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Application of hyaluronic acid in peri-implant diseases: a literature review

Application of hyaluronic acid in peri-implant diseases: a literature review

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SUMMARY:

With the worsening and problems that arise with the clinical progression of dental implant cases, hyaluronic acid (HA) emerges as an alternative for the treatment of peri-implant diseases. This study aims to review the literature from the last 10 years to understand the efficacy of HA in the treatment of peri-implant diseases. This was achieved by searching the *PubMed, Scielo ,* and gray literature databases through Google Scholar. The results revealed that its use combined with bone grafting resulted in better vertical bone gain, decreased PS and IL-1ÿ marker levels in the crevicular fluid, and also promoted regulation of peri-implant microbiome dysbiosis, minimizing periodontal pathogens. In mucositis, topical use of HA effectively moderated bleeding and inflammation. It is concluded that, although the use of HA in the management of peri-implant diseases has shown anti-inflammatory and regenerative effects, and has also modulated peri-implant microbial dysbiosis, the evidence is limited by studies with small samples, lack of an independent control group, and short follow-up period, requiring further robust investigations for the clinical application of HA.

Keywords: Hyaluronic Acid Synthetase. Dental Implants. Peri-Implantitis. Mucositis.

ABSTRACT:

With the worsening and problems that arise during the clinical evolution of dental implant cases, hyaluronic acid (HA) emerges as an alternative treatment for peri-implant diseases. This study aimed to review the literature from the past decade to understand the efficacy of HA in treating peri-implant diseases. This was achieved by searching the PubMed, Scielo, and gray literature databases through Google Scholar. The results revealed that its combined use with bone grafting resulted in better vertical bone gain, decreased levels of PS and IL-1ÿ markers in the crevicular fluid, and also promoted the regulation of peri-implant microbiome dysbiosis while minimizing the presence of periodontal pathogens. In mucositis, the topical use of HA effectively moderates bleeding and inflammation. It is concluded that, although the use of HA in the management of peri-implant diseases has shown anti-inflammatory and regenerative effects, and has also modulated peri-implant microbial dysbiosis, the evidence is limited by studies with small samples, lack of an independent control group, and short follow-up period, requiring further robust investigations for the clinical application of HA.

Keywords: Hyaluronic Acid. Dental Implants.Peri-implantitis. Mucositis.

1. INTRODUCTION

Dental implant treatment to replace missing or lost teeth is considered the gold standard for these conditions. However, the success of therapy is directly related to maintaining healthy peri-implant tissue, preventing the development of complications, such as peri-implant diseases, an infectious-inflammatory condition that leads to the loss of integrity and durability of dental implants (DERKS et al., 2016; MARTÍNEZ-GÓMEZ et al., 2022).

This concern is emerging, since the prevalence of peri-implant diseases is

growing (RENVERT et al., 2019). Regarding its diagnosis and treatment, there are clear and
therefore, the study of new therapies is crucial, for example, the use of hyaluronic acid (HA), which appears
as a possibility to improve healing and reduce inflammation in the peri-implant region.
(AGARWAL et al., 2019; LEE et al., 2019).

Therefore, this literature review aimed to explore the use of HA for the treatment of diseases
peri-implant conditions. To this end, studies that evaluated outcomes such as stability were included
implant, radiographic bone gain and clinical and biochemical parameters, with the purpose of
consolidate evidence on the application of HA in implantology, identifying gaps for research
future and optimization of AH usage strategies.

2 THEORETICAL FRAMEWORK

For successful dental implant treatment, healthy periodontitis tissue is essential.
implant, avoiding complications. In patients with peri-implantitis, gingival index scores
modified and the probing depth of the bag are significantly greater in relation to
healthy patients (ATA-ALI et al., 2015). Furthermore, points contaminated by the microbiotic process, one of the
main causal factors for peri-implantitis (MARTÍNEZ-GÓMEZ et al.,
2022), present a more diverse bacterial load, including significantly higher
number of periodontal bacteria, such as *Porphyromonas gingivalis, Treponema denticola* and
Tannerella forsythia. In addition, a significant amount of *Candida spp.* is also present in these locations (MARTÍNEZ-
GÓMEZ et al., 2022). This change is related to the higher proportion
of inflammatory markers such as IL-1ÿ, IL-6, IL-10 and TNF-ÿ in these environments, presenting a
enhanced inflammatory response (ATA-ALI et al., 2015).

These findings, combined with reduced mobility, due to the peri-implant mucosa having
desmosomes and hemidesmosomes of the epithelium and junctional epithelium attaching directly to the surface
of the implant, the lesser formation of vessels in the subepithelial area contributing to a lower
vascularization of the peri-implant tissue, can lead to inflammatory diseases in implants. Another fact
is that the subgingival connection of the implant to the abutment presents specific challenges, and the continuity of this
connection is essential to preserve the health of the peri-implant soft tissue. The shape of the implant,
including the connection of the implant and the abutment, in addition to the abutment surface, ensures the integrity of the
soft tissues. In addition, iatrogenic factors (inadequate adjustment of the abutment or restoration and the
presence of residual subgingival cement) may cause this integrity to be compromised.
compromised by the risk of peri-implant diseases (IVANOVSKI, LEE, 2018).

The new classification of peri-implant disease was introduced in 2017 and divided the diseases
peri-implant mucositis and peri-implantitis. Mucositis describes a process

reversible inflammatory condition induced by bacteria of the peri-implant soft tissue with redness, swelling and bleeding on periodontal probing (SMEETS et al., 2014). In contrast to mucositis, peri-implantitis is a progressive and irreversible disease of the hard and soft tissues surrounding the implant and is accompanied by bone resorption, decreased osseointegration, increased formation of pockets and purulence (MARTÍNEZ-GÓMEZ et al., 2022).

Several patient-related risk factors can decrease implant longevity. smoking habit impairs the immune response by decreasing leukocyte function and increasing adhesion bacteria, leading to higher microbial loads and elevated levels of periodontal pathogens. The poor oral hygiene leads to more extensive peri-implant bone loss, especially in smokers. Patients with a history of periodontitis are more susceptible to peri-implantitis. Furthermore, Osteoporosis is another risk factor for bone loss. The cause of diabetes mellitus, especially type II, is associated with difficulties in healing and a greater risk of implant loss (MIRANDA et al., 2022; DERKS et al., 2016; MARTÍNEZ-GÓMEZ et al., 2022).

Short implants were considered risk factors, since, due to less contact with the bone and greater susceptibility to biomechanical overload, were associated with higher failure rates. Furthermore, rough implant surfaces increased the risk of accumulating a greater number of bacteria compared to smooth implants, leading to a higher incidence of peri-implantitis. At the same time, however, rough or treated surfaces allow the migration of osteoblastic cells, accelerating the osseointegration process, unlike smooth surfaces that delay the process healing (CAMILO, GERSON, 2008). Furthermore, the type of prosthesis can influence the risk of develop peri-implantitis: cemented prostheses, due to cement residue, can be a factor in risk for peri-implant inflammation, while screw-retained prostheses are generally used preferably to avoid these problems (MIRANDA et al., 2022)

In the literature, the prevalence of peri-implant diseases varies widely, and this difference is due to the characteristics of the study populations and the differences in the criteria used for diagnosis of peri-implant diseases. In order to assess the prevalence, incidence and factors of risk factors associated with peri-implantitis, a meta-analysis revealed that the prevalence of peri-implantitis varied widely, from 1.1% to 85.0% at the implant level, and the incidence ranged from 0.4% at three years to 43.9% in five years (DREYER et al., 2018). Furthermore, in a systematic review, the prevalence of peri-implant mucositis ranged from 19 to 65 percent, while that of peri-implantitis ranged from 1 and 47% (RENVERT et al., 2019).

The diagnosis of peri-implant mucositis involves symptoms of inflammation around the implant, without the presence of bone loss; cases of peri-implantitis, in addition to the presence of bleeding and ongoing inflammatory process, also involve the depth of the peri-implant of at least 5 mm. Periapical radiographs and computed tomography

conical are used to evaluate bone defects, revealing a marginal bone loss of 2 mm or more (MARTÍNEZ-GÓMEZ et al., 2022; HEITZ-MAYFIELD, 2024).

The main objective of treating peri-implant diseases is to remove bacterial plaque of the implant surface (RENVERT, POLYZOIS, 2015). Two forms of treatment are known. Non-surgical treatment, using mechanical or chemical means, using antiseptics or antibiotics, or a combination of the two, aims to control infection by debridement of the implant surface, without access to the bone level, which reduces the resolution of peri-implantitis. In the case of findings of the disease remain after initial non-surgical treatment, only then should surgery be considered (RENVERT et al., 2019; ROKAYA et al., 2020). The treatment of perioperative pathological conditions implants must be accompanied by periodic maintenance programs with supportive care individualized, showing a high survival rate of implants after five years (ROKAYA et al., 2020).

Some therapies are proposed to treat the surface of implants and stabilize and reverse the bone loss. The use of hyaluronic acid is an example. Hyaluronic acid is composed of units repeating disaccharides in a linear chain, with each unit containing N-acetyl-d-glucosamine and d-glucuronic acid connected by ÿ-1,3-glycosidic and ÿ-1,4-glycosidic bonds. Found in various tissues such as connective tissue, synovial fluid and extracellular matrix, hyaluronic acid is synthesized by a group of isoenzymes called hyaluronan synthases, which are anchored to plasma membrane. These enzymes transport activated monosaccharides to form the chains of non-sulfated glycosaminoglycan and release uridine diphosphate directly into the extracellular space (AGARWAL et al., 2019).

Hyaluronic acid has been proposed as a material for healing periodontal wounds, treatment of gingival recession and regeneration of intrabony periodontal defects. The results were promising, showing improvements in clinical insertion level and reduction in depth of probing. This can be explained by the positive effect of hyaluronic acid in increasing viability and proliferation of periodontal ligament fibroblasts and differentiation of osteoblasts, resulting in a significant increase in collagen production and new bone formation (LEE, PARK, HWANG, 2019; ZHENG, PATEL, 2022).

Hyaluronic acid is found in different locations of the periodontium, covering both tissues mineralized tissues, such as cementum and alveolar bone, and non-mineralized tissues, such as gums and the periodontal ligament. In periodontal tissues, hyaluronic acid is produced by fibroblasts, periodontal ligament cells, cementoblasts and osteoblasts, with higher concentrations in the tissue connective tissue of the gingiva and periodontal ligament and lower concentrations in cementum and bone alveolar (MANSOUR et al., 2024).

Studies show that hyaluronic acid can be used in different applications

related to dental implants, such as promoting healing and reducing inflammation, but the evidence is still heterogeneous (ABDULLAH THAIDI, 2023).

2. MATERIAL AND METHOD

This study adopted a literature review as a method in order to consolidate the evidence scientific research over the last 10 years on the use of hyaluronic acid (HA) in resolving diseases peri-implant. The search for studies was carried out in the PUBMED, Scielo and literature databases grayscale of Google Scholar, using the combined strategies of filtered descriptors in *Medical Subject Headings* (MeSH) and health sciences descriptors (DeCS): *"Dental implants"; "Dental implants"; "Peri-Implantitis"; "Peri-Implantitis"; "Mucositis"; "Mucositis"; "Hyaluronic Acid"; "Hyaluronic Acid Synthetase"; "Bone regeneration"; "Bone Regeneration".*
The following inclusion criteria were adopted: studies with groups of cases diagnosed with mucositis or peri-implantitis, with availability for clinical outcomes of PS, SS and CIN. When Inflammatory biomarkers were verified and implant stability assessment records were made. *In vitro* or animal studies without sufficient outcome data or without access to the full text were excluded.

3. RESULTS AND DISCUSSION

In total, 6 (six) studies were selected for this literature review. An analysis of the available studies indicated that HA is a promising adjuvant therapy for perioperative diseases. implants. Its application interfered with the inflammatory response, tissue regeneration and also in the challenges of peri-implant microbial dysbiosis.

For example, in the work of Rakaševiÿ et al. (2023), involving thirteen patients, in situations more invasive, which required a reconstructive surgical maneuver of peri-implantitis, the addition of AH to a bovine bone substitute led to significantly superior vertical bone gains and greater implant stability (ISQ) at 3 and 6 months than in sites treated with BBS alone, providing and increasing implant stability compared to the use of the graft alone bovine.

Studies show that HA directly stimulates the development and differentiation of mesenchymal cells into osteoblasts (PRIYANKA, SADASIVAN, KOSHI, VALLABHAN, 2024; MANSOUR et al., 2024), which may have favored the observed superior vertical bone gains in the study by Rakaševiÿ et al. (2023). Literature data reveal that AH serves as a framework biological, assisting in cell migration and the formation of the extracellular matrix, thus presenting

a synergy with the bovine bone substitute matrix (POLIZZI et al., 2024). The ability of HA of increasing the effects of non-HA agents corroborates the approach of integrating it with grafting, generating the structural and functional favoring that appears to be beyond conventional clinical parameters (POLIZZI et al., 2024).

In addition, Friedmann et al. (2024) confirm the benefits of using HA in reconstructive procedures, and the good results presented, including marginal bone gain of 1.02 ± 0.64 mm and radiographic filling of 62.8% of the defect, show the regenerative potential of HA, when combined with structurally engineered biomaterials.

When it comes to conventional clinical parameters, the results of this review contain nuances that seem to be intrinsically linked to the therapeutic protocol for applying HA. For on the one hand, Sánchez-Fernández et al. (2021), through a clinical trial involving sixty-three patients (104 dental implants), demonstrated a significant reduction in PS in the treated group with HA compared to the control groups at 45 and 90 days. In addition, the levels of IL-1ÿ biomarker in crevicular fluid with topical use of HA in a non-surgical protocol to 45 days showed a reduction in the case group compared to the control group, mainly in patients with PS ÿ5 mm (49±47 pg/mL compared to 100±96 pg/mL), with no change between groups of the TNF-ÿ biomarker. This result is especially important because IL-1ÿ is a crucial cytokine in the pro-inflammatory process of the pathogenesis of peri-implantitis, which is directly associated with osteoclastic activation and tissue destruction (DUARTE et al., 2016). The use of HA, in this non-surgical context, is supported by the literature, demonstrating its ability to modulate the microenvironment of the peri-implant pocket, inhibiting neutrophil migration and reducing the expression of metalloproteinases (MMPs) (CHROSTEK, CYLWIK, 2025).

On the other hand, Rakaševiÿ et al. (2023) did not observe significant differences in PS and SS in a reconstructive surgical protocol. This may be justified because complete removal of the tissue granulation and aggressive decontamination of the implant surface alone promote a drastic reduction in inflammatory burden and PS (MANSOUR et al., 2024; HEITZ-MAYFIELD et al., 2018). Consequently, it is suggested that the anti-inflammatory side effect of HA is less accurate to be quantified statistically in these conventional clinical parameters, due to the very existence of residual inflammation minimized. In this scenario, the benefit of HA appears to be move to aspects more related to the quality of regeneration, as demonstrated by significantly greater vertical bone gain and implant stability (ISQ) observed in the work of Rakaševiÿ et al. (2023). Therefore, this literature review infers that the anti-inflammatory effect of AH may be more pronounced and easily demonstrated in non-surgical protocols, where its action was directed against the biofilm and established inflammation.

Furthermore, this review showed that the benefit of HA is also in the modulation of

peri-implant microbiome. For example, in the study by Soriano-Lerma et al. (2020), the application topical high molecular weight HA was able to control the disorderly expansion of the community pathogenic microbial, reversing the dysbiosis state associated with peri-implantitis, especially with greater effect on initial colonizing bacteria.

This dynamic is associated with positive clinical outcomes, as a less pathogenic is directly linked to a less evident host inflammatory response and less tissue destruction (BERGLUNDH et al., 2019). Thus, HA, in addition to controlling the host immune response, with reduced IL-1ÿ and reorganizing the microbial community for a less pathogenic profile, thus creating a path to recover peri-implant health.

In the initial phases, such as peri-implant mucositis, studies by Lopez et al. (2017) and Cardoso et al. (2020) indicated that the use of HA, even in the form of nebulization and rinsing, respectively, can be efficient in controlling inflammatory signs in mucositis, preventing, thus, the progression of the disease to its most invasive form, peri-implantitis. However, it is important evaluate these results with caution due to limiting factors of the studies, to which they correspond the small sample size, the lack of an independent control group and the brief follow-up, indicating that there is a need for further investigation to test such results. With this, even though studies are revealing for the beneficial use of HA in peri-pathological situations implants, these studies should be considered as preliminary proposing a theory that deserves follow-up with a better study design, as the authors themselves reinforced.

In general, due to its biological properties, as well as recent positive results addressed in this literature review, the importance of using HA in periodontal practice is evident, as well as in implantology, as a promising adjuvant biomaterial in the treatment of diseases peri-implant.

FINAL CONSIDERATIONS

The results of this literature review showed anti-inflammatory characteristics, more easily demonstrated in non-surgical, regenerative and antimicrobial HA protocols, which qualified it as a potential adjuvant for the treatment of peri-implant diseases. In However, the evidence is limited and future long-term randomized studies are required.

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