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REVIEWS

THE POTENTIAL ROLE OF COLLAGEN BIOMATERIALS IN PERIAPICAL SURGERY—A REVIEW

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ABSTRACT

INTRODUCTION: Apical surgery is a method belonging to endodontic surgery, applicable in cases where conventional endodontic treatment or retreatment cannot lead to a healing process by itself. The primary objective is to create optimal conditions for the recovery of the periradicular tissue. The success of this procedure depends on various factors. Among them is the size of the bone defect. The formation of bone around the tooth root following apical surgery is crucial for its long-term prognosis. Tissue engineering has the potential to overcome the limitations of already existing bone regeneration methods through the application of scaffolding materials for the migration and attachment of cells with osteogenic potential. Natural polymers like collagen demonstrate significant suitability for these purposes.

AIM: The aim of this study is to summarize the data in the literature regarding the application of collagen biomaterials in the field of bone regeneration. The healing processes after apical surgery were examined and the potential role of collagen materials in stimulating osteogenesis was also evaluated.

MATERIALS AND METHODS: The present literature review is based on different researches in Google Scholar, PubMed, and Web of Science databases to obtain the needed information. The keywords used were: collagen-based materials, bone repair, apicoectomy, tissue engineering, and periapical surgery. All the articles that were researched were in English.

RESULTS: There is evidence for the positive impact of collagen materials on bone regeneration processes. Applied alone or in combination with other materials, the porous structure of the collagen sponge has been proven to be a favorable environment for cell adhesion and proliferation. It possesses suitable structural characteristics to be used as a potential substrate to enhance bone regeneration.

CONCLUSION: Despite collagen's favorable biological characteristics, the question regarding its influence on the proliferation of connective tissue in complicated periapical lesions remains uncertain. Presently, there is a lack of data in the literature de-

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scribing complete bone recovery in these defects achieved only by the application of collagen sponges. Further clinical studies are needed.

Keywords: *collagen, apicoectomy, collagen sponge, bone regeneration, biomaterials, tissue engineering*

INTRODUCTION

Apical surgery is a method belonging to endodontic surgery, applicable in cases where conventional endodontic treatment or retreatment by themselves cannot lead to a healing process in the periapical area (1). Periapical surgery is regarded as a final therapeutic option to preserve teeth before extraction (2). The primary objective is to create optimal conditions for the recovery of the periradicular tissue. The success of this procedure depends on various factors, including the size and location of the lesion and the extent of bone loss (3). Regeneration of lost bone tissue continues to be a challenge in contemporary dentistry. The formation of bone around the root following apical surgery is crucial for its long-term prognosis. Tissue engineering has the potential to overcome the limitations of already existing bone regeneration methods through the application of scaffolding materials for the migration and attachment of cells with osteogenic potential (4). Indeed, natural polymers such as collagen exhibit significant suitability for bone tissue engineering purposes (5).

AIM

This review aims to summarize the data in the literature regarding the application of collagen biomaterials in the field of bone regeneration. The healing process after apical surgery was examined and the potential role of collagen materials in stimulating osteogenesis was also evaluated.

MATERIALS AND METHODS

The present literature review is based on different researches in Google Scholar, PubMed, and Web of Science databases to obtain the needed information. The keywords used were: collagen-based materials, bone repair, apicoectomy, tissue engineering and periapical surgery. All the articles that were researched are in English.

RESULTS

The healing process of large lesions treated only by conventional surgery is often incomplete due to the ingrowth of fibrous connective tissue into the volume of the defect (6). This type of healing process is indicated as insufficient, despite the absence of objective clinical symptoms. Instead of the expected regeneration through the growth of new osteogenic tissues at the site of bone loss, the proliferation of connective tissue on the root surface results in repair with cells and structures different from those originally present (7,8). The criteria for assessing the presence or absence of a healing process are divided into two main groups: clinical and radiographic. Clinically, healing is indicated by the absence of symptoms such as pain, swelling, sinus tract formation, apico-marginal communication, and sensitivity during palpation and vertical percussion (9). Radiographically, assessment can be made using Rood and Shehab's classification, which defines four types of healing processes (10):

1. Complete bone regeneration around the root apex with/without a recognizable periodontal space.
2. Incomplete healing, where periradicular thinning is stationary or decreased—scar tissue
3. Uncertain healing, characterized by a partial reduction of the postoperative radiolucency.
4. Unsatisfactory healing—the radiographic signs are similar to those seen in uncertain healing, but the area of radiolucency remains the same or is increased compared to the postoperative state.

The classification of periapical lesions aims to help clinicians choose the appropriate treatment methods and materials, ensuring long-term success. Several classifications of these lesions have been described by von Arx and Cochran (11), Dietrich et al. (12), and Kim and Kratchman (2). Based on the distribution of pathological tissue, bone defects are categorized as limited to the periapical zone (four-wall defects), through-and-through defects (with resorption of the vestibular and/or palatal/lingual plate), and apico-marginal defects (where the entire vestibular bone plate is lysed) (13). According to their size, defects can be divided into three groups: equal to or smaller than 5 mm, between 6 and 10 mm, and over 10 mm (14). The pace of thehealing process is directly related to the extent and spread of the pathological lesion and the size of the bone loss.

The incisional wound following apical surgery heals through epithelial proliferation. The healing of periapical tissues involves the migration of stem and progenitor cells from the bone marrow, endosteum, periosteum, and periodontal ligament, which differentiate into osteoblasts, fibroblasts, and cementoblasts. Osteotomy healing can be broadly categorized into bone healing and dentoalveolar healing (15). Bone healing starts with hemostasis, involving the formation and stabilization of the blood clot (16). Wound healing comprises three major, overlapping stages: inflammatory phase, proliferative phase, and remodeling phase (17). These phases encompass a complex and coordinated series of events. The inflammatory phase includes chemotaxis and phagocytosis. During the proliferative phase, epithelialization and angiogenesis result in the formation of the periodontal ligament and endosteum. The remodeling phase involves active collagen remodeling and tissue maturation, potentially resulting in either scar tissue or complete healing. For bone wounds, this leads to a sequence of blood clot revascularization and the formation of a mineralizing matrix, from which immature bone matures into lamellar bone. New bone formation begins in the center and progresses outward to the cortical plates. As the newly formed bone approaches the lamina propria, the covering membrane transforms into a functional periodontium.

The dentoalveolar healing process involves the proliferation of viable cells from the neighboring periodontium onto the exposed resected root (16). These periodontal stem cells will differentiate into cementoblast-like cells and ultimately regenerate the cementum (18). Root resection, which includes both a layer of cementum and dentin, can only be restored by cementoid tissues, as periodontal stem cells cannot differentiate into odontoblasts. In the absence of infection or severe inflammation, cementum can regrow to cover the resected dentin surface.

Simultaneously, as bone formation occurs within the defect, bone is also formed peripherally by cells from the periosteum (19). Many clinical cases of large periradicular lesions and cysts involve the lysis of the periosteum. This leads to the closure of the bone wound solely with gingival tissue (subepithelial mesenchymal tissue). The primary cells in this tissue are fibroblasts, which have shorter cell division cycles and higher proliferative activity than osteoblasts. Consequently, fibroblasts invade the bone defect during the early healing processes, resulting in fibrous healing and the formation of scar tissue. This type of healing process is observed in through-and-through defects and apicomarginal defects. In most cases, four-wall defects heal through complete bone regeneration (20,21,22).

Regeneration of lost bone tissue continues to be a challenge in contemporary dentistry. The formation of bone around the tooth root following apical surgery is crucial for its long-term prognosis. The bone determines its stability and proper function. Still applicable today, many techniques for bone regeneration have been proposed and considered over time. Along with the advantages that each technique has, it also has its disadvantages, which stimulates the development of newer alternative techniques (23,24).

Tissue regeneration is defined as reproduction or reconstruction of lost, injured, or surgically removed tissue with the goal of restoring proper tissue architecture and function (25). The application of regenerative therapy in periapical surgery aims to accelerate periapical healing and create optimal conditions for restoring lost tissues in complex clinical situations (13). Although it is obvious that regeneration of the resected part of the tooth root is not feasible, tissue regeneration in apical surgery means the following: regrowth of the periradicular and alveolar bone, as well as the reformation of periodontal ligament and cementum on the resected dentinal surface.

Tissue engineering has the potential to overcome the limitations of already existing bone regeneration methods through the application of scaffolding materials for the migration and attachment of cells with osteogenic potential. Bone tissue engineering is a field focused on promoting the regeneration of bone through the synergistic combination of biomaterials and cells from the body. The goal is to create scaffolds or frameworks that mimic the natural extracellular matrix of bone, providing structural support and cues for cell attachment, proliferation, and differentiation. By utilizing the body's own regenerative capabilities and leveraging advanced biomaterials, bone tissue engineering aims to facilitate the repair and regeneration of damaged or lost bone tissue, ultimately restoring function and improving patient outcomes. Natural polymers like collagen demonstrate significant suitability for these purposes (26).

It is a well-known fact that collagen is a protein constituting a major part of the extracellular matrix in the human body. This characteristic makes it an absolutely biocompatible material suitable for in vivo application. Collagen, also called tropocollagen, is a major protein in the structure of bone tissue (27, 28). Bone tissue typically consists of approximately 18% collagen type I, 2% non-collagen proteins (such as osteocalcin and osteopontin), 70% hydroxyapatite, and 10% tissue fluids. Collagen serves as a natural scaffold for osteoblast migration, possessing unique biological characteristics such as excellent biocompatibility, osteoconductivity, and plasticity (29). These properties significantly impact cell adhesion, migration, and proliferation (30,31,32,33).

In dentistry, collagen finds widespread use in various forms such as barrier membranes, cones, fleeces, and matrices for regeneration of hard and soft tissues (34). In its various forms, it isused in the field of dental implantology, oral surgery, endodontic surgery, and periodontology, alone or in combination with other biomaterials. Collagen hemostatic sponges are made from purified and lyophilized animal substrates. They are highly absorbent and can retain many times their own weight. In medicine, they are used as local hemostatic agents because, in addition to acting as a mechanical barrier during bleeding, they also effectively influence the hemostasis (35). Thanks to their three-dimensional porous structure, combined with the ability of capturing and retaining the elements involved in hemostasis processes, they also help to stabilize the blood clot. They act as a supporting framework for platelet aggregation and subsequent formation of a stable fibrin clot (36).

Various sources are used to extract and manufacture collagen. They can be divided into two large groups—natural and synthetic. Natural collagen is obtained from animal and plant species. The most common are bovine collagen, porcine collagen, human collagen, and collagen derived from marine organisms (sea sponges, fish, and jellyfish) (37). Synthetic collagen was created in order to eliminate the main disadvantage of natural collagen—high immunogenicity and the risk of transmitting a number of diseases (e.g., bovine spongiform encephalopathy (BSE)).

The formation of a blood clot is the first step in the tissue healing process. This process is particularly critical in the oral cavity, where wounds are usually subjected to mechanical stress caused by the masticatory function, salivary invasion, and the presence of a variety of microorganisms that inevitably come into contact with the operative field during surgery or in the postoperative period. Various types of local hemostatic agents have been introduced to limit blood loss and help coagulum formation. Among the many collagen-based materials, sponges are widely used as hemostatic tools. The increased requirements for the materials used for bone regeneration predetermine and add additional requirements to them, which are reduced not only to immediate bleeding control, formation and stabilization of the blood clot, but also to the creation of a suitable microenvironment for migration, adhesion, and repopulation of new cell cultures capable of differentiation. In particular, the repair of bone defects requires a material with a structure that makes it a favorable environment for the repopulation of osteoblasts, as well as for promoting the adhesion of other cells—fibroblasts that secrete signals such as fibroblast-growth-factor 2 (FGF2), which affects osteoblast proliferation (38,39).

Several studies have explored the structural features and biological activity of collagen sponges, highlighting not only their efficacy as hemostatic agents, but also the specific characteristics favoring their application in regenerative dentistry. D'Amico E et al. (40) conducted a study in which they established the biological activity of collagen sponges. They observed the behavior of cell cultures consisting of human gingival fibroblasts (HGFs) and human osteoblasts (HOs) in vitro obtained by biopsy.

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The results were followed up by histological studies. Human gingival fibroblasts and HOs were cultured on the collagen material and their adhesion was observed under a scanning electron microscope (SEM) on day 3, and their viability—on day 3 and day 7 after culture. The mineralization capacity of the osteoblasts was also assessed on days 7 and 14 by alkaline phosphatase (ALP) enzyme assay using alizarin staining. Gene expression of ALP and osteocalcin was examined on days 3, 7, and 14. A control group was used—cells cultured of the bottom of the plate. Histological evaluation of the structure of the collagen sponge shows extremely high porosity and homogeneity, which facilitates the population of cell cultures (41). Micrographs observed by SEM show that the 3D porous structure of the collagen sponge is favorable for cell adhesion and proliferation (42). Cell species form a dense network on its surface. The size of the pores, the presence of multiple channels, and the systems inside them create optimal conditions for intercellular communication and nutrient transfer, which stimulates new cell growth. In the conclusion of the study, it is stated that the topographical and biological characteristics of the studied collagen material show that it has suitable structural characteristics to be used both as a hemostatic material and as a biomaterial which favors cellular interactions, tissue repair, and as a potential substrate to potentiate bone regeneration as well.

An in vivo study following the influence of collagen sponges on the repair of bone defects on the calvaria of rabbits proved the positive influence of collagen materials on the speed of repair of defects, compared to the control group. Histological and histomorphometric analysis at the eighth week of the study showed new bone formation in the study group and the absence of such in the control group (43).

Numerous studies have demonstrated positive outcomes with the application of collagen hemostatic sponges in various dental procedures:

1. **Ridge preservation:** Studies by Anderud et al. (44), Schnutenhaus et al. (45), and Lin et al. (46) have reported favorable results with the application of collagen hemostatic sponges for ridge preservation purposes.
2. **Elevation of the maxillary sinus floor with lateral approach:** Researches conducted by Berberi et al. (47) and Menassa et al. (48) have shown successful elevation of the maxillary sinus floor using only autologous blood and collagen sponges.
3. **Periodontal regenerative therapy:** Binlateh et al. (49) described studies indicating positive outcomes in periodontal regenerative therapy with the use of collagen hemostatic sponges.

Despite the availability of various collagen substrates, the predominant focus in the literature regarding collagen application in endodontic surgery is on its use in the form of barrier membranes (50,51,52,53). The aim is to prevent the migration of rapidly proliferating oral epithelium and gingival connective tissue into the bone defect, thereby allowing endosteal and periodontal ligament cells to colonize the blood coagulum and regenerate lost bone tissue. (54) However, the utilization of barrier membranes is associated with several drawbacks, including the risk of infection, challenges in flap repositioning and adaptation, potential for mechanical tissue trauma leading to microcommunications with the oral environment, and the occurrence of secondary postoperative infections. Some studies also suggest the risk of root resorption and ankylosis following barrier membrane application (55). In periapical defects where lysis of the vestibular plate is absent, the membrane barrier may prevent periosteal osteoprogenitor cells from proliferating into the bone defect, the aim of which is promoting new bone formation (16). It has been established that the inner cambial layer of the periosteum harbors numerous osteoprogenitor cells and osteoblasts, actively participating in initiating and driving cell differentiation during bone repair process.

Collagen, as a natural biopolymer, plays an important role in bone regeneration processes. However, despite its numerous positive qualities, its poor mechanical properties, lack of osteoinductive potential, and rapid resorption raise concerns about the success of its standalone application (6,57,58). Nevertheless, due to its excellent plasticity, it is effectively combined with other materials such as β-tricalcium phosphate, mineralized freeze-dried bone allograft (FDBA), and HA to synthesize hard scaffolds with stable mechanical characteristics (59,60,61). Collagen scaffolds can undergo further surface modifications by attaching bioactive substances like growth factors (e.g., BMP-2), cells, and drugs to promote bone regeneration (62,63).

DISCUSSION

The exact nature of regenerated periapical tissues following regenerative therapy in apical surgery remains incompletely understood. While histological examination would provide the most accurate assessment of true tissue regeneration, it is often not feasible in clinical studies, which typically rely on clinical and radiological parameters to evaluate healing outcomes. Collagen, being a major component of the natural bone matrix, is frequently utilized for bone regeneration and biomimetic applications. In comparison to many other biomimetic materials, collagen exhibits good biodegradability, biocompatibility, and adequate plasticity, leading to its wide-ranging applications. However, despite its favorable biological characteristics, the question regarding its influence on the proliferation of connective tissue in through-and-through defects and in apicomarginal defects remains uncertain.

CONCLUSION

Presently, there is a lack of data in the literature describing complete bone recovery achieved only by the application of collagen sponges. Further clinical studies are needed. Overall, collagen-based biomaterials hold great promise in facilitating the development of effective strategies for bone regeneration and tissue engineering.

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