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A Review polylactic acid and gelatin biomaterial GBR (Guided Bone Regeneration) and multilayer GBR membranes

Polilaktik asit ve jelatin biyomateryali GBR (Kılavuzlu Kemik Rejenerasyonu) ve çok katmanlı GBR membranları çalışmaları

***Yazar(lar) (Author(s))**: Ozge Kamaci[1], Necla Yucel[2], Hasan Koten[3], Erdi Bulus[4], Gulseren Sakarya Bulus[6]*

ORCID[1]: 0000-0002-8660-0597

ORCID[2]: 0000-0003-0093-2521

ORCID[3]: 0000-0002-1907-9420

ORCID[4]: 0000-0002-2045-2499

ORCID[5]: 0000-0001-6096-8177

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Highlights

- *Tissue engineering*
- *GBR*
- *PLA*
- *Material Engineering*
- *Gelatin*

Graphical Abstract

The subject of this review is to examine the general properties of GBR systems, which is an innovative medical device, and to make a general evaluation in terms of osteoconductivity. The purpose of this review is to examine GBR membrane systems as an overview of GBR membrane systems and multilayer GBR applications made from gelatin (GEL) and polylactic acid (PLA) polymers, which are easy to find as materials and more affordable in price. In addition, it is aimed to contribute to the work of young scientists who will work on GBR membrane systems.

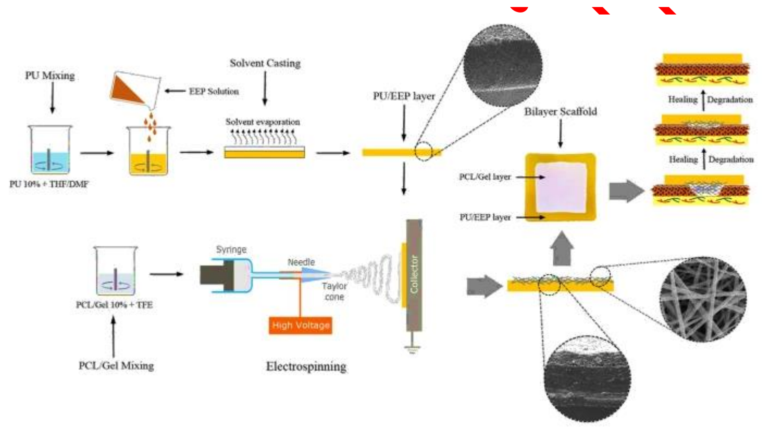

Figure 1. Preparation of double-layer dressing [18].

Aim

The subject of this review is to examine the general properties of GBR systems, which is an innovative medical device, and to make a general evaluation in terms of osteoconductivity.

Design & Methodology

Different studies are summarized and interpreted together in literature.

Originality

The study will fill an important gap in the literature.

Findings

Different studies are summarized and interpreted together.

Conclusion

The subject of this review is to examine the general properties of GBR systems, which is an innovative medical device, and to make a general evaluation in terms of osteoconductivity.

Declaration of Ethical Standards

The author(s) of this article declare that the materials and methods used in this study do not require ethical committee permission and/or legal-special permission.

A Review Polylactic Acid and Gelatin Biomaterial GBR (Guided Bone Regeneration) and Multilayer GBR Membranes

Derleme Makalesi/Review Article

Ozge Kamaci[1], Necla Yucel[1,2], Hasan Koten[3*], Erdi Bulus[4,5], Gulseren Sakarya Bulus[6]

[1]Nanoscience and Nanoengineering Master's Program, Graduate Education Institute, Istanbul Medeniyet University, Turkey,
[2]Istanbul Arel University, Faculty of Engineering and Architecture, Biomedical Engineering Department, Bioinspired Functional Polymers and Nanomaterials Laboratory, Turkey, necla-ycl@hotmail.com
[3]Engineering and Pure Science Faculty, Mechanical Engineering Department, Istanbul Medeniyet University, Turkey,
[4]Polymer Science and Technology Program, Institute of Science and Technology, Kocaeli University, Turkey
[5]ArelPOTKAM (Polymer Technologies and Composite Applications and Research Center), Istanbul Arel University, Turkey,
[6]Silivri District Health Directorate, Turkey,

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ABSTRACT

The reflections of the rapid development of technology are clearly seen in the health sector, especially in the field of tissue engineering. The road covered by tissue engineering and nanotechnology branches is frequently encountered in the field of innovative medical devices. It is an undeniable fact that the innovations brought by materials science in the dental field such as dental prostheses and implants within the scope of medical devices increase the quality of life. There are various brands and models of oriented bone membrane (GBR) membrane systems in the dental medical market. The subject of this review is to examine the general properties of GBR systems, which is an innovative medical device, and to make a general evaluation in terms of osteoconductivity. The purpose of this review is to examine GBR membrane systems as an overview of GBR membrane systems and multilayer GBR applications made from gelatin (GEL) and polylactic acid (PLA) polymers, which are easy to find as materials and more affordable in price. In addition, it is aimed to contribute to the work of young scientists who will work on GBR membrane systems.

Keywords: Tissue engineering, dental, oriented bone membrane (GBR), gelatin, polylactic acid (PLA).

Polilaktik Asit ve Jelatin Biyomateryali GBR (Kılavuzlu Kemik Rejenerasyonu) ve Çok Katmanlı GBR Membranları Çalışmaları

ÖZ

Teknolojinin hızlı gelişiminin yansımaları sağlık sektöründe özellikle doku mühendisliği alanında açıkça görülmektedir. Doku mühendisliği ve nanoteknoloji dallarının kapladığı yol, yenilikçi tıbbi cihazlar alanında sıklıkla karşımıza çıkmaktadır. Tıbbi cihazlar kapsamında diş protezleri ve implantlar gibi diş hekimliği alanında malzeme biliminin getirdiği yeniliklerin yaşam kalitesini artırdığı yadsınamaz bir gerçektir. Diş hekimliği pazarında çeşitli marka ve modeller yönlendirilmiş kemik membran (GBR) membran sistemleri bulunmaktadır. Bu derlemenin konusu, yenilikçi bir tıbbi cihaz olan GBR sistemlerinin genel özelliklerini incelemek ve osteokondüktivite açısından genel bir değerlendirme yapmaktır. Bu incelemenin amacı, GBR membran sistemlerine genel bir bakış olarak ve malzeme olarak bulunması kolay ve fiyatı daha uygun olan jelatin (GEL) ve polilaktik asit (PLA) polimerlerinden yapılan çok katmanlı GBR uygulamalarını incelemektir. Ayrıca GBR membran sistemleri üzerinde çalışacak genç bilim adamlarının çalışmalarına katkı sağlanması hedeflenmektedir.

Anahtar Kelimeler: Doku mühendisliği, diş hekimliği, yönlendirilmiş kemik membranı (GBR), jelatin, polilaktik asit (PLA).

1. INTRODUCTION

Today, the rate of people with periodontal diseases is determined to be 50% even in developed countries such as the USA [1]. It is known that the process that starts with gingivitis ends with tooth loss [2]. Stopping this rapidly progressing mechanism, defects, ie areas of bone loss, are intervened with biomaterials called guided bone membrane (GBR) systems.

**Sorumlu Yazar (Corresponding Author)*
e-posta : hasan.koten@medeniyet.edu.tr

The first discovery of the GBR membrane emerged in the 1980s, based on the observations made by dentists during the treatment of tooth roots in a group of patients who underwent periodental treatment. A group of scientists noticed that during the periodontium treatment, the cells coming from the alveolar bone structure in the root of the tooth were directed to the tooth root of the patient and multiplied there, and they realized that the alveolar bone cells act as a barrier because the resulting structure prevents the entry of epithelial and connective cells around the tooth; They proposed the artificial membrane hypothesis. In this context, based on the hypothesis, the first artificially oriented bone membrane was produced in 2009 by Mateo Chiapasco. The purpose of guided bone membranes is to restore bone regeneration in the damaged area and prevent the entry of surrounding epithelial or gingival tissues into the area during bone development [3].

The most important purpose of the membrane system is to provide bone and tissue regeneration of the defected area, re-establish angiogenesis lines and create a barrier area to prevent epithelial cells such as fibroblast from entering the relevant area [4].

The purposes in creating space for the defected area can be listed as follows;

• Separating gingival (gingival) junction cells from tooth root, especially in gum diseases

• preventing the tissues formed by the periodental ligament cells from sinking in,

• Re-development of damaged bone tissue in the area left empty.

GBR membrane system is a technique used not only in gum diseases but also in maxillofacial surgery and diseases such as bone atrophy [5].

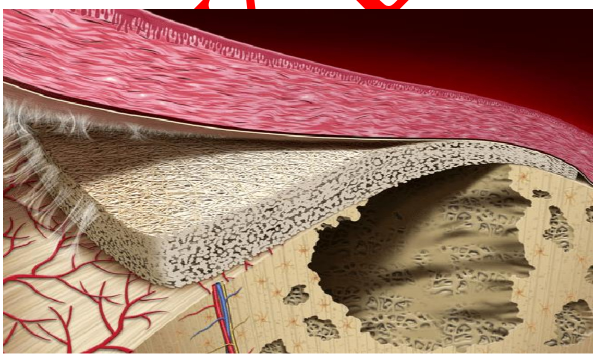

Figure 1. GBR membrane technology placed in the tooth root [5].

Like many medical devices that concern human health and are applied directly or indirectly to humans, GBR membrane systems must be biocompatible. The reason for the biocompatibility criteria in medical devices is sought because they are in direct or indirect contact with blood, body fluids, tissues and organs, so they should not cause side effects on the body.

GBR types and characteristics

Oriented bone membranes are divided into two as absorbable membranes and non-absorbable membranes according to the material and application areas.

Non-absorbable membranes:

Non-absorbable membranes are divided into two according to the materials they are made of: these are defined as expanded polytetrafluoroethylene (PTFE), high density PTFE. In addition, titanium, which is the main implant material frequently encountered in medical devices, is also used with the PTFE group [6].

Non-absorbable membranes are biocompatible like all GBR membranes. Since they are generally used on hard and high pressure floors such as maxillofacial surgery, oral and maxillofacial surgery, they are made of more durable materials than mechanically absorbable membranes. However, it is known that it has some disadvantages during application. Namely; A second surgical intervention may be required while some non-absorbable GBR membranes are applied to the patient, while they are removed [7].

Lee et al conducted a study on the efficiency of PTFE types on the healing effect of Teflon, one of the non-absorbable membrane materials, on the defect area. In the study, they compared two non-absorbable GBR membranes made of e-polytetrafluoroethylene (expanded teflon) and d-polytetrafluoroethylene (high density teflon) material. In the study, two different non-absorbable Teflon-based GBR membranes were applied to two different patient groups; The healing volumes and dimensions of the defected areas of the teeth of the patients were measured. After GBR membrane application, the membranes were removed from the patients' mouths with a second surgical intervention. In the meantime, according to different GBR models in the defective areas, the absorption of the membranes and how much of the wounds were covered was measured. According to this evaluation, it was observed that the closure of wounds was equivalent in both the high density Teflon GBR membrane and the expanded Teflon GBR membrane, and there was no statistically significant difference [8].

Absorbable GBR membranes:

Another type of absorbable membranes are divided into natural, synthetic and hybrid membranes according to the origin of the material from which they are made.
Natural GBR membranes; It can be diversified into collagen (Type I) (Col), chitosan (CS), chitosan-collagen (CS-Col), alginate (ALG) and their hybrids. Absorbable synthetic membranes; Generally, aliphatic polyester sourced PLA, polyglycolide (PGA), polycaprolactone (PCL) and their derivatives are used [9]. Both absorbable membranes and non-absorbable membranes have advantages and disadvantages in terms of mechanical and osteoconductive properties. It is listed in the tables below [10].

Table 1. Advantages and disadvantages of non-absorbable GBR membrane systems [10].

Advantages	Disadvantages
Mechanical stability of the graft or the space under the membrane	Increased risk of exposure
Excellent biocompatibility	Increased risk of soft tissue ingrowth
Stiffness which is suitable for space maintenance, wound stability and successful bone regeneration	Increased risk of infection after exposure
Plasticity, allows for bending, contouring and adaptation to any defect morphology	Necessary primary fixation of the membrane at the initial surgery
	Necessary second surgery to remove it
	Technique-sensitive approach

Table 2. Advantages and disadvantages of absorbable GBR membrane systems

Advantages	Disadvantages
Decreased patient morbidity	Uncontrolled duration of barrier function
No need for second stage surgery to remove the membrane	The need for tenting screws and bone to support the membrane and to avoid its collapse
Simplified surgical procedure	Remnants of the membrane found in direct contact with dental implants
Lower rate of exposure	Micromovement of the membrane leads to movement of grafting material and disruption of the blood clot
	Memory, especially for the highly cross-linked membranes

In addition to these shapes; Col sourced membranes, one of the most used GBR membrane systems, are widely used. However, it is known to be expensive in terms of price and weak mechanically [11]. Bovine membranes from Col membranes have been shown to delay vascular penetration, and there are studies indicating that they inhibit bone regeneration [12]. Another disadvantage that can be added to the use of synthetic GBR membranes is that it is metabolized and broken down by the whole body during absorption, but during this process, the cells in the tissue with the barrier decrease the pH balance and increase inflammation [13].

In terms of these shortcomings and problems, GBR membrane techniques; With the advancement of materials science, it creates an area open to continuous improvement, where new strategies can be applied.

2.USE OF PLA AND GEL POLYMERS IN TISSUE ENGINEERING APPLICATIONS

Both PLA and GEL are biomaterials frequently used in the production of separate cytoskeletons and dressings. Although there are different techniques in the use of both polymers in the literature, the use of hydrogel composite is the most suitable method of use for artificial cell scaffolds and grafts.
Due to its structure close to GEL hydrogel, it is best used with PLA in this way. The use of hydrogels as a scaffold in bone tissue engineering has some advantages; Mechanical stability, gradual degradation of the material to aid tissue regeneration, repair of irregular shapes and defects with minimally invasive surgery, and finally, transport of small molecules and their controlled release are among these advantages [14].

GBR membrane studies made from PLA and GEL biopolymer and features of multi-layer GBR membranes:

The first double-layer membrane system developed is Guidor Matrix Barrier. PLA, poly-L-lactide (PLLA) were used as ingredients and acetyl tri butyl citrate (ATBC) were used as additives. In addition, a Col-based double-layer membrane called BioGide is now available to patients [15].
In the latest double-layer membrane samples, it was studied in two layers. The first hard layer is produced to act as a barrier, and the other is a soft porous layer, produced to support cell passage. Another reason for double-layer membrane production is based on the hypothesis that two layers can be stronger than a single layer [16].
It is known that material scientists and bioengineers have increased their work to produce multilayer GBR membranes and produce multilayer GBR membranes with new biopolymer combinations.
There are many absorbable and non-absorbable multi-layer products in the medical market. The origin of the material from which they are made are given in the tables given below [17].

Table 3. Non-absorbable GBR membrane brand and material contents [17].

Product (Company)	Material	Resorption Period
BoneShields® (FRIOS)	Titanium	Non-resorbable
Cytoflex® Tefguard (Unicare Biomedical)	PTFE	Non-resorbable
Cytoplast™ Ti- Reinforced (Osteogenics Biomedical)	Ti-PTFE	Non-resorbable
Gore-Tex® (Gore-Tex®)	e-PTFE	Non-resorbable
T-Barrier membrane (B&B Dental)	Titanium	Non-resorbable
TefGen-FD	PTFE	Non-resorbable
(Keystone Dental, Inc.)		
Ti-Micromesh (ACE)	Titanium	Non-resorbable
Tocksystem (MeshTM)	Titanium	Non-resorbable

Table 4. Absorbable synthetic origin GBR membrane brand and material contents [17].

Product (Company)	Material	Resorption Period (months)
Guidor® (Sunstar)	PLA (Polylactic Acid)	1.5 - 2
Resorb X® (KLS Martin)	PDLLA (Poly-DL-Lactic Acid)	1.5 - 2
Cytoflex Resorb® (Unicare Biomedical)	PLGA (Poly-Lactic-Glycolic Acid)	4
Resolute® (Gore®)	PGA-TMC (Polyglycolic Acid Trimethylene Carbonate)	4 - 6
Epi-Guide® (Curasan, Inc.)	PDLLA (Poly-DL-Lactic Acid)	6 - 12
Atrisorb (Tolmar)	P(DL)LA – NMP (Poly-DL-Lactic Acid)	9 - 12
Inion™ GTR (Inion)	PLDLGA-TMC (Poly-LD-Lactic-Glycolic Acid Trimethylene Carbonate)	12 - 24
Vivosorb® (Polyganics)	PDLLCL (Poly-DL-Caprolactone)	16

Table 5. Absorbable natural polymer origin GBR membrane brand and its contents [17].

Product (Company)	Material	Resorption Period (months)
CollaPlug® (Zimmer Dental)	Type I bovine collagen	0.5
BioMend® (Zimmer Dental)	Type I bovine collagen	2
Healiguide™ (Encoll)	Type I collagen	1-3
GenDerm (Genius biomaterials)	Type I bovine collagen	3
Surgidry Dental F (TechoDry Liofilizados Médicos Ltda Brazil)	Type I bovine collagen	3
conFORM™ (ACE Surgical Supply Co., Inc.)	Type I bovine collagen	3-4
Mem-Lok® Pliable (BioHorizons)	Type I porcine collagen	3-4
Renovix™ (Salvin®)	Type I porcine collagen	3-4
creos™ xenoprotect (Nobel Biocare®)	Porcine collagen and elastin	3 - 4
EzCure™ (Biomatlante Biologic Solutions)	Type I and III porcine collagen	3 - 6
BioMend® Extend (Zimmer Dental)	Type I bovine collagen	4 - 5
OSSIX® PLUS (Datum Dental)	Type I porcine collagen	4 - 6
Kontour™ (Implant Direct)	Type I porcine collagen	4 - 6
Mem-Lok® Pericardium (BioHorizons)	Allograft of human pericardium tissue	4 - 6
BioGide® (Geistlich Biomaterials Switzerland)	Type I and III porcine collagen	6

Studies have been carried out indicating that the multi-layer application idea in GBR membrane systems has recently been used in wound dressings. Since the working principle of wound dressings is to prepare an environment that will allow stench and tissue regeneration in the defected area, it is among the new developments in this field that systems such as multi-layer GBR membrane systems are used in wound dressings.

Eskandarinia et al, developed the multi-layer dressing in 2020, consisting of more than one polymer and composite. Namely; A two-layer dressing was made as a dense layer and a top layer. Dense layer consists of knitting PCL and GEL with electrospinning technique. The top layer, on the other hand, was prepared from etonolic (PE) extract of propolis and polyurethane (PU) and an innovative two-layer wound dressing was developed by bonding two different layers together. In this way, since the content of PCL / GEL-based substrate is GEL, it attracts the fibroblast cells to the substrate, adheres and develops, while the upper layer provides bacterial prevention, which is the most important condition sought in wound dressings, especially since it contains etonolic propolis (EP). Thus, each layer has its own advantages: it has been observed that the top layer protects the wound from infection and mechanical stress, and also ensures that the injured area remains moist, while the lower layer provides cell adhesion and proliferation by mimicking the extra cellular matrix [18].

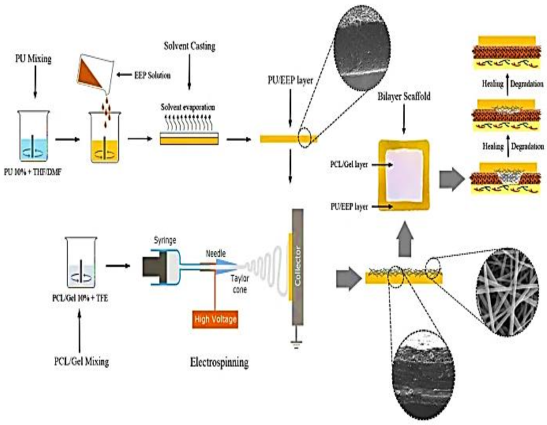

Figure 2. Preparation of double-layer dressing [18].

Speaking of GEL biopolymer; It is seen in the literature that it is frequently used in many wound dressings and especially in bone membrane systems. The reasons why GEL is widely used as a polymer in tissue engineering applications is that it is a natural polymer that is biocompatible, suitable for cell adhesion, and flexible as a protein structure. In addition, the most important feature of GEL is that it is formed as a result of different processing of Col. Another important feature is that the cytoskeleton binds to actin and myosin filaments, providing a suitable environment for cells to adhere and proliferate [19].

Considering an example where GEL is used as a double-layered artificial tissue material with PLA, it has been revealed that GEL is suitable for use as an artificial vein material due to its structural properties such as elasticity. Verduzco et al, in 2019, developed artificial veins with electrospinning technique in order to eliminate the discomfort caused by vascular occlusion, one of the cardiovascular diseases. The artificial vascular system made is called the "core-shell" because, as the inner structure of the vein must be harder and more durable, a syringe of the electrospinning device to act as a core is called PLA; GEL was placed in the other syringe of the electrospinning device to act as a shell in order to provide elasticity and cell adhesion. In this way, the inner layer of the artificial vein consists of PLA and the outer layer of GEL. In addition, while creating this artificial vein, 8 different samples were prepared as PLA only, GEL only, or composite; Genepin rich in carbon was used as crosslinker. Accordingly, the PLA / GEL artificial vein sample prepared as a composite was observed as a more suitable candidate for cell proliferation [20]. As it can be understood from this example, it is a good example that PLA and GEL can actually be knitted with electrospinning method similar to the two-layer membrane system and create an artificial vessel scaffold.

3.PLA AND GEL BASED GBR MEMBRANE CASE STUDIES

In addition to the advantages that PLAs, which are synthetic polymer derivatives, provide to GBR systems such as three-dimensional porous structure and mechanical stability, they have some disadvantages when used as a material due to their chemical structure. These; Due to the hydrophobic surface properties of PLA, it is a structure that is open to inflammation due to the low rate of cell adhesion to the surface, slow fragmentation, stable structure, acidic environment formed during its degradation [21]. Due to the limitation of the use of PLA in the field of tissue engineering, which is formed as a result of its chemical bond structures, it has been observed that it would be more appropriate to use it with PLA nanomaterials in recent studies.

Hwank et al. Prepared GBR membranes by covering PLA fibers prepared with electrospinning in 2020 with tantalum nano material. Tantalum has recently been known to increase the strength of materials and to increase osteoconductivity in cell scaffolds where it is used. In the study, some of the PLA fiber samples prepared by electrospinning method were coated by spraying tantalum; some are not covered. The prepared GBR membranes were subjected to mechanical and cellular tests. In the result; It has been observed that Ta-PLA coated membranes are mechanically more stable and most importantly their osteoconductive effects are more intense than GBR membranes containing PLA alone. In addition, when looking at collagen activity in the rest of the study, it was observed that Ta-coated PLA membranes had greater activity and contributed to bone regeneration [22].

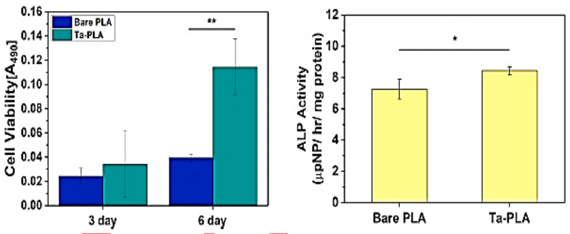

Figure 3. Cellular activation and Col formation rates (ALP activation) in PLA and Ta-PLA GBR membranes [22].

When the study of Pyzik et al, which took into account the diameter of the pore in 2016, was examined, it was seen that PCL and PLA biopolymers prepared fibers with two different processing methods. They produced GBR membranes knitted with PLA electrospinning and PCL milling drying method. Then a combination of both processing methods was prepared, that is, the new GBR membranes were subjected to application and testing with electrospinning-freezedrying methods. Accordingly, in the combination method, it was observed that the pore diameters were tighter since PLA was processed with electrospinning. It has been noted that when processed in PCL freezedrying, it forms a larger pore diameter fiber structure depending on the concentration. They have formed asymmetric pore structures by applying two methods. This asymmetry in pore structures prevented soft tissue cells from entering the defect area; It paved the way for bone cells to settle and proliferate in the GBR membranes produced. In this respect, the use of GBR membranes with different asymmetric pore diameters has been found appropriate [24]. Since mechanical stability is as important as osteoconductive effect in GBR membranes, the mechanical strength of the GBR membrane created with the PLA / PCL two production combination is higher than the PLA membrane produced by the electrospinning method and the PCL membrane produced only by freeze drying. This shows that it takes an appropriate approach to the ideal GBR membrane structure.

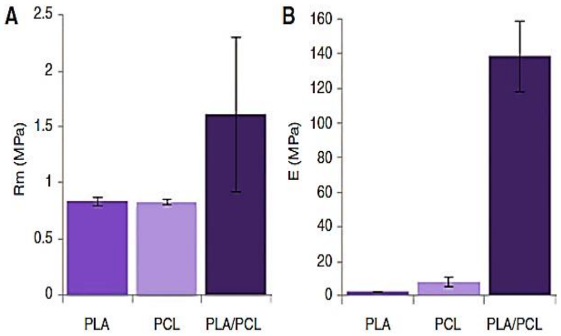

Figure 4. (A) Tensile-tensile strength B) Maximum flexural strength [24].

According to the study conducted by Noritake et al. In 2014, it was thought that the designed membrane, which is expected from oriented bone membranes, should be able to mimic the physical structure of the bone mechanically in the most appropriate way, therefore, they used GEL biopolymer in their studies. However, since GEL alone could be insufficient mechanically, beta-tricalcium phosphate (β-TCP), which is a protein that increases bone development and gives bone hardness, was used as a powder. They prepared GEL as a hydrogel by freeze drying method and added β-TCP as a powder. According to the results of the study; It has been subjected to a stretch test with Col-GBR membrane, which is available in the market, to evaluate the mechanical stretching of the bone. It has been revealed that the GEL based membrane prepared accordingly is more flexible than the Col membrane sold in the market. Likewise, bone marrow cells were planted on both membranes. It has been observed that the GEL based membrane has a faster osteoconductive effect than the Col membrane in the market. The reason is thought to be caused by the combination of GEL and β-TCP [25].

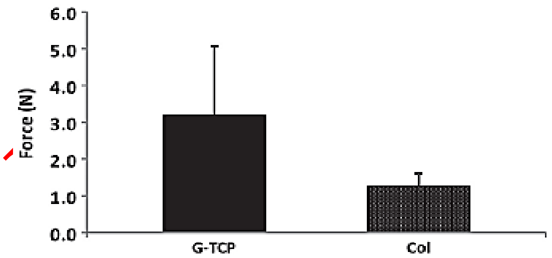

Figure 5. Tensile-tensile strength ratios of G-TCP and commercially available Col GBR membrane [26].

It is known that GEL is generally used in the use of GBR membranes, not as a single material, but as double or triple biomaterial composites as mentioned before. When looking at a study in which GEL was made as a triple composite, it is stated that the bone enhancer-TCP added in the content should be added in sufficient concentration. Accordingly, Ezati et al. Created a composite from PCL, GEL and CS polymers in their study in 2019. GBR membrane systems were prepared by electrospinning method (PGC, PGCT1, PGCT3, PGCT5) by adding β-TCP in different concentrations (1%, 3% and 5%) to the composites formed. The formed membranes were subjected to mechanical (stretching, stretching-pull), water retention angle and cell activation tests. It has been observed that as β-TCP concentration increases, the angle made by the membranes with water decreases. Considering the mechanical strength, it is understood that the GBR membranes with high concentration β-TCP are more durable and their elongation percentage is higher in tensile tensile tests. The reason for this is that β-TCP, which is usually added to GBR membranes, is understood to reduce the pore diameter of the membranes. When looking at cellular activity, β-TCP is known to increase bone development and Col activation (ALP). Similarly, there is an increase in osteoblast cells planted on GBR membranes with high concentration β-TCP, but when a certain time threshold is exceeded, the cells themselves It has been found that it tears itself apart [26].

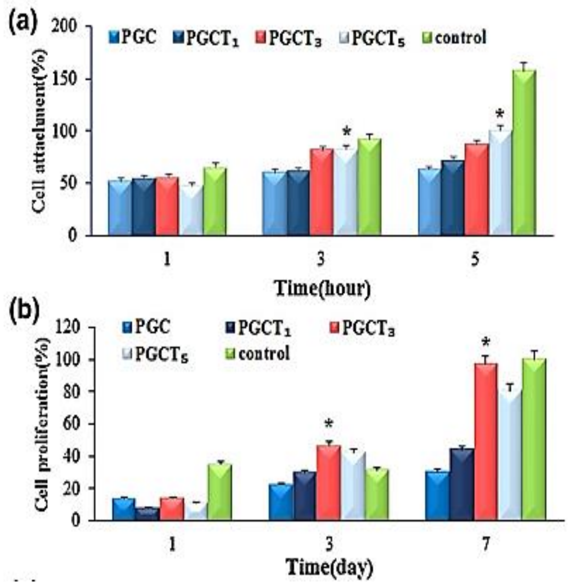

Figure 6. Ezati et al, Time dependent cell proliferation in GEL, PCL and β-TCP composite membranes [26].

4.MULTILAYER GBR MEMBRANE WORKS

When the building materials of GBR barrier membranes are examined, it has been mentioned before that synthetic polymers, natural polymers and hybrid composite materials are produced. Especially absorbent GBR membranes are produced from Teflon and its derivatives. When absorbable GBR membranes are examined closely, the first building materials that attract attention are known to be produced from PLA, PCL, PGA and other copolymers as synthetic polymers. Synthetic polymers give GBR membranes sought-after properties such as excellent biocompatibility, flexibility due to their plasticity structure, processability and especially ease of drug transport systems. Apart from that, proteins such as silk (FB), Col, fibronogen (FBR), elastin (ELA), as well as cellulose with glycosaccharide properties, glycosaminoglycans and chitin are used as absorbable GBR membrane building materials. These natural polymers are more biocompatible than synthetic polymers. However, it also has undesirable features such as faster fragmentation [27].

The low cell adhesion to the surface due to the hydrophobic nature of synthetic membranes, as well as the rapid fragmentation of natural polymers and insufficient mechanical properties have led to the idea of forming a two or three layer membrane. In addition, controlled fragmentation, which is the most important point in GBR membranes, is possible thanks to two or three layers of polymer layers.

When we examine the above-mentioned GBR membrane building materials kit, it is known that CS, which is a different form of the kit, is used in many artificial materials in tissue engineering applications. CS is the de-acidified form of chitin, and its reasons for using in tissue engineering applications and GBR membrane systems; It is biocompatible, does not cause inflammation in the body when broken down, and has antimicrobial properties [28].

Although it is known that the use of CS is intensive in multi-layer GBR membranes, the reason is that the amine groups in the chemical content of CS can easily break down by-products such as polyhydroxyacid and also the glucosamine groups in its content in the ecastrasellular matrix, which creates the idea that it is a suitable building material in terms of biocompatibility [29].

When examining the multi-layer GBR / GTR membrane application of CS, biomaterial; In the multi-layer guided tissue regeneration (GTR) membrane design study by Ku et al. They decided to create the outer layer of the membrane from CS using PLLA. Multi-layer GBR composite membranes from PLLA and CS polymers are prepared by the cast-drying method.

Membranes have been subjected to mechanical, cellular evaluation tests. According to the results; Since it is formed from the CS polymer on the outer surface, it has a rough structure and enables the cells to adhere. In addition, since the outer surface is from CS, CS has similar groups with the extracellular matrix, allowing osteoblast cells to adhere. PLLA prevents the rapid dispersion of CS due to its mechanical tensile-tensile strength; It has met the desired mechanical strength in the GBR membrane. In the study, it was observed that the defect opened in the upper part of the skull started to close the outer border line of the wound in 4 weeks and the entry of soft tissues was prevented. With this, the formation of new bone form has begun [30].

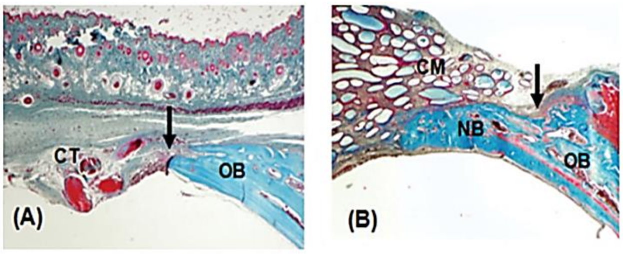

Figure 7. (A) non-membrane skull defect (4 weeks after wound opening), (B) skull defect with multiple layers of membrane with PLLA and CS; CM: PLLA / CS, NB: new bone formation, OB: old bone formation [30].

Another major problem in defective areas is known to be the antihygienic environment that can occur during wound care. To prevent this problem, antibiotic groups are recently mixed with GBR membrane composites in order to eliminate the pathogens formed around bone defects and used to provide a hygienic environment to the wound. Various antibiotic groups are thought to be effective in preventing infections in the wound, since it is possible that there is an invasion of gram (+) and gram (-) bacteria in the area where the defect is opened. When looking at a study on this; Ma et al., In the antibacterial multilayer GBR membrane design they made in 2016; Minocycline, an antibiotic group designed from the CS and Col biopolymers of the membrane and filled with CS, were used as nanomaterials. Namely; The asymmetric model application, which is thought to provide convenience in cell entry and exit in the design of GBR membrane, was also used in this study. The design was loaded on the encapsulated minocycline antibiotic CS. The antibiotic containing CS part is determined as the light layer forming the inner surface of the multi-layer GBR membrane in contact with the defective area. The dense soft layer with Col produced in the study was determined as the part connecting with the outer surface, and a two-layer GBR membrane was formed. The antibacterial GBR membrane was designed with the idea that minocycline loaded on CS nanoparticles will release controlled over time. Looking at the results; It has been observed that the asymmetrical structure of the GBR membrane consisting of Col / CS enables the development of osteoblast cells primarily due to its Col structure. In the part with myocycline filled CS, it has been noted that the controlled release of myocycline prevents bacterial infection on the surface.

Thus, it was stated in the study that fibroblast cells developing from the surrounding connections on the outer surface adhere to the surface, but the entry of fibroblast cells was prevented due to the asymmetric structure of the membrane [31].

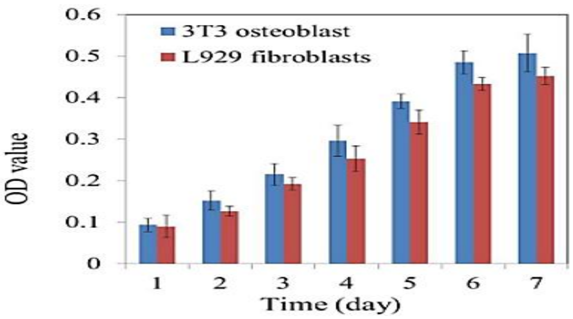

Figure 8. Fibroblast and ocetobalt distribution ratio on both surfaces after application of Col-minocycline / Col GBR membrane in the defected area [31].

5.CONCLUSION

In general, when literature studies were evaluated, it was seen that synthetic origin aliphatic origin PLA and its derivatives and natural polymers were used in GBR membranes. It is seen in the studies that absorbable and non-absorbable GBR membranes are selected according to the defective areas of the patient. It is known that nonabsorbable GBR membranes are susceptible to complications when bone development is achieved in the defected area, removed from the defected area with a second operation, and if care is not taken during the operation. It is understood from the excess of manufacturing companies that GBR membranes, which are mostly Col content, are used among absorbable polymers.

The application of different double-layered polymers in artificial vein and wound dressing is one of the study topics of the compilation. It was understood from the studies that GEL and PLA, among the most mentioned polymers in the review, increase the osteoblast and Col activity in the designs of GBR membranes, and PLA provides stability to the membranes mechanically. In addition, it is seen that the asymmetric pore structure, which is another issue mentioned in the review, is created with large and small pore sizes, and the controlled migration of cells to the defective area is prevented, however, the entry of epithelial and fibroblast cells is prevented. Finally, studies have shown that the design of multi-layer GBR membranes provides controlled disruption, increased cell regeneration and membrane strength. In addition, it is seen that drug release is possible thanks to the GBR membranes consisting of two-layer layers. It was stated that the multi-layer GBR membrane design methods are changing day by day and different polymers combinations can be tried, and further studies can be done.

DECLARATION OF ETHICAL STANDARDS

The authors of this article declare that the materials and methods they use in their work do not require ethical committee approval and/or legal-specific permission.

AUTHORS' CONTRIBUTIONS

Özge Kamacı: Wrote and interpretation the manuscript.
Necla Yucel: Wrote and interpretation the manuscript.
Hasan Köten: Wrote and interpretation the manuscript.
Erdi Buluş: Editing the manuscript.
Gülseren Sakarya Buluş: Editing the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

REFERENCES

[1] Rodriguez, IA., et al., "Barrier membranes for dental applications: A review and sweet advancement in membrane developments", ***Mouth Teeth***, 2: 1-9, (2018).

[2] Bottino, Marco C., et al. "Recent advances in the development of GTR/GBR membranes for periodontal regeneration—a materials perspective", ***Dental materials***, 28:703-721, (2012).

[3] Zhang, Y., et al. "Membranes for guided tissue and bone regeneration", ***Annals of Oral & Maxillofacial Surgery***, 1:10, (2013).

[4] Norıtake, K., Kuroda, S., & Kasugai, S. "Guided Bone Regeneration: Membrane Characteristics and Future Perspectives", ***Nano Biomedicine***, 4:42-46, (2012).

[5] Rodella, L. F., Favero, G., & Labanca, M. "Biomaterials in maxillofacial surgery: membranes and grafts", ***International journal of biomedical science***: IJBS, 7:81, (2011).

[6] Lee, J. Y., Kim, Y. K., Yun, P. Y., Oh, J. S., & Kim, S. G. "Guided bone regeneration using two types of non-resorbable barrier membranes", ***Journal of the Korean Association of Oral and Maxillofacial Surgeons***, 36:275-279, (2010).

[7] Caballé-Serrano, J., Munar-Frau, A., Ortiz-Puigpelat, O., Soto-Penaloza, D., Peñarrocha, M., & Hernández-Alfaro, F. "On the search of the ideal barrier membrane for guided bone regeneration", ***Journal of Clinical and Experimental dentistry***, 10:477, (2018).

[8] Lee, J. Y., Kim, Y. K., Yun, P. Y., Oh, J. S., & Kim, S. G. "Guided bone regeneration using two types of non-resorbable barrier membranes", ***Journal of the Korean***

Association of Oral and Maxillofacial Surgeons, 36: 275-279, (2010).
[9] Jo, Y. Y., & Oh, J. H. "New resorbable membrane materials for guided bone regeneration", ***Applied Sciences***, 8:2157, (2018).
[10] Soldatos, N. K., Stylianou, P., Koidou, V. P., Angelov, N., Yukna, R., & Romanos, G. E. "Limitations and options using resorbable versus nonresorbable membranes for successful guided bone regeneration", ***Quintessence International***, 48:2, (2017).
[11] Lee, S. W., & Kim, S. G. "Membranes for the guided bone regeneration", ***Maxillofacial Plastic and Reconstructive Surgery***, 36:239, (2014).
[12] Rothamel, D., Schwarz, F., Fienitz, T., Smeets, R., Dreiseidler, T., Ritter, L., ... & Zöller, J. "Biocompatibility and biodegradation of a native porcine pericardium membrane: results of in vitro and in vivo examinations", ***International Journal of Oral and Maxillofacial Implants***, 27:146, (2012).
[13] Higuchi, J., WoÅºniak, B., Higuchi, J., Chodara, A., & Fortunato, G. "Recent Advances In GTR/GBR Barrier Membranes Design for Periodontal Regeneration", ***Biomedical Journal of Scientific & Technical Research***, 16:11818-11820, (2019).
[14] Díaz-Rodríguez, P., Garcia-Triñanes, P., López, M. E., Santoveña, A., & Landin, M. "Mineralized alginate hydrogels using marine carbonates for bone tissue engineering applications", ***Carbohydrate polymers***, 195:235-242, (2018).
[15] Wang, J., Wang, L., Zhou, Z., Lai, H., Xu, P., Liao, L., & Wei, J. "Biodegradable polymer membranes applied in guided bone/tissue regeneration: a review", ***Polymers***, 8:115, (2016).
[16] Abe, G. L., Sasaki, J. I., Katata, C., Kohno, T., Tsuboi, R., Kitagawa, H., & Imazato, S. "Fabrication of novel poly (lactic acid/caprolactone) bilayer membrane for GBR application", ***Dental Materials***, (2020).
[17] Rodriguez, I. A., et al. "Barrier membranes for dental applications: A review and sweet advancement in membrane developments", ***Mouth Teeth***, 2: 1-9, (2018).
[18] Eskandarinia, A., Kefayat, A., Agheb, M., Rafienia, M., Baghbadorani, M. A., Navid, S., ... & Ghahremani, F. "A Novel Bilayer Wound Dressing Composed of a Dense Polyurethane/Propolis Membrane and a Biodegradable Polycaprolactone/Gelatin Nanofibrous Scaffold", ***Scientific Reports***, 10: 1-15, (2020).
[19] Hoque, M. E., Nuge, T., Yeow, T. K., Nordin, N., & Prasad, R. G. S. V. "Gelatin based scaffolds for tissue engineering-a review", ***Polymers Research Journal***, 9: 15-32, (2015).
[20] Leyva-Verduzco, A. A., Castillo-Ortega, M. M., Chan-Chan, L. H., Silva-Campa, E., Galaz-Méndez, R., Vera-Graziano, R., ... & Santos-Sauceda, I. "Electrospun tubes based on PLA, gelatin and genipin in different arrangements for blood vessel tissue engineering", ***Polymer Bulletin***, 1-19, (2019).
[21] Liu, S., Qin, S., He, M., Zhou, D., Qin, Q., & Wang, H. "Current applications of poly (lactic acid) composites in tissue engineering and drug delivery", ***Composites Part B: Engineering***, 108238, (2020).
[22] Hwang, C., Park, S., Kang, I. G., Kim, H. E., & Han, C. M. "Tantalum-coated polylactic acid fibrous membranes for guided bone regeneration", ***Materials Science and Engineering: C***, 111112, (2020).
[23] Rakhmatia, Y. D., Ayukawa, Y., Furuhashi, A., & Koyano, K. "Current barrier membranes: titanium mesh and other membranes for guided bone regeneration in dental applications", ***Journal of prosthodontic research***, 57: 3-14, (2013).
[24] Domalik-Pyzik, P., Morawska-Chochół, A., Chłopek, J., Rajzer, I., Wrona, A., Menaszek, E., & Ambroziak, M. "Polylactide/polycaprolactone asymmetric membranes for guided bone regeneration", ***e-Polymers***, 16: 351-358, (2016).
[25] Noritake, K., Kuroda, S., Nyan, M., Atsuzawa, Y., Uo, M., Ohya, K., & KASUGAI, S. "Use of a gelatin hydrogel membrane containing β-tricalcium phosphate for guided bone regeneration enhances rapid bone formation", ***Dental Materials Journal***, 33: 674-680, (2014).
[26] Ezati, M., Safavipour, H., Houshmand, B., & Faghihi, S. "Development of a PCL/gelatin/chitosan/β-TCP electrospun composite for guided bone regeneration", ***Progress in biomaterials***, 7: 225-237, (2018).
[27] Abdelaziz, D., Hefnawy, A., Al-Wakeel, E., El-Fallal, A., & El-Sherbiny, I. M. "New biodegradable nanoparticles-in-nanofibers based membranes for guided periodontal tissue and bone regeneration with enhanced antibacterial activity", ***Journal of Advanced Research***, (2020).
[28] Xu, C., Lei, C., Meng, L., Wang, C., & Song, Y. "Chitosan as a barrier membrane material in periodontal tissue regeneration", ***Journal of Biomedical Materials Research Part B: Applied Biomaterials***, 100: 1435-1443, (2012).
[29] Jiang, T., Abdel-Fattah, W. I., & Laurencin, C. T. "In vitro evaluation of chitosan/poly (lactic acid-glycolic acid) sintered microsphere scaffolds for bone tissue engineering", ***Biomaterials,*** 27:4894-4903, (2006).
[30] Ku, Y., Shim, I. K., Lee, J. Y., Park, Y. J., Rhee, S. H., Nam, S. H., ... & Lee, S. J. "Chitosan/poly (l-lactic acid) multilayered membrane for guided tissue regeneration", ***Journal of Biomedical Materials Research Part A:*** An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 90:766-772, (2009).
[31] Ma, S., Adayi, A., Liu, Z., Li, M., Wu, M., Xiao, L., & Gao, P. "Asymmetric collagen/chitosan membrane containing minocycline-loaded chitosan nanoparticles for guided bone regeneration", ***Scientific Reports***, 6:31822, (2016).