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Original Research Article

Therapeutic and Regenerative Properties of Chitosan Hydrogel in Guided Tissue Regeneration

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Abstract: Chitosan, a biocompatible and biodegradable polysaccharide, is anti-inflammatory, antimicrobial, and osteogenic. When formulated as a hydrogel, chitosan can be used as a scaffold for the release of growth factors, drugs, and stem cells, promoting periodontal tissue regeneration. This article examines the mechanisms by which chitosan hydrogel facilitates periodontal regeneration and explores its potential in clinical applications.
Keywords: Chitosan, Periodontics, Hydrogel, Regeneration.

INTRODUCCIÓN

Periodontal disease is a chronic inflammatory condition that affects the supporting tissues of the teeth, including the gingiva, periodontal ligament, alveolar bone, and root cementum. When periodontitis progresses, it can lead to loss of clinical attachment and alveolar bone, resulting in the formation of periodontal pockets and, in severe cases, tooth mobility or tooth loss. In the advanced stages of the disease, conventional treatments such as scaling and root planing may not be sufficient to restore the lost tissue. At this point, surgical regenerative approaches, such as guided tissue regeneration (GTR), may be indicated.

GTR is a periodontal surgical technique designed to stimulate the regeneration of lost periodontal tissues, including bone, periodontal ligament, and root cementum. The objective of this technique is to prevent epithelial soft tissue from proliferating into the bone defect, thereby allowing bone and periodontal ligament to regenerate more effectively. To achieve this, barrier membranes are used to protect the treated area, creating a space where periodontal tissues can regenerate without interference.

With advances in nanotechnology, the development of advanced techniques for the fabrication of structures that closely mimic the microenvironment of the natural extracellular matrix (ECM) has become possible, facilitating periodontal tissue regeneration. These new approaches not only replicate the structural and functional properties of the ECM but can also be engineered to provide controlled release of growth factors, proteins, and other bioactive elements, further enhancing the regenerative process.

In addition, these innovations have enabled the creation of surfaces with nanometric characteristics that improve cellular interactions, promoting greater adhesion, proliferation, and differentiation of periodontal cells. By allowing the integration of combined therapies, such as the incorporation of antimicrobial and anti-inflammatory agents, a more comprehensive approach to the repair and regeneration of damaged periodontal tissues can be achieved.

One biomaterial that exemplifies these advances is chitosan hydrogel, which has emerged as a promising biological compound due to its regenerative and therapeutic properties. The biocompatibility of chitosan, its ability to modulate the inflammatory response and promote angiogenesis, as well as its

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capacity to interact with growth factors and stem cells, position it as a promising biomaterial for periodontal tissue regeneration.

In the context of this review, the process of GTR would involve a non-resorbable or slowly resorbable membrane combined with the EPX trans-operative gel, meaning after thorough debridement and root planing, the periodontal defect is filled or coated with the EPX biomolecule, which is expected to provide antimicrobial and anti-inflammatory effects that stabilize the wound environment.

The aim of this review is to critically synthesize and evaluate the existing evidence comparing trans-operative biomolecule EPX gel with conventional agents for reducing periodontal probing depth and enhancing clinical attachment gain, thereby clarifying current knowledge, methodological gaps, and directions for future research.

METHODS

To carry out the literature search related to the topic, scientific databases recognized for their academic rigor were used, including PubMed, Wiley, MDPI, and Elsevier. These platforms were selected due to their broad scope and specialization in biomedical sciences and materials science, ensuring access to relevant and high-quality publications.

Specific keywords such as Chitosan, Periodontics, Hydrogel, Regeneration, and Guided Tissue Regeneration were used. These terms were combined using Boolean operators such as “AND” and “OR” to refine and optimize the search results, ensuring their relevance to the focus of the study.

Composition and Characteristics of Chitosan

Chitin is a highly relevant natural polysaccharide produced by a wide variety of living organisms. The main sources of this biopolymer are the shells of marine animals such as crab, shrimp, krill tendons, and lobster. Its extraction involves an acid treatment to remove calcium carbonate, followed by an alkaline solution to eliminate proteins. Depending on the organism from which the chitin is obtained, a decolorization step is also performed to remove pigments and obtain chitin with a clear and purified appearance.

Once high-quality chitin is obtained, it can be converted into chitosan through a process of partial deacetylation. Chitosan can be dissolved in liquid solution and mixed with different compounds to create a wide variety of products, such as fibers, hydrogels, membranes, microspheres, resins, sponges, pastes, tablets, and microgranules. This versatility makes it an essential material in various biomedical and technological applications.

According to Muhammad and collaborators (2022), chitosan membranes fabricated through electrospinning exhibit a fibrous architecture composed adhesion of both aligned and randomly oriented fibers that promote cellular adhesion. These membranes not only support extracellular matrix deposition but also act as a barrier against the junctional epithelium, maintaining the space necessary for periodontal regeneration. Furthermore, the multifunctional structure combining chitosan, polycaprolactone, and gelatin demonstrated low immunogenicity and a degradation rate compatible with the requirements of tissue regeneration. (Muhammad *et al.,* 2022)

Chitosan-based biomaterials present vary unique characteristics, including biocompatibility, which allows their safe use in contact with human tissues, and biodegradability, which facilitates their natural breakdown in the body without causing toxicity. In addition, chitosan exhibits mucoadhesive properties, enabling it to effectively adhere to moist surfaces such as mucosal tissues. It also demonstrates broad antimicrobial activity, including both antibacterial and antifungal effects, making it particularly suitable for use in environments prone to microbial contamination.

The properties of chitosan, such as its positive charge, allow it to interact with the cellular membranes of microorganisms. This interaction alters cellular permeability, thereby reducing microbial proliferation. Furthermore, chitosan exhibits additional beneficial biological properties such as cytocompatibility, biodegradability, and anti-inflammatory effects, making it a promising material for applications in periodontal regeneration. (Atia *et al*., 2022)

The hemostatic activity of chitosan, attributed to its positively charged structure, facilitates coagulation and promotes cellular proliferation, demonstrating its broad applicability in tissue regeneration and drug delivery systems. In addition to these properties, chitosan can form polyoxosalts and films, allowing it to be used in the fabrication of membranes that facilitate tissue regeneration. It also stands out for its ability to adsorb molecules, making it useful for the controlled release of drugs and growth factors, thereby enhancing tissue repair in regenerative processes. (Kołodziejska *et al*., 2021).

Characteristics of Periodontal Biomaterials

The properties of membranes used in regenerative procedures are essential to ensure effective clinical outcomes. These membranes must be biocompatible, non-toxic to the surrounding tissues, and well tolerated for achieving proper integration with periodontal fibers. Currently, two main types of membranes are used: non-resorbable membranes and resorbable membranes.

Resorbable membranes, such as collagen membranes, offer the advantage of not requiring a second surgical procedure for their removal, thereby reducing the risk of complications. However, their rapid degradation before complete tissue regeneration remains a challenge. To address this limitation, cross-linked natural or synthetic polymers are being used to develop membranes capable of maintaining their barrier properties for longer periods of time.

Hydrogels as Regenerative Biomaterials

A key aspect of hydrogels is their ability to be fabricated through different techniques. In the case of chitosan, two main types of hydrogels can be developed: those formed through chemical crosslinking and those generated by physical crosslinking. Chemically crosslinked hydrogels are produced through the covalent bonding of chitosan polymers using compounds such as epichlorohydrin or glutaraldehyde. These covalent bonds are permanent, providing greater structural stability and resistance to environmental conditions. In addition, hydrogels can also be created through photopolymerization, a process that uses light to induce crosslinking between polymer chains.

On the other hand, physical crosslinking depends on ionic interactions between chitosan (positively charged) and anions or other negatively charged polymers. Although physically crosslinked hydrogels may be less stable when exposed to external factors, they offer a significant advantage in terms of biocompatibility, since they do not require the use of chemical crosslinking agents, thereby reducing the risk of toxicity.

Ho *et al*., (2022) further explored the characteristics of natural hydrogels such as chitosan, which possess inherent biocompatibility and biodegradability. However, they also pointed out that these hydrogels present limitations in terms of mechanical strength and stability, which may restrict their application in certain regenerative treatments, although their capacity to promote cellular regeneration remains a significant advantage.

Hydrogels possess the ability to encapsulate therapeutic agents within their polymeric network, protecting them from premature degradation while enabling controlled and sustained drug release. This property has been used for the delivery of therapeutic compounds such as tetracycline and metronidazole, in varying concentrations, showing promising results in preclinical studies. These delivery systems are useful in the treatment of oral or periodontal infections, where prolonged mucoadhesion is essential to maintain the drug in contact with the affected surface. (Ho *et al*., 2022).

Chitosan in Guided Tissue Regeneration

Chitosan has been widely investigated both as a scaffold in tissue engineering and as a controlled drug delivery system due to its unique properties, including biocompatibility, biodegradability, low immunogenicity, and antimicrobial activity against bacteria and fungi. This polymer also exhibits osteoinductive effects, acts as a moisturizing agent, and enhances tissue healing. Chitosan membranes produced through electrospinning display a fibrous morphology that promotes cellular adhesion, supports matrix deposition, and maintains the space required for periodontal regeneration by preventing epithelial attachment.

Zang *et al*., (2019) investigated the effects of thermosensitive chitosan/β-glycerophosphate hydrogels loaded with Bone Morphogenetic Protein (BMP-7) and ornidazole on periodontal regeneration. Their results showed that these hydrogels not only provided a stable release of growth factors but also exhibited antimicrobial activity against *P. gingivalis*. Furthermore, bone regeneration was significantly greater in the groups treated with these hydrogels, highlighting their potential for periodontal regeneration.

Chitosan presents low immunogenicity and high biocompatibility due to its structural similarity to glycosaminoglycans, which are major components of the extracellular matrix. In 2019, Marta Calvo Catoira and her team studied chitosan as part of a vascular scaffold combined with gelatin. Their research demonstrated that chitosan modified with dextran sulfate promoted the proliferation of endothelial and smooth muscle cells, resulting in a significant improvement in tissue regeneration. These findings were observed both in vitro and in vivo, emphasizing the effectiveness of chitosan in tissue repair and regeneration.

Moreover, chitosan is the only natural alkaline polysaccharide that contains numerous free amino groups, which allow it to form hydrogels through electrostatic interactions without the need for additional agents. It can also be chemically modified to improve control over drug release through the introduction of other functional groups, such as carboxyl groups.

Xing *et al.,* (2022), developed a polymeric hydrogel membrane that rapidly crosslinks under irradiation for application in GTR in periodontal defects. Their results demonstrated that the hydrogel is biocompatible, biodegradable, and possesses favorable physicochemical properties that contribute to periodontal tissue regeneration, in addition to exhibiting antibacterial activity.

Bertsche *et al*., (2022) investigated the use of injectable self-healing hydrogels for the modulation of inflammatory processes. Their study showed that the rigidity of these hydrogels can promote fibroblast migration to affected areas, while compounds such as hyaluronic acid and exosomes modulate macrophage polarization. These hydrogels also demonstrated a positive effect on the osteogenic differentiation of mesenchymal stem cells, thereby promoting bone regeneration.

Yarahmadi *et al*., (2024) described a study in which sandwich-type scaffolds composed of polycaprolactone, gelatin, and chitosan were fabricated. These scaffolds demonstrated favorable biocompatibility and improved blood coagulation properties.

Chitosan Hydrogels

The biocompatible, antimicrobial, and osteoinductive properties of chitosan, which make it a promising biomaterial for the repair of periodontal tissues. Its structure, like the glycosaminoglycans of the extracellular matrix, facilitates cellular adhesion and promotes tissue healing. (Xing *et al*., 2022) **(Fig. 1)**

Main Properties of Chitosan Hydrogels

- High biocompatibility and low immunogenicity, ensuring safe integration with surrounding tissues. (Thambiliyagodage *et al.,* 2023)
- Ability to act as a controlled drug and growth factor delivery system, optimizing regenerative processes. (Alqahtani *et al.,* 2023)
- Antimicrobial activity, dependent on factors such as molecular structure and pH, effective against both bacteria and fungi.

Chitosan hydrogels represent a promising class of biomaterials, particularly in the context of self-healing materials, due to their dynamic nature compared to other materials. These hydrogels, which can be assembled through covalent or non-covalent interactions, are widely recognized for their potential in biomedical applications. Chitosan hydrogels, mainly composed of N-acetylglucosamine and glucosamine, are structurally similar to the glycosaminoglycans of the extracellular matrix, making them suitable for tissue regeneration applications.

The antimicrobial effectiveness of chitosan depends on several factors, including the type of microorganism, the concentration of chitosan, its molecular structure, pH, and environmental conditions. Chitosan with a lower molecular weight tends to be more effective, as its greater solubility allows better penetration into bacterial membranes.

Enzymatically solidified chitosan hydrogels have demonstrated high potential for periodontal regeneration. After implantation, these hydrogels degrade in a controlled manner without causing adverse effects on the surrounding tissues, making them a viable option for promoting periodontal ligament regeneration and tissue recovery. (Li *et al.,* 2022).

According to Thambiliyagodage *et al*., (2023), chitosan hydrogels are also ideal for reducing pain and minimizing damage to surrounding tissues during surgical procedures. Their solubility in slightly acidic environments allows them to form a solid structure once neutralized, which supports their use in guided tissue regeneration and other therapeutic applications.

A study conducted on a hydrogel composed of chitosan and carboxylated polyvinyl alcohol demonstrated excellent mechanical and adhesive properties. This hydrogel accelerated skin reconstruction by promoting processes such as angiogenesis and collagen deposition, while also exhibiting significant hemostatic and antibacterial capacity, making it suitable for tissue regeneration. (Elizalde-Cárdenas *et al*., 2024).

Recent Advances

Recently, chitosan hydrogels combined with β-glycerophosphate (β-GP) and nanohydroxyapatite (HA) have been used to enhance cellular differentiation and promote the formation of structures similar to alveolar bone.[13] Although these hydrogels are biocompatible, biodegradable, and non-toxic, their rapid degradation may represent a limitation for the regeneration of tissues that require stable volume over time.

The importance of incorporating growth factors and other bioactive molecules into hydrogel membranes to promote bone and tissue regeneration continues to grow. Advances in drug delivery technologies, particularly the controlled and localized release of these factors, may significantly improve therapeutic outcomes. (Alqahtani *et al*., 2023).

DISCUSSION

Chitosan, derived from chitin, has proven to be a highly versatile and effective material in the field of GTR, particularly in periodontal treatment. This polysaccharide is obtained from marine organisms such as crustacean shells and is processed to obtain a biocompatible and biodegradable structure, making it suitable for biomedical application. Its relevance in the treatment of periodontal diseases lies in its ability to form hydrogels, membranes, and other controlled drug delivery systems that optimize tissue repair.

Among its most notable properties, chitosan exhibits antimicrobial, osteoinductive, and mucoadhesive characteristics, which are key factors in periodontal regeneration. These properties not only help inhibit bacterial proliferation in affected areas but also promote cellular adhesion and proliferation. Furthermore, its ability to form hydrogels through covalent or non-covalent interactions makes it an ideal material for encapsulating drugs and releasing them in a controlled manner, which is particularly useful for managing microbial contamination and promoting wound healing.

Chitosan hydrogel stands out in periodontal regeneration due to its capacity to provide sustained release of therapeutic agents, such as antibiotics (tetracycline and metronidazole) and growth factors. This property is essential for the management of periodontal infections and the promotion of wound healing. Its mucoadhesive nature also ensures that it remains in contact with the affected surface, maximizing its therapeutic effectiveness. Its polymeric network encapsulates the biomolecule and releases it in a sustained manner. Its strong mucoadhesion keeps the agent in intimate contact with the root surface, providing intrinsic antimicrobial activity, by limiting colonization by pathogens such as *P. Gingivalis*, and it down-regulates early inflammatory mediators like TNF-α and IL-1β, stabilizing the wound and promoting coordinated tissue in-growth. (Li *et al.,* 2022).

This biomaterial has transformed the approach to tissue regeneration in periodontics. Nonetheless, important limitations remain, such as clinical evidence is currently restricted to pilot studies with follow-ups shorter than 12 months. The soft gel can collapse in deep vertical defects unless paired with a rigid scaffold, rapid degradation in highly exudative sites may exhaust the bioactive payload before the proliferation phase is complete, along with high production costs, also stand as a major obstacle to its broad-scale implementation.

Future research is therefore focused on hybrid formulations that combine EPX with bio ceramics or nanoparticles to add structural stiffness and staggered drug release, on 3-D bioprinting of patient-specific scaffolds, and on large, multicenter randomized trials with 12–24-month endpoints to define efficacy and long-term safety.

CONCLUSION

Chitosan hydrogel is a promising biomaterial in GTR due to its biocompatible, antimicrobial, and osteoinductive properties. It acts as a scaffold for the delivery of drugs and growth factors, promoting wound healing, cellular adhesion, and stabilization of the regenerative space.

Despite limitations such as rapid degradation and low mechanical strength in some cases, recent advances involving its combination with other materials have improved its properties, opening new opportunities in regenerative therapies. With continued improvements, chitosan holds great potential for periodontal regeneration and regenerative medicine.

APPENDIX

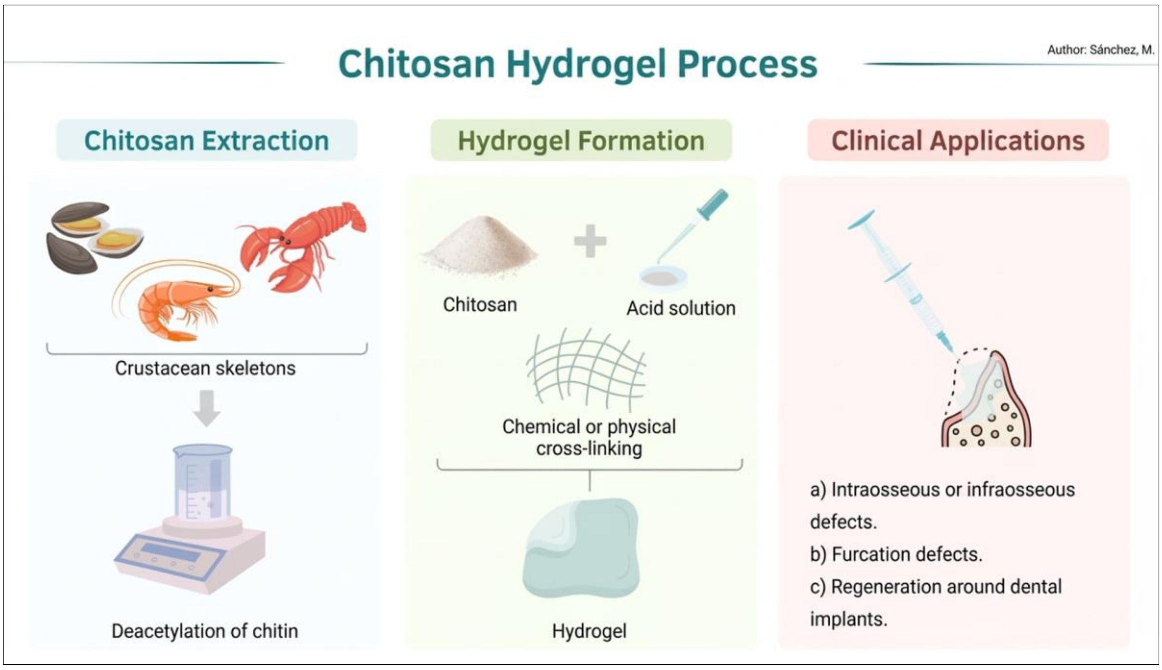

Fig. 1: Chitosan-hydrogel workflow

Exoskeletons from crustaceans are first deacetylated to convert chitin into chitosan. The resulting powder is dissolved in a mild acid solution and cross-linked (chemically or physically) to create a viscoelastic hydrogel. This injectable matrix can then be applied to intra-/infra-bony defects, furcation lesions, or peri-implant sites to support periodontal and bone regeneration.

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