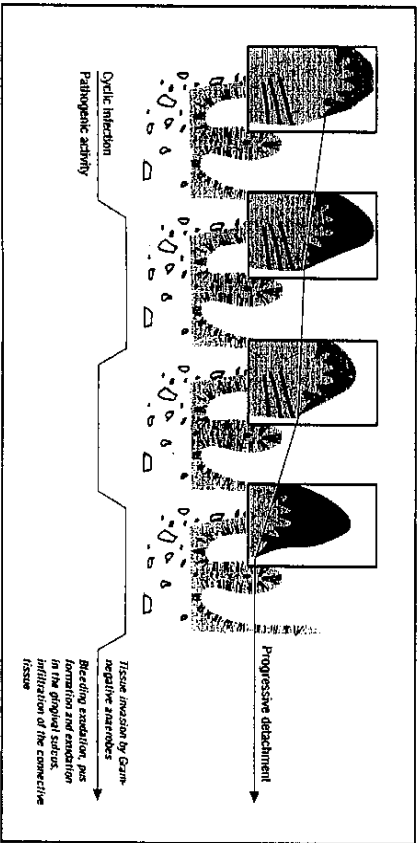


Fig. 4. The clinical recurrence of gingivitis and the development of periodontitis lead to the progressive and irreversible detachment from the alveolar bone.

ditional tests to identify the subgingival flora (5-7). A typical example of gingivitis is the desquamative type, which corresponds to a chronic alteration with a clinical course of redness, oedema, erosion and desquamation of the gums. It is

an unspecific gingival reaction that can be associated with dermatological disorders such as cicatricial pemphigoid or lichen planus, and with infectious or contact-allergenic agents. It occurs without any specific cause, and can only be di-

agnosed through a detailed anamnesis, and by ruling out other forms of gingivitis (8). Necrotising ulcerative gingivostomatitis is an infectious affection of rare occurrence associated with a decrease in the defence mechanisms of the body (its prevalence is on the increase due to the spread of infection produced by the human immunodeficiency virus) (9).

### Aetiology and Physiopathogenesis of Periodontal Disease

Gingivitis and periodontitis are conditions that are helped by a diversity of local and general factors (table 1). The aetiology for most cases of gingivitis and periodontitis is an infection caused by pathogenic flora of the dental plaque (*P. gingivitis*, *Prevotella intermedia* and *Actinobacillus actinomycetem comitans* are some examples of Gram-negative anaerobes responsible for pigmented periodontal infections. Other pathogenic organisms that trigger these infections include *Mycoplasma salivarium*, yeasts, etc.). A typical case of gingivitis is caused by *P. gingivitis* infection, a bacterium that produces a specific argi-

nine systemic proteinase capable of degrading important physiological proteins such as collagen (types I and IV) and capable of preventing the inactivation of the physiological inhibitors of proteases. Moreover, this protein can degrade immunoglobulins (preventing the reaction of immunological defence mechanisms) and inhibit the bactericidal action of polymorphonuclear leukocytes. This can easily result in a perpetuation of the clinical picture leading to periodontitis (10). The plaque and the connective tissue are separated by a very permeable sulciform epithelial tissue that allows fast interaction between these two structures and thus facilitates the passage of toxins and enzymes. Conversely, the marginal gingival and oral epithelium has a certain degree of keratinisation that makes it impermeable (Fig. 5).

Gingivitis is therefore essentially an infectious disease and, as with practically all infectious diseases, the treatment is based fundamentally on good preventive hygiene (5, 6, 11, 12). Nonetheless, an epidemiological review carried out in 1993 in Sweden showed that despite the improvement in the oral health of the

Table 1. Local and general factors that can enhance the development and modify the clinical course of inflammatory gingivitis.

Local factors	General factors
Microorganisms	Dietary imbalance
Calcium	Hormonal imbalance
Influence of food	Pregnancy
Breathing through the mouth	Puberty
Tooth grinding	Menstruation
Mechanical lesions	Diabetes
Chemical lesions	Adverse reactions to drugs
Thermal reactions	Avitaminosis
	Haemopathy

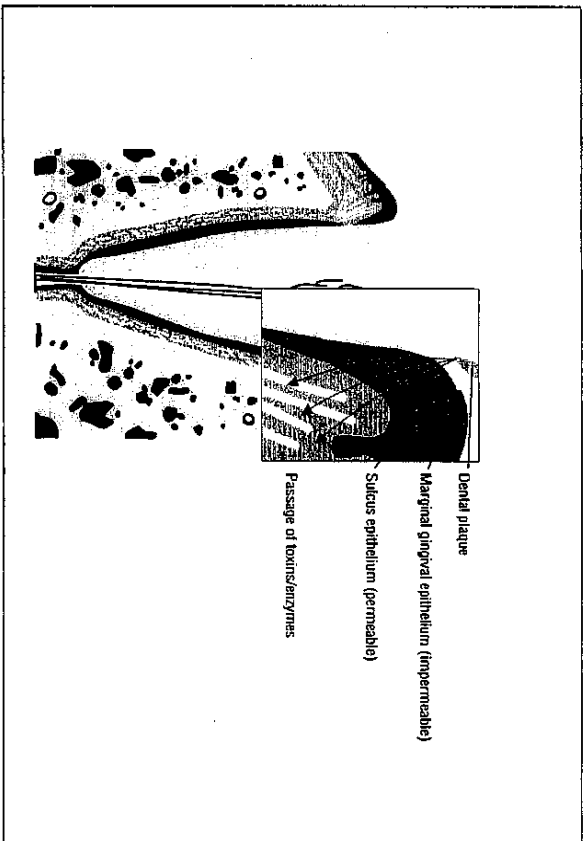


Fig. 5. The epithelium of the gingival sulcus differs from the epithelium of the marginal or interdental gum in that it lacks permeability due to a total absence of keratinisation. This allows a rapid and extensive interaction between the dental plaque and the connective tissue of the gum, resulting in the diffusion of toxins and enzymes produced by the bacterial flora of the tooth. In the event of an infection by *Porphyromonas gingivalis*, the permeability of the sulcus epithelium allows cysteine proteinase to reach the connective matrix of the gum, where it degrades the collagen fibres and inactivates the physiological inhibitors of proteases.

community compared with two decades before, a satisfactory level had not yet been reached and that there was a significant incidence of silent gingival cases presenting few symptoms (13); moreover, in Iceland the prevalence of gingivitis has been demonstrated to be 74% in 6 year olds (14).

The differential diagnosis of the different types of gingivitis and periodontitis requires time, investments of large sums of money, and is an inconvenience for the patients. For this reason, it is often necessary to employ empirical therapies which are aimed at helping to cure the

disease. It must also be taken into ac-

count that gingivitis can signal the prelude of destructive periodontitis, since it

favours the establishment of pathogenic flora (especially spirochetes such as *Treponema denticola*) (15). Hence, the implementation of generalised, effective, preventive and curative therapy schemes is of extreme importance. Among these

therapeutic measures, adequate and regular dental hygiene is of prime importance as it plays a significant role in the prevalence and clinical course of this disease.

Anti-inflammatory drugs can play a role in incipient cases of gingivitis as well as in more advanced cases. However, the limited availability of topical applications has curbed their use due to the risk of unwanted side-effects posed by the systematic regular administration of these drugs.

Furthermore, histochemical studies have demonstrated an increase of the lactoferrin/elastase quotient in gums affected with gingivitis and especially periodontitis. This equates to a decrease of elastase in the tissular content and an increase in the release of granules in the polymorphonuclear tissues, and to parallel increases in  $\alpha_2$ -microglobulin, C-reactive protein, cathepsin G,  $\beta$ -thromboglobulin, granulocytic elastase, platelet factor IV and  $\beta$ -glucuronidase (16-19). Cystatins (physiological inhibitors of cysteine proteinases) increase significantly in the saliva of patients with gingivitis or periodontitis, probably due to a

higher production in the salivary glands (20).

### Periodontal Connective Tissue: Role and Structure of Collagen

Connective tissue is formed by a complex network of cells, fibrous structures and an amorphous substance present in different proportions, depending on the physicochemical properties, the location and the function of each tissue (Fig. 6). Fibrous structures are formed mainly by collagen, reticulin and elastin fibres, while the interstitial amorphous substance is made of different mucopolysaccharides, one of which is hyaluronic acid, as well as chondroitin sulphate, heparan sulphate, heparine, keratan sulphate, dermatan sulphate, etc. The connective tissue allows intercellular communication by diffusion of mediators, cytokines, etc. It brings nutrients to the epithelium by means of haematic irriga-

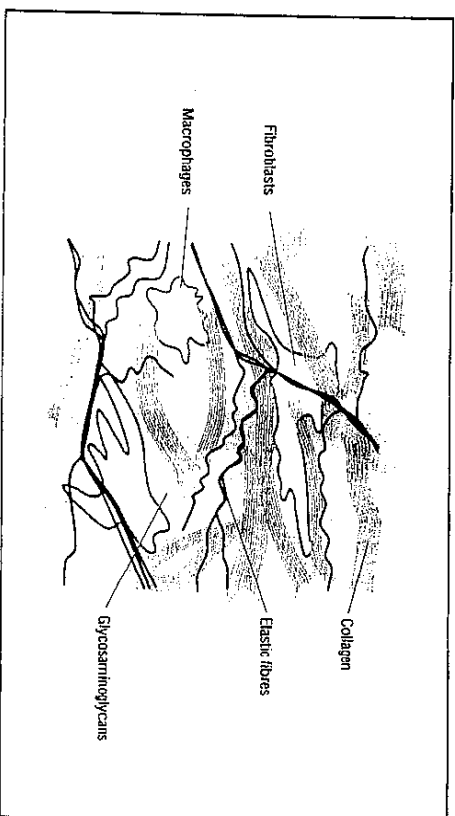


Fig. 6. General structure of connective tissue. The connective tissue contains cells (fibroblasts, macrophages, other inflammatory cells) and fibrillary structures (collagen, elastic fibres, reticular fibres) in an amorphous matrix made up of glycosaminoglycans.

tion and draws out noxious substances through blood or lymphatic vessels. It can be seen as a "gel" into which amino acids, hormones, fatty acids, electrolytes, etc. diffuse.

The teeth are therefore related to three main structures: the gums, the alveolar bone (also called cribrum) and the periodontal ligament, all of which constitute the Trotter periodontal triangle (Fig. 7) (1, 2). The fundamental reason for the development of periodontal conditions is a mesenchymopathy (a disease of the matrix of connective tissue) where a depolymerisation of the fibres and mucopolysaccharide constituents is observed. This depolymerisation facilitates the passage of noxious substances and makes the distribution of nutrients and intercellular mediators difficult (21).

Histologically, in periodontal structures the following elements must be distinguished: the teeth (composed of dentin, enamel, cementum and pulp), the ligament or periodontal membrane, and the gums (Fig. 1). The periodontal ligament is composed of thick fibrous connective tissue situated between the alveolar bone and the cementum. It functions both as alveolar periosteum and a suspensory ligament to hold the teeth in their socket. It contains mainly a large number of collagen fibres and fibroblasts embedded in a dense matrix of mucopolysaccharides. As for the gum, it surrounds each tooth like a collar and is a prolongation of the buccal mucosa that covers the alveolar periosteum above the necks of the teeth forming a ridge. It is composed of a stratified flat epithelium, superimposed on the connective tissue consisting of interlaced bundles of collagen fibres, with fibroblasts and numerous blood capillaries which form an abundant vascular network right beneath the epithelium.

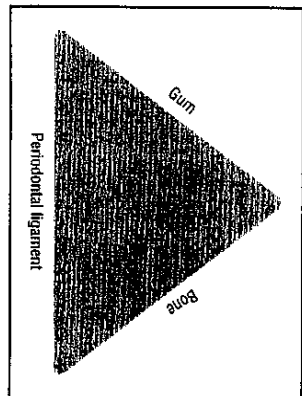


Fig. 7. Trotter's periodontal triangle. The gum, the alveolar bone and the periodontal ligament are the structures that cover the hidden portion of the teeth. These tissues can be affected by periodontal disease such as gingivitis or periodontitis, depending on whether the periodontal bone is affected.

Very narrow gingival sulci are found between each tooth and the gingival margin. It is at the base of these sulci that the gums adhere to the circumference of the crown and the enamel. The attachment between the gum and the enamel is not firm. With age the gingival sulcus becomes deeper until it reaches the point where the gum detaches from the enamel and only remains attached to the cementum, thus exposing the entire crown. Moreover, the loss of enamel progressively widens this gingival sulcus and becomes one of the main reservoirs of periodontal pathogenic organisms in the buccal cavity (Fig. 8) (1, 3, 22).

### Physiological Role of Hyaluronic Acid

Hyaluronic acid is a major constituent of the matrix of connective tissue, especially in the gums (23-25). It is a polymer of glucuronic acid and *N*-acetylglucosamine, joined alternatively by  $\beta$ -glycosidic (1-3) and  $\beta$ -bonds (1-4) (Fig. 9). Its

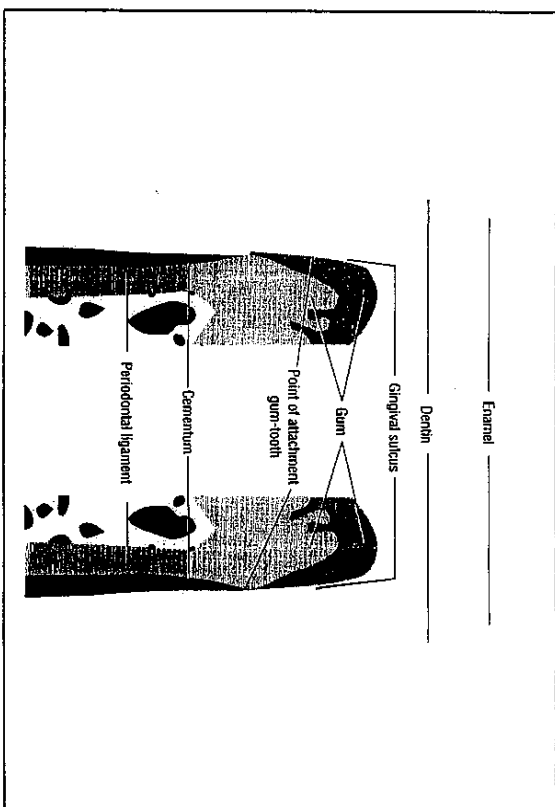


Fig. 8. Evolution of the gingival sulcus with age. In young people (left) the gum adheres to the tooth by means of the enamel, leaving a shallow, narrow groove referred to as the gingival sulcus. With age (right), there is a loss of enamel and the gingival sulcus deepens. The gum is then only attached to the teeth by the cementum, exposing the entire crown and forming a much wider and deeper groove, which creates a reservoir for the proliferation of diverse buccal pathogenic organisms.

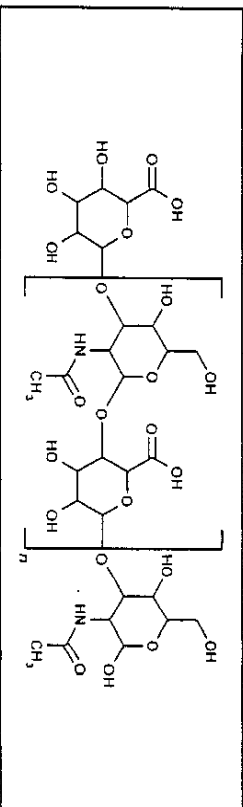


Fig. 9. Chemical structure of hyaluronic acid.

interaction with other proteoglycans and collagen give stability and elasticity to the extracellular matrix of connective tissue. Hyaluronic acid binds to different proteins and water molecules by means

of hydrogen bonds (Fig. 10) to form a viscous macroaggregate whose primary function is to regulate the hydration of tissues and the passage of substances in the interstitial compartment. Apart

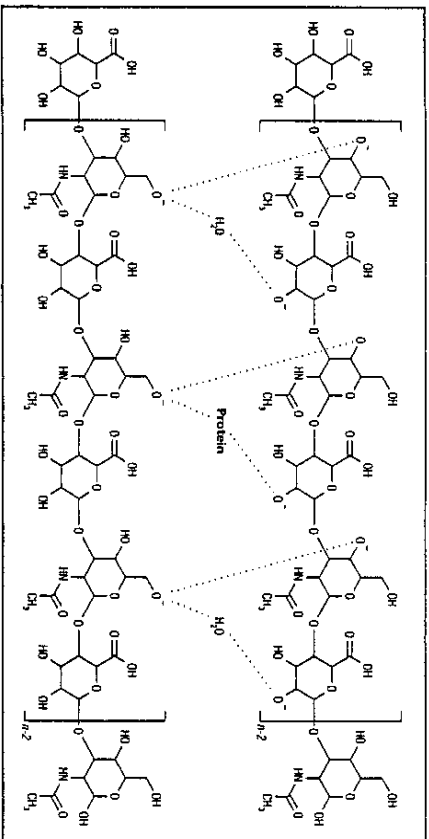


Fig. 10. Model of a macroaggregate of hyaluronic acid with water and proteins in the intercellular substance of the connective tissue. Polymers of hyaluronic acid bind to water molecules and protein chains by means of hydrogen bonds, forming a viscous macroaggregate that retains a significant amount of water and which favours the distribution of compounds through the connective matrix.

from this, when hyaluronic acid binds to cellular receptors that are expressed only in cells in active division, it acts as a regulator of migration and cellular division mechanisms which are especially important in wound healing and tissue repair. Hyaluronic acid probably binds with CD44, a sulphate-containing heparan-type proteoglycan that is specifically found on the epithelial cells at the epitheliomesenchymal border, and that regulates the reactions between the cells and the extracellular matrix, especially their bonding with hyaluronic acid. This same type of receptor is involved in the interaction between gingival fibroblasts and T- and B-lymphocytes, and can prompt a gingival immune response when pathogenic bacterial flora are present. Its production is at the same time increased by the stimulation that bacterial endotoxin (lipopolysaccharide) exerts on the fibroblasts (26-35).

As previously demonstrated in other indications, hyaluronic acid has a significant anti-inflammatory and anti-oedematous effect, helping healing and improving elasticity (36-40). Its usefulness in the topical treatment of gingivitis has already been determined. One of the advantages with the application of hyaluronic acid is that thanks to its adhesive properties, the topical effect remains localised on the area of the gums where it is applied.

### Pharmacological Action of Hyaluronic Acid

Hyaluronic acid is a high molecular weight glycosaminoglycan. It is present in the extracellular matrix of connective tissue where it contributes to tissue cohesion. It is the most abundant glycosaminoglycan in the extracellular matrix of connective tissue, especially in dental

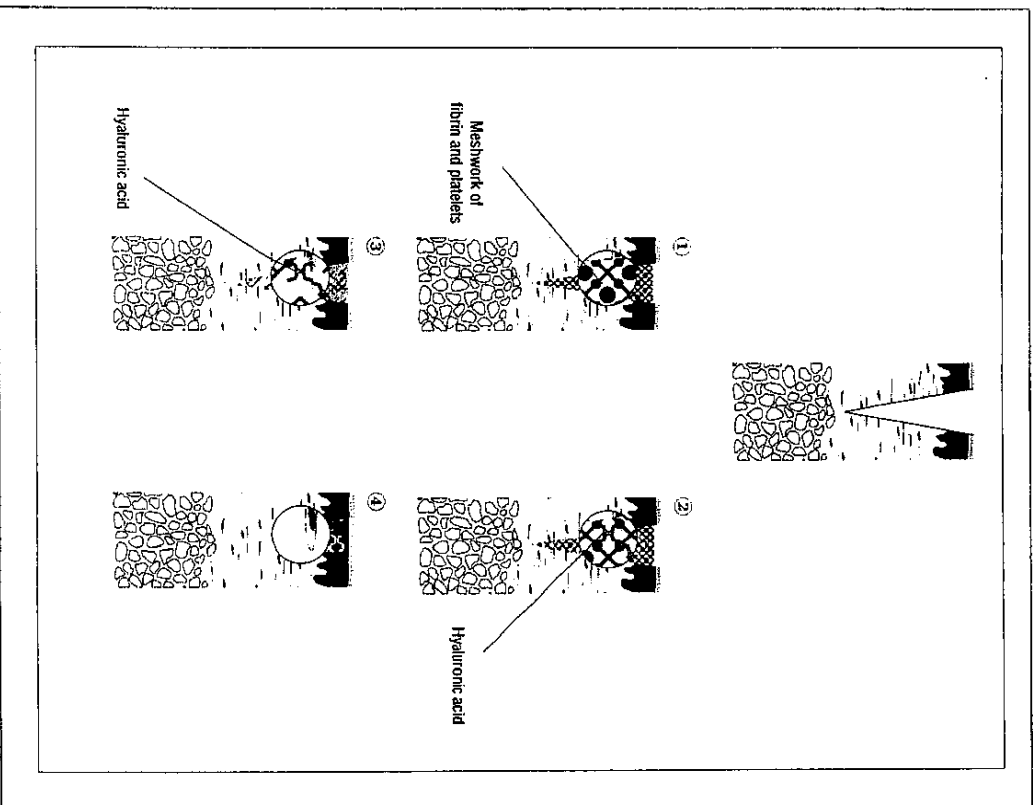


Fig. 11. Participation of hyaluronic acid and fibrin in tissue reconstruction after sustaining a wound or injury. The first step in the healing process is the formation of a fibrin and platelet meshwork (1). When this meshwork interacts with the hyaluronic acid (2) produced by the fibroblasts or haematic cells, it guides the mechanisms that regulate the reforming of tissues by gradually substituting the fibrin mesh (3) until the total histological re-establishment of the tissues has been achieved (4).

and periodontal tissues. One important physical property of hyaluronic acid is that it is capable of absorbing water 50 times beyond its normal dry weight. This makes the tissue matrix highly compact and enhances the exchange of gases and the diffusion of small molecules, while at the same time acting as a barrier in the diffusion of macromolecules and invading substances. Nonetheless, a progressive depolymerisation takes place during inflammation that alters the architecture of the tissue, making metabolic exchange difficult.

Exogenous hyaluronic acid has an anti-inflammatory, anti-oedematogenic, healing and elastinising effect on connective tissue in dermatological disorders (re-epithelialisation after cauterisation, ulcers) (41), in ophthalmological disorders (cataracts) (42-44) and in rheumatological disorders (arthritis, arthrosis) (45-53). Some authors have also reported certain osteogenic and immunostimulating effects. During the first phase of healing, fibrin threads form a meshwork for the basis of a platelet clot (Fig. 11), which is followed by the production of hyaluronic acid (by stimulation of different mediators of inflammation, especially interleukin- $\beta$  and platelet growth factor). Hyaluronic acid penetrates the pores of the fibrin mesh gradually substituting it, while enhancing at the same time cell migration, especially fibroblasts from adjoining tissues and the new production of collagen. Lastly, the fibrin meshwork disappears and the normal structure of the tissue is re-established. Hyaluronic acid, constituting a meshwork that interacts with fibrin, plays an important role in tissue repair (54-58).

In bovine cartilaginous articular tissue, hyaluronic acid exerts an anti-oxidant effect, which is probably due to the effects of free radical sequestration (59).

Hyaluronic acid has been used in the treatment of arthritis and arthrosis, particularly of the knee (48-50, 52, 53, 60-64) and of the temporomaxillary (65-67). It has also proven useful in surgery and radiotherapy in the prevention of adhesion formation and other cutaneous reactions (36-40). Lastly, its capacity to absorb water has led to its use in xerophthalmia where it enhances tear film stability (68, 69).

### Pharmacokinetics and Toxicology of Hyaluronic Acid

When systematically administered, hyaluronic acid is readily distributed with a plasma half-life of approximately 10 min and is metabolised in the liver. Nonetheless, after topical application, plasma concentrations are very low, which indicates scarce percutaneous absorption and thus, optimal permanence of the drug at the site of desired therapeutic action.

Moreover, studies carried out in rats and mice have failed to demonstrate acute toxic effects or chronic or reproductive effects of any sort at doses of up to 200 mg/kg, with an excellent topical tolerability. Mutagenicity and antigenicity studies have also ruled out any risks associated with the therapeutic use of hyaluronic acid.

### Hyaluronic Acid in Gingivitis

Inflammatory lesions cause changes in the composition of connective tissue and in the structure of the extracellular matrix that compromise and jeopardise the function of these cells. *In vivo* and *in vitro* tests run on samples of fibroblasts removed from the gums of healthy individuals and from individuals with chronic gingivitis have demonstrated that during

inflammation there is a significant increase in the production of hyaluronic acid (70, 71). Additionally, trials have shown that recombinant interleukin-1 $\beta$  stimulates, in a concentration-dependent manner, the proliferation of gingival fibroblasts and the production of prostaglandins, proteoglycans and hyaluronic acid, in a fashion very similar to that of cutaneous reparative mechanisms in which these inflammatory mediators are involved (72). Furthermore, normal gingival tissue contains 0.8% hyaluronic acid (in dry tissue weight), whereas in gingival hyperplasia the content of hyaluronic acid increases up to 2.1%, with a relative decrease in the content of collagen (73, 74). This clearly shows a relationship between hyaluronic acid and the proliferation of connective tissue. In addition, hyaluronic acid has proven useful in wound healing after odontostomatological and maxillofacial interventions (75).

A study in rats with fragments of dental pulp removed further corroborated that the administration of hyaluronic acid over a 2-day period enhanced the reconstruction and healing of wound surfaces by means of a fibrin clot and inflammatory cells. After a week's treatment, fibroblast and odontoblast differentiation was seen, and regenerative layers of dentin had formed at 2 weeks (76). These observations substantiate other studies that have been carried out on the healing effect of exogenous hyaluronic acid in gingivitis. In one of the initial documented clinical evaluations on hyaluronic acid comprising 30 patients with either hyperplastic gingivitis, marginal periodontitis or dystrophic periodontopathy, the submucosal administration of hyaluronic acid (4 mg) on each hemiarach of the gums was well tolerated in comparison with a placebo adminis-

tered on the contralateral hemiarach. The replenishment of connective tissue and tissue healing increased significantly with a strong fibrogenic, anti-inflammatory and anti-exudative action. Moreover, the patients experienced symptomatic relief soon after administration (21).

The effect of high molecular weight (0.2%) hyaluronic acid gel was studied in 10 outpatients who suffered periodontal disorders of varying severity. In nine of these patients, the clinical condition cleared up in a period of 2-10 days, which represents a healing rate of 90%. In the remaining patient, a 27-year-old woman with interproximal gingival inflammation, the symptoms improved and the subjective symptoms decreased, but there were concurrent signs of persistent inflammation after 7 days of treatment. After 2 days, a full symptomatic recovery was noted in all cases. With regards to tolerability, no signs or symptoms of intolerance were noted, and no signs of sialism or xerostomia developed (77).

In a double-blind randomised clinical study (78), a 4-week treatment regimen was used as a complement to daily oral hygiene following the advice of a specialist. The treatment consisted of applying a high molecular weight hyaluronic acid gel at 0.2%, or placebo (two applications per day) in 60 patients with marginal gingivitis. A significant therapeutic and prophylactic effect was found to result from the administration of hyaluronic acid. This was demonstrated by an improvement of the redness and inflammation of the marginal mucosa and the interdental papilla, with excellent tolerability and acceptability by patients.

There is a significant difference in the rate of the proximal plaque as well as in the rate of bleeding of the gingival sulcus (Fig. 12).

An added advantage in treating gingivitis with hyaluronic acid is the fact that *T. denticola*, a pathogen that causes periodontitis in already inflamed gums, binds selectively to this proteoglycan by means of a superficial protein that is related to chemotrypsin. The exogeneity of hyaluronic acid limits its binding to the

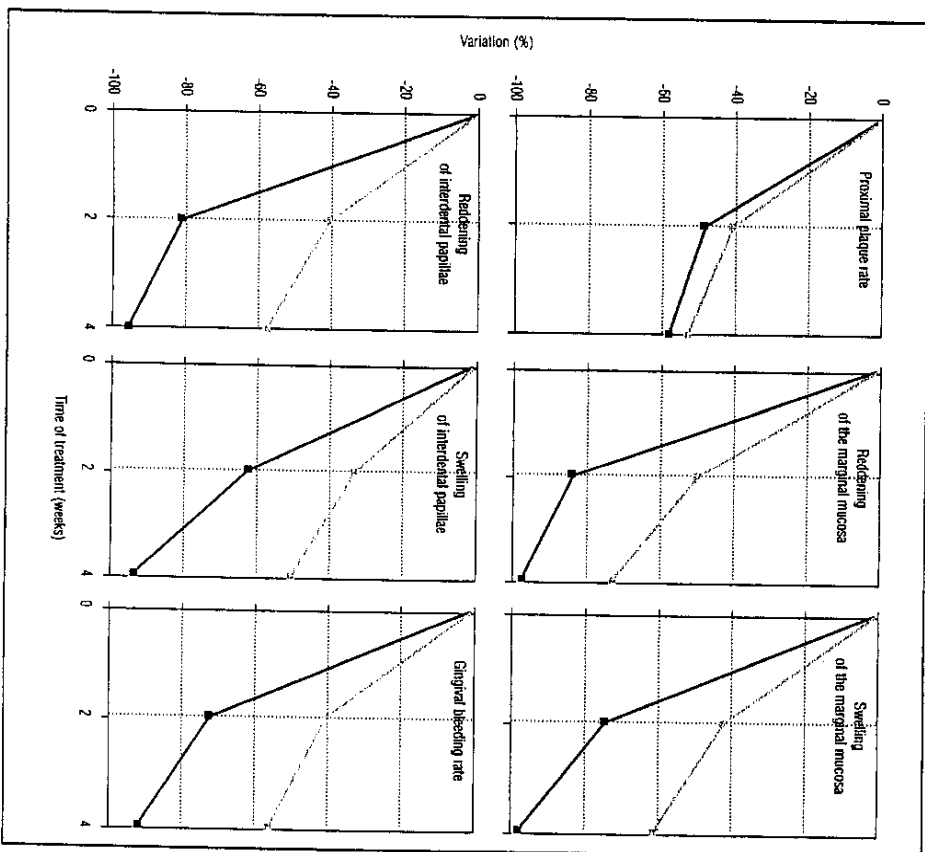


Fig. 12. Changes in gingival parameters after topical treatment with hyaluronic acid (blue) or placebo (grey) in patients with marginal gingivitis. The treatment significantly reduced all studied parameters ( $p < 0.001$ ) and was significantly more effective than the placebo in most of the cases (data from ref. 7B).

endogenous component of gingival tissue, reducing the possibility of infection (79).

### Conclusion

Hyaluronic acid is a physiological component of the extracellular matrix of connective tissue. When applied exogenously, it does not produce any unwanted or toxic effects. It does however produce a noticeable anti-inflammatory and anti-coedematous effect (56, 75, 80). Physiologically, hyaluronic acid intervenes in the control mechanisms of tissue repair, a property that has enhanced its exogenous use as a healing agent in different disorders, especially in the healing of surgical wounds, and in arthritis and arthritis. This same principle is applied to tissue repair in gingivitis, and consequently, its mode of action has been appraised in different stages of this disorder.

Clinical studies carried out to date on hyaluronic acid in the treatment of gingivitis have shown the high effectiveness of this compound in terms of healing, symptomatic clinical improvement and the good tolerability and acceptability by the patients, as well as the strong local adherence due to the adhesive properties of the compound after topical application of the gel.

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