The role of hyaluronic acid in managing inflammation in periodontal diseases

*Peter N Galgut

Introduction

Gingivitis and periodontitis are inflammatory conditions of the oral cavity. They are characterised by bleeding, redness and tissue breakdown around the teeth. Increasingly, it has been shown that, in most cases, the tendency for people to develop gingivitis is directly related to the presence of dental plaque. However, genetic factors have been shown to be important in the initiation of the inflammatory response, and subsequent tissue break down to form periodontal pockets. Genetic factors, which control the host response, are particularly relevant in respect of the more aggressive forms of periodontitis such as early onset periodontitis, juvenile periodontitis, rapidly progressive periodontitis, and refractory periodontitis.

The Adult Dental Health Survey of 1998 has shown that approximately 54% of the adult population, of England and Wales, has moderate periodontal pocketing, while approximately 5% of the population has severe periodontal pocketing. Although people who suffer from mild to moderate periodontitis respond well to mechanical treatment such as scaling, root surface debridement, maintenance of meticulous oral hygiene, and regular visits for periodontal maintenance, the more aggressive forms of periodontitis characteristically do not respond well to simple mechanistic treatment.

It is also important to recognise that gingivitis and periodontitis are not the only inflammatory conditions that occur in the mouth. Aphthous ulceration has been found to occur in approximately 20 per cent of the population.[1] Another increasingly common cause of distress and pain is caused by atrophic gingivitis (often associated with xerostomia), and also, mild dermatoses such as lichen planus. These common conditions cause pain, resulting in reduced function, which may continue over protracted periods of time. Treatment of these distressing conditions is largely palliative with little effective treatment is available.

There is clearly a clinical need to manage these inflammatory conditions more effectively.

An introduction to hyaluronic acid

Hyaluronic acid is a natural substance occurring throughout the animal kingdom. It is a major part of the tissue ground substance in which cells of the body grow. It is a polymer of glucuronic acid and glycosamine. It is the most common substance in a group of substances known as glycosaminoglycans (abbreviated GAGS), which form the glue-like extracellular matrix of connective tissue. These substances provide stability and elasticity to the tissues. Hyaluronic acid binds to water molecules to regulate the hydration of tissues. By binding to water it enables small molecular weight soluble substances and gasses to pass through the ground substance matrix, while blocking larger protein molecules such as endotoxin. Hyaluronic acid (probably acting together with heparin sulphate) has a particular role in active cell growth in that it binds to cellular receptors regulating the migration and cellular division of cells during tissue repair and wound healing. It is also produced in the presence of endotoxin by cells such as fibroblasts. In this regard it has an important anti-inflammatory role, facilitating healing and inhibiting destruction of the tissues.

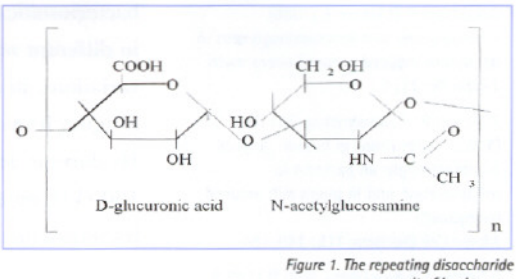

Figure 1. The repeating disaccharide unit of hyaluronan

Actions of hyaluronic acid in wound healing

After formation of a blood clot, hyaluronic acid is produced naturally by fibroblasts from stimulation by platelet growth factor and Inlerleukin-1ß.

*Correspondence Address:

28 Rundell Crescent, Hendon, London NW4 3BP.

Tel: (0)20-8202-8360
Fax: (0)20-8202-4231
e-mail:png@periodontal.co.uk

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It infuses into the fibrin matrix dissolving it, encouraging angiogenisis and cell migration into the clot. This has the greatest effect on collagen producing fibroblasts. Proliferation of human gingival fibroblasts has been shown to be stimulated, as well as the synthesis of hyaluronic acid and proteoglycans from Interleucin-1ß secretion, in a dose dependant fashion.[2] This stimulates early tissue repair. Hyaluronic acid therefore plays a crucial role in the repair and regeneration of damaged tissues.[3] Several papers have demonstrated that hyaluronic acid has significant bone induction properties and it therefore is active in repair of both soft and hard tissues such as bone.[4] A recent study has confirmed that hyaluronic acid also has significant antimicrobial effects, acting as a bacteriostatic agent. Hyaluronic acid can polarise in different ways to form different structural variations, in a wide variety of molecular weights, ranging from 141 kiloDaltons (kD) to 1300 kD. Hyaluronic acid molecules in the higher range of 1300 kD seem to be associated with high levels of bacteriostatic activity.[5]

A synthetic form of hyaluronic acid called Hyaluronan has recently been produced for clinical use for the management of oral inflammation.

Characteristics of hyaluronan

1. It is a natural and essential extra-cellular matrix substance in which cells grow, develop and live.
2. It encourages healing by stimulating angiogenisis.
3. It has bacteriostatic and antiseptic properties and it may also possibly be active against yeasts.
4. It maintains the structural integrity of the tissues.
5. It regulates tissue hydration by binding to water molecules and maintaining osmotic balance.
6. It regulates cell physiology by forming a matrix for the passage of nutrients and elimination of by products.
7. It protects the tissues by forming a barrier to the passage of high molecular weight substances such as endotoxins.
8. It stimulates the production of pro-inflammatory cytokines by fibroblasts in inflammation.
9. It regulates the migration of phagocytes into inflamed sites.
10. It prevents bacterial colonisation and inhibits bacterial proliferation by means of its bacteriostatic action.
11. It interacts with fibrin to stimulate granulation tissue formation and more rapid wound healing.
12. It interacts with growth factors to stimulate the differentiation, growth and development of both mineralised and non-mineralised tissues.
13. It is absorbed locally, but not systemically when applied to tissues.

Hyaluronic acid has been used extensively in Ophthalmology, Rheumatology and Dermatology (particularly in the treatment of diabetic ulcers) over many years, to enhance tissue repair and cell growth. Its uses in the more effective management of oral conditions has only recently been advocated and studied.

Dental research

Hyaluronic acid produced specifically for dental use is called Hyaluronan, to distinguish it from the naturally occurring substance. Naturally occurring hyaluronic acid suffers from the major disadvantage in that its molecular size and structure varies depending on its source. For medical use, hyaluronic acid is generally obtained from coxcombs, but hyaluronan is produced by fermentation from vegetable matter (algae). Its molecular characteristics are therefore standardised and it has the additional advantage of being free from all animal products. This unique substance is produced at a standard molecular weight of 1.2 x 10^6 daltons, which is a higher molecular weight than in the naturally occurring form. It is known that high molecular weight hyaluronic acid is associated with improved healing of the tissues.

Normal gingival tissues have been shown to contain 0.8 per cent hyaluronic acid, whereas the tissues in gingival hyperplasia contain as much as 2.1 per cent. This illustrates the important relationship between hyaluronic acid and

proliferation of connective tissue cells.[6,7] Animal studies have demonstrated enhanced reconstruction and healing of amputated and exposed dental pulp tissue by more rapid formation of fibrin clot, and inflammatory cell activity, when hyaluronic acid was applied to the sites. More rapid fibroblast and osteoblast differentiation and repair of dentine was also observed.[8] Other studies have also demonstrated stimulation of early tissue repair in gingival tissues arising from enhanced hyaluronic acid secretion.[2] Accelerated wound healing from increased hyaluronic acid production has been shown to be associated with platelet derived growth factor, which is known to stimulate proliferation of gingival fibroblasts.[9] It has also been shown that the marked bacteriostatic effects of hyaluronic acid may have the ability to inhibit the establishment of periodontal pathogenic organisms in periodontal pockets.[10]

Pistorius et al[11] have shown significant improvements in gingival bleeding and crevicular fluid flow (although no effect on plaque scores) in a group of gingivitis patients using Hyaluronan spray daily in addition to their normal oral hygiene regimens. These results are confirmed by other workers[12] using the professionally applied Hyaluronan gel. Other workers have reported more rapid resolution of symptoms after professional prophylaxis[13] and anti inflammatory/anti-oedematous effects of Hyaluronan when used clinically on gingivitis patients.[14] Hyaluronan has been shown to have the potential to modulate matrix synthesis and enhance cell growth in periodontal wounds.[15] Published research has also suggested that increased bone height may be achieved when Hyaluronan is used as an adjunct to surgical debridement.[16]

A recent paper has investigated the efficacy of bioabsorbable membranes in achieving tissue regeneration using the technique of guided tissue regeneration. In an in vitro study, human osteoblasts were cultured on different membranes and cellular proliferation analysed. The greatest proliferation of osteoblasts was seen on collagen and Hyaluronan containing membranes. This increased proliferation was largely attributed to significantly raised levels of Type 1 collagen (which forms the majority of the organic matrix of bone) and transforming growth factor-1ß (which stimulates secretion of matrix components and osteogenesis and inhibits collagenase (matrix metalloproteinase) synthesis.) [17]

Clinical uses

Hyaluronan may therefore be used:

1. To achieve improved healing during and after therapy for gingivitis and periodontitis. This is particularly useful in those individuals who demonstrate impaired tissue healing and a tendency for rapid recurrence of inflammation after treatment.
2. To encourage healing in traumatic injuries such as denture abrasion, post surgery, after extractions, or during and after radiotherapy.
3. In the management of uncomfortable soft tissue conditions such as stomatitis, aphthae, and xerostomia.
4. As an adjunct to tissue regeneration procedures to stimulate fibrinogen conversion to fibrin and to stimulate angiogenisis.
5. To encourage more rapid wound healing after surgery.
6. To reduce the chances of tissue breakdown after surgery, particularly where tissue regeneration is being attempted.
7. To reduce bleeding during impression taking, particularly when the gingival margins are inflamed and tend to bleed easily.
8. In cosmetic dentistry, where restorations may approach the gingival margin and be discoloured by the slightest amount of blood in the area.

Conclusions

Although the use of Hyaluronan is relatively new in dentistry, its use in promoting healing and reducing inflammation in medicine is well established. Recent research in dentistry has demonstrated its potential in a number of oral conditions when used to reduce inflammation and encourage healing.

Hyaluronan is the first topically applied anti-inflammatory product that has been specifically developed for dental use. Its clinical use to reduce inflammation in those individuals who demonstrate poor healing after treatment, is increasingly being shown to be effective and safe.

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