American Journal of Medical and Biological Research, 2020, Vol. 8, No. 1, 12-16
Available online at http://pubs.sciepub.com/ajmbr/8/1/2
Published by Science and Education Publishing
DOI:10.12691/ajmbr-8-1-2

Cross-linked versus Natural Collagen Membrane for Guided Bone Regeneration? A Literature Review

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Received May 31, 2020; Revised June 23, 2020; Accepted July 02, 2020

Abstract Guided bone regeneration (GBR), a method which originates from guided tissue regeneration (GTR), is based on a concept of dividing bone from soft tissue, preventing apical migration of the gingival epithelial and connective tissue inside the defect with a membrane as a barrier which favorites proliferation of regeneration potent cells and their differentiation in the desired tissue type. Depending on the reaction to their biological surroundings, membranes can be grouped as non-resorbable and resorbable. Due to biological degradation, resorbable membranes induce tissue response, which may negatively impact wound healing and disturb regeneration. The aim of this study is to provide a review on the performance and the main outcomes of two different types of collagen membranes (Native Vs cross linked) used in conjunction with GBR in order to gain awareness of the limits and to be able to choose the right membrane required by the clinical condition.

Keywords: *guided bone regeneration, membrane, collagen, cross-linked*

Cite This Article: Adel Bouguezzi, Aymen Debibi, Abdellatif Chokri, Sameh Siou, Hajer Hentati, and Jemil Selmi, "Cross-linked versus Natural Collagen Membrane for Guided Bone Regeneration? A Literature Review." *American Journal of Medical and Biological Research*, vol. 8, no. 1 (2020): 12-16. doi: 10.12691/ajmbr-8-1-2.

1. Introduction

The reconstruction of bone defects is a complex process influenced by age, bone structure, vascularization, defect morphology and adjacent soft tissue.

The concept of guided bone regeneration (GBR) has been used in experimental maxillofacial reconstruction since the mid-1960s [1]. According to Dahlin et al. [2] the use of a membrane technique prevents the migration of fibroblasts and soft connective tissue cells into the intended regeneration site. In the intervening period, the evolution of these bone volume growth techniques has improved [3,4]. In 1996 Hermann and Buser, [5] discussed the critical surgical factors in undertaking an adequate and predictable regeneration: use of an appropriate membrane, attaining primary soft tissue healing, creation and maintenance of a membrane-protected space, close adaptation and stabilization of the membrane to the surrounding bone and sufficient length of healing period. Wang and Boyapati in 2006 [6] also published the PASS principles: primary wound closure without tension to enable proper healing by means of first intention and reduction of the risk of membrane exposure, angiogenesis to promote blood supply, space maintenance to create a bed for the undifferentiated mesenchymal cells and clot stability to allow for the proper development of these cells.

Most of the commercially available non resorbable membranes made up of expanded polytetrafluoroethylene (e-PTFE) have proven to be effective in preventing connective and epithelial tissue invasion into the healing area and could therefore promote osteogenesis. However, the membranes could be exposed prematurely, and the graft materials might become contaminated by microorganisms, leading to infections, thus hindering bone regeneration [7]. To avoid this problem, clinicians have investigated the benefits of using biodegradable collagen membranes .

This article aims to review available collagen membranes used in guided bone regeneration applications and to compare vascularization, durability, risk of exposure and regeneration volume of two different types of collagen membranes (Native Vs cross linked).

2. Materials and Methods

A literature search was performed in the PubMed/MEDLINE database and including in vitro, in vivo , human studies and reviews that reported data on Collagen membranes for bone regeneration in order to provide a review of the main characteristics, and to

compare outcomes of native collagen versus cross-linked collagen membranes .

3. Current Status of Knowledge

Collagen has many features, other than structural, including low immunogenicity, good hemostatic capacity, a chemotactic action on regenerative cells such as fibroblasts and osteoblasts and, lastly, good dimensional stability. Collagen molecule alone is not stable. Therefore, in nature it is arranged into a triple helix structure, also called collagen fibril. Many fibrils are then arranged together with a covalent cross-linked bond to obtain a collagen fiber [8]. There are different types of collagen, depending on the location and function. To date, more than 20 types have been classified. Collagen from type I to type IV are the most common in the human body and their localization is shown in Table 1.

To improve the resistance to degradation and prolonging the effect of resorbable CM, physical, chemical and enzymatic processes were developed to improve durability by cross-linking the existing collagen fibers and thus creating resorbable cross-linked CM [9,10,11]. The formation of collagen cross-links is due to the presence of two aldehyde-containing amino acids which react with other amino acids in collagen to generate difunctional, trifunctional, and tetrafunctional cross-links. The collagen molecules assembled in the naturally occurring fibrous polymer is a prerequisite for the development of these cross-links. When this is achieved, cross-linking occurs in a spontaneous, progressive fashion. The chemical structures of the cross-links dictate that very precise intermolecular alignments must occur in the collagen polymer. This seems to be a function of each specific collagen because the relative abundance of the different cross-links varies markedly, depending on the collagen tissue origin [12]. Various chemical and physical cross-linking methods, such as ultraviolet light, glutaraldehyde (which is a reference agent for the cross-linking reactions), glutaraldehyde plus irradiation, hexa-methylenediisocyanate (HMDIC), diphenylphosphorylazide, and enzymatic ribose cross-linking, have been used to boost the biomechanical properties of the collagen fibers [11]. The manufacturing process involves the extraction of collagen into monomeric fibrils, which are then reconstructed and cross-linked to form an improved collagen-based biomaterial [13].

Currently, most resorbable membranes are made of collagen and there are a variety of membranes commercially available (Table 2) [14]. It is important to be able to choose a membrane that maintains its structural integrity for the time necessary to the proliferation and maturation of the desired cells inside the wound. Commercially available CM provide different resorption time.

Table 1. Principal types of collagen [8]

Collagen Type	Principle Tissue Distribution	Cells of Origin
I	Loose and dense ordinary connective tissue; collagen fibers	Fibroblasts and reticular cells, smooth muscle cells
	Fibrocartilage	
	Bone	Osteoblasts
	Dentin	Odontoblasts
II	Hyaline and elastic cartilage	Chondrocyts
	Vitreous body of the eye	Retinal cells
III	Loose connective tissue; reticular fibers	Fibroblasts and reticular cells
	Papillary layers of dermis	
	Blood vessels	Smooth muscle cells; endothelial cells
IV	Basement membranes	Epithelial and endothelial cells

Table 2. Non exhaustive list of available collagen membranes for clinical use (n.d.=not declared) [14]

Commercial name	Produced by/For	Origin	Cross-link	Barrier effect(weeks)
Biomend	Collagen Matrix Inc.	Bovine Tendon	Yes	8
Biomend Extend	Collagen Matrix Inc.	Bovine Tendon	Yes	18
Copios Extend	Collagen Matrix Inc.	Porcine Dermis	No	24-36
Osseoguard	Collagen Matrix Inc.	Bovine Tendon	Yes	26-38
Bio Gide	Geistlich Pharma Ag	Porcine Dermis	No	24
Mem-Lock RCM	Collagen Matrix Inc.	Bovine Tendon	Yes	26-38
Mem-Lock Pliable	Collagen Matrix Inc.	Porcine Peritoneum	Yes	12-16
Ossix Plus	Datum Dental Ltd.	Porcine Tendon	Yes	16-24
Creos Xenoprotect	Nobel Biocare	Porcine	No	12-16
Biocollagen	Bioteck S.P.A.	Equine Tendon Type I Collagen	No	4-6
Heart	Bioteck S.P.A.	Equine Pericardium	No	12-16
Cytoplast	Collagen Matrix Inc.	Bovine Tendon Type I	Yes	26-38
Collatape	Zimmer -Biomet	Bovine Collagen	No	1-2
Jason	MBP Gmbh -Botiss Biomaterials	Porcine Pericardium	No	8-12
Collprotect	Botiss Biomaterials	Porcine Dermis	Yes	4-8
Dynamatrix	Keystone Dental	Porcine Submucosa	No	n.d
Ez Cure	Biomatlante	Purified Porcine-Based Type I And III Collagen	Yes	12
Conform	Ace Surgical Supply Company	Bovine Type I Collagen	Yes	12-16

4. Membrane Vascularization

There is a controversy arising from whether to apply cross-linked or non-cross-linked membranes in GBR. Although many studies have proved that with cross-linking the biodegradation of the collagen membrane is being expanded, and that they have shown positive, but limited effect on GBR in different types of experimental defect models [15,16], other studies have shown that their application associated with the initial reaction of foreign body, reduces tissue integration and with compromised trans membrane vascularization [17,18]. Despite all the disagreements, it has been shown that membrane vascularization is being improved in 2 weeks after its submucosal implantation in rats by using certain procedures of cross linking [19]. This is probably because the initial hyperemia is being caused in the neighboring tissue, which directs angiogenesis toward experimental membrane. In 2006 Schwarz et al. [19] examined the model of angiogenesis in natural and crossed-linked collagen membranes, because previous tests have shown that vascularization is weaker in cross-linked membranes. The conclusion was that angiogenesis in different types of membranes is without statistical significance. In two studies done in the Military Medical Academy, defects covered with cross-linked collagen membranes showed a better level of vascularization in comparison with defects with non-cross-linked membrane or with empty defects [20,21].

5. Membrane Degradation

The barrier durability and integrity on regenerated bone dehiscence's was carried out by Tal et al. [22] and Lee et al. [23] from histologic sections via biopsies to assess the membrane degradation with 6 and 4 months follow-ups respectively. The findings from the biopsy samples ranged from 77.8% to 100% on membrane remnants from the histologic observations on the cross-link group while no remnant was observed in the non-cross-link membrane group, although no statistical analysis was performed for this outcome.

Calciolari et al. [24] showed as native CM, derived from porcine type I and III collagen, were biocompatible and inert, did not elicit an inflammatory or foreign body reaction, and were able to promote the bone regeneration process. Membrane integrity was well maintained during the first 14 days but, at 30 days, pronounced signs of degradation, high levels of remodeling and a significant reduction in thickness were identified. Similar findings were published by Moses et al, showing significant reduction in membrane thickness from 14 to 30 days of healing, as well as a significant reduction in the total amount of collagen.

Moses et al. [25] evaluated the biodegradation of three different commercially available CM. Statistically significant differences in the amount of residual membrane material were recorded within each membrane (among different time moments) and among different membranes at the same time moments. At 28 days, the least amount of residual collagen area was observed in the non-cross-linked membranes (13.9% ± 10.25%), followed by the glutaraldehyde cross-linked (24.7% ± 35.11%) and ribose cross-linked (91.3% ± 10.35%) groups. Residual membrane thickness, expressed as the percentage of baseline thickness, presented a similar pattern

Rothamel [26] concluded that the processing techniques influenced the collagen properties in a different intensity. Dehydrothermal cross-linking and special defatting did not notably change the biodegradation pattern, whereas cross-linking using ethylene dioxide led to significant higher volume stability of the matrix.

Hurzeler et al [27] reported that the noncrosslinked membrane maintained the structure of collagen for more than 6 months.

Moses et al [25] reported that membranes cross-linked with ribose showed a lower degree of degradation than non-cross-linked membranes and those cross-linked with glutaldehyde.

6. Premature Membrane Exposure and Wound Infection

Post-surgical complications may appear during a GBR, premature membrane exposure being to the oral environment and subsequent bacterial colonization the most frequent. This complication has been reported to be common problems of non-resorbable membranes, which could necessitate their premature retrieval.

In a systematic review conducted by Garcia [28], he found that spontaneous non-cross-linked membrane exposures ranged from 11% to 32.1%. From the crosslinked membrane groups, Ossix® cross-linked membranes recorded rates from 12.5% to 50% and for VN® cross-linked membranes, rates ranged from 52.17% to 56%. All authors from the included studies reported statistically significant differences between the two types of membranes for this outcome.

Clinically, chemical cross-linking was accompanied by more adverse events such as wound dehiscence, graft exposure and insufficient bone regeneration [29], based on the compromised tissue integration.

Chemically cross-linked CM have longer degradation times but also have significantly higher membrane exposure rates, up to 70.5% [25,30]. In case of a premature exposure, cross linked collagen membrane was associated with an increased frequency of wound infections [31].

7. Volumetric Bone Regeneration

The efficacy of these membranes is still controversial. Friedmann et al [32] reported that on exposure, cross-linked collagen membranes maintained more grafted bone volume than e-PTFE membranes. In contrast, Bornstein et al [16] reported that in animal studies, cross-linked membranes showed limited bone regeneration when compared to other collagen membranes. When these membranes were exposed early, complications associated with soft tissues increased.

In a recent human study [31], comparisons of cross-linked to non-crosslinked conventional collagen membrane, placed at implant dehiscence sites showed that both membranes yielded comparable bone regeneration

results. Nevertheless, it was concluded, that premature membrane exposure of the cross-linked membrane might impair soft tissue healing or may even cause wound infections.

Brunel et al. and Mattson et al. [10,33] noted that the slower resorption degree of the collagen membranes depends on the intensity of crosslinking between the collagen fibers of the resorbable membranes and therefore suggest an increase in regenerated bone volume in membranes with longer resorptions.

Simion et al [34] reported that exposed membranes showed significantly decreased bone regeneration (41.6% vs 96.6%).

8. Conclusion

In the collagen membrane family, the choice between cross-linked and non-cross-linked CM may affect their clinical use. Within the limitations of the present systematic review w, it can be concluded that the degree of cross-linking of collagen fibers, indeed, have shown to affect the degradation rate, and the preservation of the underlying bone graft. Longer degradation times and membrane resistance to resorption, however, are also linked to a significantly higher exposure rates for cross-linked collagen membranes, and, sometimes, a foreign body reaction during resorption.

9. What Is Known About This Topic

- Currently, most resorbable membranes are made of collagen and there are a variety of membranes commercially available.
- To improve the resistance to degradation and prolonging the effect of resorbable collagen membranes, physical, chemical and enzymatic processes were developed to improve durability by cross-linking the existing collagen fibers

10. What This Study Adds

- It is important to be able to choose a membrane that maintains its structural integrity for the time necessary to the proliferation and maturation of the desired cells inside the wound.
- Chemically cross-linked CM have longer degradation times but also have significantly higher membrane exposure rates.
- Exposed membranes showed significantly decreased bone regeneration.

Competing interests

Authors declare that they have no conflict of interest.

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