Role of Hyaluronic acid in various diseases with special emphasis on Periodontal inflammation - A review

Ahmed Elhassan 1, Karthikeyan Ramalingam 2*, Syed Wali Peeran 3, Rajendran Ganesh 4, Khalid Awidat Abdalla 5.
1Associate Professor, Libyan Authority of Scientifics Research, Tripoli, Libya. Email: elhassan1929@yahoo.com
2Professor and Associate Dean, Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India, E-mail: karthikeyanr.sdc@saveetha.com
3Department of Preventive Dental Sciences, Jazan University, Jazan, KSA. Email: doctorsyedwall@yahoo.in
4Assistant Professor of Pediatric Dentistry, Department of Preventive Dental sciences, Faculty of Dentistry, Al Baha University, Al Baha, KSA. Email: rrajendran@bu.edu.sa
5Department of Oral Biology and Orthodontics, Faculty of Dentistry, Sebha University, Sebha, Libya. Email: awidat@hotmail.com

Abstract

Hyaluronic acid is a naturally occurring polysaccharide of extracellular matrix of connective tissues, synovial fluid, and other body tissues. It has an important role in regulating interactions intra and extracellularly between different growth factors, in addition to regulating osmotic pressure, maintaining tissue volume and lubrication.

Periodontitis is a multifactorial inflammatory disease that affects teeth supporting structures which results in teeth loss. It is considered a wide world cause of teeth loss in adults. In addition to its local effect, teeth loss, it can have systemic impacts on many systemic organs. Although its main cause is bacteria, exaggerated host response and risk factors such as smoking, diabetes mellitus, HIV/AIDS, family history, and certain medications increase the disease progress.

Hence teeth supporting structures are connective tissues and hyaluronic acid is a main component of connective tissues, a correlation of both in health and disease is explained in this article.

Keywords: Hyaluronic acid, Hyaluronan, Periodontitis, Health, Disease

DOI: 10.47750/pnr.2022.13.S07.041

INTRODUCTION

Hyaluronic acid (HA) is a naturally occurring linear non sulfated anionic polysaccharide.

The primary structure of the polysaccharide comprises an unbranched linear chain with the monosaccharides (d-gluconic acid and N-acetyl-d-glucosamine) linked together through alternating β1,3 and β1,4 glycosidic bonds.
Ahmed Elhassan et al.: Role of Hyaluronic acid in various diseases with special emphasis on Periodontal inflammation - A review

Figure 1: Hyaluronan structure - Hyaluronan is composed of repeating polymeric disaccharides D-glucuronic acid (GlcA) and N-acetyl-D-glucosamine (GlcNAc) linked by a glucuronidic β(1→3) bond. Three disaccharide GlcA-GlcNAc are shown (Jiang, Liang and Noble, 2011)

Distribution of HA

HA is present in the connective tissue, epithelial tissue and neural tissue. It is one of the chief components of the extracellular matrix. Hyaluronic acid is also a component of the group A streptococcal group capsule and play a role in its virulence (Wessels et al., 1991). It is primarilly synthesized by mesenchymal cells (Gerdin and Hällgren, 1997). The highest concentrations of HA are found in soft connective tissues (umbilical cord, synovial fluid, and skin) and the lowest in blood serum (Laurent and Fraser, 2007). It is found in periodontal tissues in varying quantities and is more prominent in the non mineralized tissues (the gingiva and the periodontal ligament) than the mineralized tissues (the cementum and alveolar bone) (Waddington and Embery, 2001; Murakami et al., 2019)

Physiological functions of HA

1) Lubricants as it is the main component of synovial fluid and it is responsible for the resilience of cartilages (Tamer, 2013).
2) A Main component in the skin. It maintains skin shape and it is involved in the repair process, for instance from trauma and excessive ultraviolet sunlight (Averbeck et al., 2007)
3) Proliferation and cell migration. It has primary receptors, CD44 and RHAMM CD44 which are widely accepted as a marker of cell activation in lymphocytes. HA provides conducive environment for the migration of cells into this temporary wound matrix (Murakami et al., 2019)
4) Anti-inflammatory: hyaluronan degradation products transduce their inflammatory signal through toll-like receptor 2 (TLR2), TLR4 or both TLR2 and TLR4 in macrophages and dendritic cells. Exogenous hyaluronan acts as a scavenger by draining prostaglandins, metalloproteinases and other bioactive molecules (Bansal, Kedige and Anand, 2010)
5) Anti-oedematous: The anti-oedematous effect of HA may be related to osmotic activity (Jentsch et al., 2003)
6) Bone regeneration: HA induces bone formation like bone morphogenetic protein-2 and osteopontin (Mendes et al., 2008)
7) Angiogenesis: low molecular weight HA has marked angiogenic effect (Deed et al., 1997; Mendes et al., 2008)
8) Granulation it helps in replacing blood clot in healing wound to fibrous connective tissue (Granulation tissue)
HA and systemic diseases

Since HA is a pivotal component of connective tissue, it has been found to be associated with pathogenesis of many systemic diseases. For instance; it has been found to increase in Dermatomyositis, polymyositis, systemic sclerosis, Rheumatoid arthritis, critically ill patients, Breast cancer, Covid 19, kidney diseases, intestinal inflammation and periodontal disease. (Table 1)

<table>
<thead>
<tr>
<th>HA Level</th>
<th>Systemic diseases</th>
<th>Possible reason of HA level change</th>
<th>Literature support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised</td>
<td>Dermatomyositis</td>
<td>HA stimulates the release of inflammatory factors such as TNF-α and IL-1β, and fibroblast cytokines, aiding in the inflammatory response and tissue repair</td>
<td>(Silva and Shinjo, 2018)</td>
</tr>
<tr>
<td>Raised</td>
<td>Dermatomyositis</td>
<td>The disease activity were greatly improved after corticosteroid therapies that reduced HA level</td>
<td>(Kubo et al., 1999)</td>
</tr>
<tr>
<td>Raised</td>
<td>Disease</td>
<td>Description</td>
<td>Reference</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Breast Cancer</td>
<td>Hyaluronan was significantly increased in sera of metastatic patients compared to sera of non-metastatic patients</td>
<td>(Delpech et al., 1990)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular Disease</td>
<td>Serum HA increased in dyslipidemia patients</td>
<td>(Papanastasopoulos et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Covid 19</td>
<td>Hyaluronan is obstructing alveoli with presence in exudate and plugs in Covid 19 patients</td>
<td>(Hellman et al., 2020)</td>
</tr>
<tr>
<td></td>
<td>Systemic sclerosis</td>
<td>Plasma HA in patients with PSS. They also suggest that lung involvement is the main feature responsible for high plasma concentrations of HA</td>
<td>(Freitas et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Concentrations of serum HA were higher in patients with RA than in healthy controls.</td>
<td>(Emlen et al., 1996; Freitas et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>Kidney Diseases</td>
<td>Serum HA level may be used as tool to differentiate Acute from chronic kidney diseases</td>
<td>(Akin, Ozmen and Yilmaz, 2017)</td>
</tr>
<tr>
<td></td>
<td>Critically ill patients</td>
<td>Hyaluronan serum concentrations are elevated in critically ill patients and associated with disease severity</td>
<td>(Yagmur et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Periodontal inflammation</td>
<td>Hyaluronic acid has shown anti-inflammatory and anti-bacterial effects in the treatment of periodontal diseases</td>
<td>(Yagmur et al., 2012; Dahiya and Kamal, 2013)</td>
</tr>
<tr>
<td></td>
<td>Intestinal inflammation</td>
<td>HA is increased in Crohn’s disease</td>
<td>(Stenson, 2010)</td>
</tr>
</tbody>
</table>

**HA and Periodontal diseases**

As periodontal tissue is a connective tissue, HA is an important component of its extracellular matrix. Moreover, Hyaluronan is found in all samples of gingival crevicular fluid (GCF) and serum of gingivitis patients with exception of acute necrotizing ulcerative gingivitis due to high hyaluronidase production (Pirnazar et al., 1999).

HA, as mentioned above, is an important factor in cell adhesion, proliferation, migration and in the periodontal repair process in general. Therefore, it could be used as a periodontal marker of inflammation in GCF (Pogrel et al., 1996). Due to its anti-inflammatory, anti-oedematous and anti-bacterial effects, HA showed a benefit in the treatment of gingivitis (Eick et al., 2013)

As adjunctive to scaling and root planing, studies showed different results. Some found that HA was statistically significant in reducing probing depth and gain in attachment level in chronic periodontitis patients. (Rajam, 2014) (Shah et al. 2016). In addition, the HA may prevent recolonization by periodontopathogens (Treponema denticola, Campylobacter rectus, Prevotella intermedia and Porphyromonas gingivalis) (Eick et al., 2013)

However, there are studies which failed to found any additional beneficial effects of HA application as adjunctive to scaling and root planing (Xu et al., 2004) (Johannsen et al., 2009)

The use of hyaluronic acid seems to have beneficial effects in periodontal surgery using open flap debridement, in terms of PD and CAL. (Onisor et al. 2022) (Fawzy El-Sayed et al. 2012) found that HA with modified widman flap (MWF) showed a
significant improvement of CAL in 3 and 6 months compared to MWF alone; however, No difference in PD nor BOP.

Regarding periodontal regenerations, most studies found positive results when HA was used as a scaffold in periodontal tissue regeneration (Takeda et al., 2011) (Prato et al. 2003) (Božić et al. 2021) (Selvaprakash et al., 2021) and few researches demonstrated no benefit (Engström et al. 2001).

Regarding mucogingival surgeries few studies were found. A randomized control study by (Pilloni et al. 2019) showed that the use of HA with coronally advanced flap (CAF) resulted in more complete root coverage in Miller Class I than CAF alone; however, (Kumar et al. 2014) found no significant clinical benefit. (Kasatwar et al. 2018) Also showed more root coverage using HA in combination with polyactic acid/polyglycolic acid membrane compared with connective tissue graft with CAF. A randomized control study (Soriano-Lerma et al. 2020) indicated that the use of HA in peri-implantitis resulted in a decrease in oral bacteria (Streptococcus, Veillonella, Rothia, and Granulicatella, Prevotella and Campylobacter) suggesting a protective action of the peri-implant site against bacteria colonization.

Topical application of HA can also help in healing oral ulcers which includes ulcers that affect the gingiva (Kapoor, Sachdeva and Sachdeva, 2011). In fact, it is as effective as dexamethasone in treating such ulcers (Yang et al., 2020).

The healing period, pain perception, number of ulcers, maximal area of ulcer and inflammatory signs significantly improved after HA application. These data allow us to suggest that HA may play a pivotal role in the treatment of oral ulcers like aphthous ulcers, lichen planus and oral ulcers in general (Casale et al., 2017).

Discussion
Hyaluronan has been found to have positive healing results for many medical diseases. The application of HA in conjunction with periodontal treatment was found generally to achieve beneficial effects especially with soft tissue healing more than with mineralized tissue.

When mineralized tissue healing effect is seeked, HA could be used as a scaffold carrying an augmentation bone material.

According to the majority of the studies, the application of 0.8 or 1 % of HA could speed the healing of chronic gingivitis, increase clinical attachment, root coverage in Miller class I, decrease PD, improve postoperative healing and treat oral ulcers.

The time of application of HA was in some studies during the non surgical phase or during the surgical phase and sometimes after the surgeries where it was used usually twice for 1 to 2 weeks.

Despite the promising results, there were studies which failed to find any positive results and we recommend more randomized long term studies for better understanding and ensuring of these results. Moreover; we need studies that involve the application of HA in medically compromised patients with periodontal diseases or in smoker patients or for instance; its application in patients with Miller Class III or IV gingival recession or comparing it with the application of cheaper alternatives like PRF.

Conclusion
And finally; to draw a clear conclusion, more adapted and well-designed clinical trials are needed to assess the advantage of Hyaluronic acid in comparison with other products.

Conflict of interest
None

Funding
This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit sectors.

REFERENCES
31. Efficacy of a Combination of b-Tricalcium Phosphate with Hyaluronic Acid in the Management of Intrabony Periodontal Defects: A Prospective Clinical Study