folia medica

Folia Medica 64(1):13-20
DOI: 10.3897/folmed.64.e60553

Review

Immunological Response to Nonresorbable Barrier Membranes Used for Guided Bone Regeneration and Formation of Pseudo Periosteum: a Narrative Review

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Received: 9 Nov 2020 ♦ **Accepted:** 13 Jan 2021 ♦ **Published:** 28 Feb 2022

Citation: Giragosyan K, Chenchev I, Ivanova V, Zlatev S. Immunological response to nonresorbable barrier membranes used for guided bone regeneration and formation of pseudo periosteum: a narrative review. Folia Med (Plovdiv) 2022;64(1):13-20. doi: 10.3897/folmed.64.e60553.

Abstract

Here we review the knowledge on the local biological immunological response (formation of "pseudo periosteum" of the host) to two types of nonresorbable membranes used in the horizontal and vertical alveolar ridge augmentation: the titanium-reinforced polytetrafluoroethylene membrane and the titanium mesh membrane. A literature search was conducted including available in vitro, in vivo, and clinical studies on cellular and molecular immunological response to these two types of nonresorbable membranes, in particular the formation of "pseudo periosteum".

Emerging data demonstrates that despite barrier membranes being considered as bioinert, they still elicit an immunological response from the body. The outcome of this reaction is the formation of a thin fibrous capsule referred to as "pseudo periosteum".

There are almost no biomaterials that are truly bioinert and this makes no exception for the nonresorbable membranes used in the guided bone regeneration. This iatrogenically made tissue is hypothesized to have a number of advantages and drawbacks. However, more research is needed in that area to truly understand its nature and importance to the guided bone regeneration process.

Keywords

barrier membrane, biocompatibility, biomaterials, bone augmentation, bone formation, foreign body reaction, GBR, histology, immunological response, inflammation, polytetrafluoroethylene, pseudoperiosteum, PTFE, titanium mesh

INTRODUCTION

Prosthetic rehabilitation of edentulous areas using osseointegrated implants has greatly improved the ability of dental practitioners to provide patients with more favourable long-term treatment options. Nevertheless, bone loss due to periodontal pathology, tumours or direct trauma to the alveolar processes of the jaws remains a major challenge for implant therapy. Moreover, the alveolar ridges are often subjected to atrophic processes, which further hinder the prosthetic rehabilitation of the patients. These factors require the use of various techniques, providing the alveolar ridges with the height and width necessary for optimal implant therapy. One of the treatment modalities used for achieving a sufficient bone volume is the guided bone regeneration (GBR).

GBR has been defined as a dental surgical procedure that uses barrier membranes to direct the growth of new bone at sites with insufficient volume or dimension of bone for proper function, aesthetics or prosthetic restoration.[1] Guided bone regeneration is presumed to be achieved when the osteoprogenitor cells are exclusively allowed to repopulate the bone defect site by preventing the entry of nonosteogenic tissue.[2] Therefore, the cells that need to repopulate the wound for the purposes of GBR are the osteoblasts. Wang et al.[3] outlined the four major principles necessary for successful GBR: primary wound closure, angiogenesis, space creation/maintenance, and stability of the initial blood clot (PASS). The barrier membranes and the bone grafting material are responsible for assurance of the second two requirements of the PASS principle and the exclusion of undesired cells from the bone defect.

There are certain general criteria that need to be fulfilled for the use of resorbable and nonresorbable membranes[4]:

- Biocompatibility: prevention of soft tissue dehiscence and minimal tissue reactions that will compromise the result;
- Host tissue integration;
- Space maintenance, structural integrity, and wound stability, especially during the early stages of healing;
- Ease of use and handling during surgery with no memory;
- Enhanced duration.

According to the recommendations, when both horizontal and vertical augmentation is planned, the grafting material should be used in association with a cell occlusive membrane and a space maintaining device.[5] The membranes that meet these criteria are the nonresorbable ones and they require a second surgical procedure to be conducted for their retrieval. The materials used for their creation are titanium and Ti-reinforced polytetrafluoroethylene.

Polytetrafluoroethylene

The polytetrafluoroethylene (PTFE) polymer is an example of a linear fluoropolymer. A simplistic form of its structure is shown in **Fig. 1**:

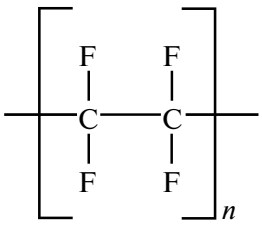

Figure 1. Structure of PTFE.

Formed by the polymerization of tetrafluoroethylene (TFE), the ($-CF_2-CF_2-$) groups repeat multiple thousands of times to form inert weave PTFE nodules and thin PTFE fibrils. The fundamental properties of fluoropolymers evolve from the atomic structure of fluorine and carbon and their covalent bonding. The backbone is formed of carbon-carbon and the pendant groups are carbon-fluorine, both being extremely strong bonds. The basic properties of PTFE stem from the chemical structure of the compound. PTFE has been shown to be biocompatible with the addition that it maintains its integrity during and after implantation. Moreover, Ti plates can be incorporated in the design of the PTFE membrane, further enhancing the product's vertical space maintaining ability. Two different types of PTFE membranes are available depending on their architecture - expanded PTFE (ePTFE) and dense PTFE (dPTFE). The semi-separable ePTFE has myriads of small pores (<8 μm)[6] which aid in the attachment of connective tissue cells thereby stabilizing the wound area. In addition, the diameter of the pores allows transmembranous transport of nutrients which is beneficial to the nurturing of the bone graft. A downside to this characteristic is that if dehiscence occurs, bacteria could easily travel through these openings and cause solution-mediated bone resorption.[7] Using dPTFE membrane prevents this since the diameter of its pores is less than 0.3 μm.[6] With the application of these membranes, the nurturing of the bone graft is extremely dependent on the blood supply from the bone marrow.[8]

Titanium mesh

The titanium mesh was introduced in 1969 by Boyne et al.[9] for the restoration of large bone defects. This medical device definitely meets the criteria for stabilization of the blood clot, as well as space creation and maintenance because of its adamant structure. Titanium is a strong lightweight metal with low density of 4.506 g/cm^3 and high durability. The material's ductility allows for its bending and shaping into the desired configuration according to the clinical scenario.[10]

The rigidity of the material also has some drawbacks. Mechanical irritation of the soft tissues may lead to their dehiscence and membrane exposure.[11] Another trait of this membrane is its macro porosity. This characteristic ensures both better nurturing of the graft and integration of the membrane with the surrounding soft tissues.[12] The large fenestrations promote the attachment of the soft tissues to the membrane in such a way that a mechano-biological stabilization of the incision wound is ensured. Many authors describe the newly formed connective tissue between the barrier membrane and the bone graft as "pseudo periosteum".[13] It is believed that this layer of connective tissue prevents the infection and resorption of the bone graft.[14] A drawback of the pseudoperiosteum is the strenuous removal of the membrane at the time of the second surgery. Lizio et al.[14] even go to the extent of suggesting that in some cases, parts of the newly formed bone should be removed so that the lattice could be detached. To eliminate this disadvantage, Chan et al.[15] proposes the use of a nitride coating of the titanium structure.

Literature search and inclusion criteria

For this narrative review, the literature survey was conducted using the Pub Med/Research Gate electronic database, without limiting the years of publication. Only papers written in English were included. The search was restricted to in vitro, in vivo human and animal studies that reported data on GBR, foreign body reactions to biomaterials and selected papers on material properties. Keywords based on MeSH terms as well as free text were used with the aim of identifying published in vitro and in vivo clinical studies that investigated cellular and molecular events around nonresorbable membranes during GBR. The following keywords were used in different combinations: "GBR", "barrier membrane", "bioinert", "biocompatibility", "membrane", "materials", "properties", "polytetrafluoroethylene", "PTFE", "nonresorbable", "mechanisms", "reaction", "foreign body", "titanium", "mesh", "lattice", "vertical augmentation", "pseudoperiosteum", "adsorbed proteins", "tissue response", "biomaterials", "fibroblasts", "macrophages", "cellular/molecular events", "adherent cells", "bone defect", "in vivo", "in vitro", "histology", "inflammation", "bone formation", "cytokines", and "growth factors".

Results of the literature survey

Biocompatibility

Biocompatibility[16] is defined generally as the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial, cellular or tissue responses in that specific situation and optimizing the clinically relevant performance of the therapy. A long-term implantable device: the ability of the device to perform its intended function with the desired degree of incorporation in the host without eliciting an undesirable local and systemic effect on that host. A biomaterial[16] is defined as a substance that has been engineered to take a form that is used to direct the course of any therapeutic or diagnostic procedure by interactions with the living organism.

Along with understanding the physical, mechanical, and chemical properties of the membrane materials, it is also necessary to gain insight into their biologic response when they come into contact with the body. Placing a material in the body creates an interface that must exhibit both biological and structural stability during the lifetime of the implanted device. Many materials used in dentistry have the capacity to alter biologic activity when they are in close vicinity to living tissue.

Both types of materials used for the creation of non-resorbable membranes are stated to be bioinert which means they do not induce any adverse tissue reactions when introduced into the biological tissue. However, it has been shown that nearly every biomaterial induces an inflammatory tissue reaction, which is unique for every material depending on its combination of physical and chemical properties.[17] The tissue reaction to a biomaterial is a cascade including mainly macrophages as key elements, which have been shown to express both pro- and anti-inflammatory molecules depending on material factors such as surface topography or surface chemistry.[18] Based on their molecule expression, macrophages are more or less divided into proinflammatory M1 and anti-inflammatory (alternatively activated) M2 subtypes.[19] Taken together, it is believed that the successful clinical application of a biomaterial has to be accompanied by an "M2 tissue reaction" to promote tissue healing, while a chronic pro-inflammatory tissue response may lead to negative consequences for tissue remodelling such as fibrous capsulation.[20] Thus, the understanding of the material-specific foreign body reaction, and of the interactions of the immune system with a biomaterial is pivotal to ensure the safety, biocompatibility, and functionality of a medical device.[21]

Cellular and molecular events/foreign body reaction (FBR)

Elimination by macrophagial phagocytosis as part of the innate immune system fails when the target is a foreign body (biomaterial). The foreign body reaction composed of macrophages and foreign body giant cells is the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis or a biomaterial.[22] Its end result is the encapsulation of the material in a fibrous mesh.

The current concept[22] of the FBR against biomaterials divides into five phases:

1. Protein adsorption
2. Acute inflammation
3. Chronic inflammation
4. Foreign body giant cell formation
5. Fibrosis or fibrous capsule formation

The very first stage of the implantation includes injury, following blood-material interactions. Subsequently, proteins of the blood plasma adsorb to the biomaterial surface, forming a blood based ephemeral provisional matrix of 2-5 nm.[23] The architecture of the early provisional matrix depends on several features including the physicochemical properties of the surface of the biomaterial and blood plasma composition.[17] The early protein adsorption is described by the Vroman effect[24], which is characterized by continuous adsorption and desorption of proteins. While high mobility proteins like albumin are adsorbed at first, they are increasingly replaced by less mobile proteins with higher affinity for the specific surface, such as fibrinogen, high molecular weight kininogen and vitronectin.[25] The Vroman effect is most prominent on hydrophilic surfaces where proteins are less tightly bound than on hydrophobic surfaces.[26] Therefore, it could be hypothesized that hydrophobic biomaterials (such as the nonresorbable barrier membranes) induce a stronger foreign body reaction because of the lesser desorption of proteins from their surfaces in comparison with the hydrophilic

biomaterial (such as the resorbable barrier membranes or bone graft material).

After the first stage of provisional matrix formation, acute and chronic inflammation occurs as is with any procedure that involves injury infliction on tissues. The degree of these events is determined by the severity of the trauma during the implantation procedure and the protein adsorption on the biomaterial's surface. Neutrophils (polymorphonuclear leukocytes PMNs) play a key role in the events in the course of the acute inflammation. Mast cell degranulation with histamine release and fibrinogen adsorption is known to mediate acute inflammatory responses to implanted biomaterials.[27] Interleukin-4 and interleukin-13 are also released from mast cells in a degranulation process; they can play significant roles in determining the extent and degree of the subsequent development of the foreign body reaction.[28] The acute inflammatory response to the biomaterials lasts no more than one week, depending on the extent of the surgical implantation procedure. Following the acute inflammation, chronic inflammation begins as expected. Its onset is marked by the presence of mononuclear cells (monocytes and lymphocytes). This stage is usually resolved within 2-5 weeks after implantation. There are myriads of events occurring throughout the development of the acute and chronic inflammation, but a thorough presentation of this topic is beyond the scope of this text.

The matrix afterwards evolves into a blood clot at the tissue/material interface. Since all involved cells interact with the provisional matrix rather than the foreign body's surface, its composition is assumed to be of major relevance for all subsequent events during the foreign body reaction in vivo.[29] Following blood-material interactions, platelets and the clot release chemoattractants, such as transforming growth factors, platelet-derived growth factor, leukotriene (LTB4), and interleukin (IL-1) that can direct macrophages to the wound site.[30] Following these events, macrophages fuse to form foreign body giant cells (FBGCs), a development that separates the FBR from chronic inflammation. In a process described by Henson (1971) as "frustrated phagocytosis", macrophages fuse together to form foreign body giant cells, seemingly to improve their effectiveness or in an attempt to avoid apoptosis.[31] FBGCs can release mediators of degradation such as reactive oxygen intermediates (ROIs, oxygen free radicals) and degradative enzymes and acid into the zone between the cell membrane and biomaterial surface.[32] Some materials are designed to withstand this degradation (such as nonresorbable membranes, joint prosthesis), while the structure of others is intentionally susceptible to this process - resorbable suture material.

Macrophages are capable of secreting growth and angiogenic factors that are important in the regulation of fibro-proliferation and angiogenesis.[33] Alternatively, activated macrophages (M2 subtype) produce profibrinogenic factors which enhance fibrogenesis by fibroblasts as opposed to classically activated (M1 subtype) which inhibit fibrogenesis.[34] Human macrophages activated by biomedical polymers in vitro have been shown to stimulate fibroblastic activity that has been shown to correlate with the in vivo fibrotic response.[35] Fibroblasts and endothelial cells are attracted to the surface of the biomaterial and deposit collagen and other extracellular matrix proteins to form granulation tissue. It is composed of a loose net of collagen fibres, proliferating capillary sprouts, collagen secreting fibroblasts and phagocytosing macrophages.[36] This granulation tissue then matures into less cellular and more collagenous, peripheral fibrous capsule. The hallmark of this process is marked by the progressive replacement of type III collagen by type I collagen.[37] The macrophages included in the process of frustrated phagocytosis can therefore secrete proteins that modulate fibrotic response and thus the fibrous capsule that develops around a material following implantation.

Formation and clinical significance of pseudo periosteum

When nonresorbable membranes are used for the purposes of guided bone regeneration, a coating of connective tissue is consistently found above the augmented sites. As mentioned above, it is occasionally referred to as "pseudo periosteum". Generally, this is a dense connective soft tissue layer with low cellularity and no mineralization.[38] It was first described by Dahlin et al.[39] who suggested a hypothesis to explain its nature. Histological animal studies have shown that the pseudoperiosteum under Ti-mesh is a dense, connective soft tissue with several fiber groups. Lim et al.[38] discovered circumferential and dense fibers interposing through the pores around the Ti-mesh. Underneath the circumferential fibers, the straight fibers are parallel to the Ti-mesh surface, and slightly loose and oblique fibers were observed below. Few blood vessels and no mineralized structures were observed.

Cucchi et al.[40] observed the formation of this tissue not only with the use of titanium meshes but also underneath Ti-reinforced PTFE membranes, hence a proposal for the classification of this tissue in 3 types was made :

Type 1: no pseudoperiosteum or a layer of soft tissue thinner than 1 mm. In this type, no histological analysis could be conducted because of the thinness of the coating.

Type 2: a regular soft tissue layer between 1 and 2 mm. The histological findings in this group were regular layer of connective tissue in which blood vessels and capillaries were detected. In some cases a small fragment of bone tissue is reported to be visible and surrounded by connective tissue composed of fibres with a multidirectional orientation.

Type 3: an irregular layer of soft tissue and/or layer thicker than 2 mm. Histological samples from this type are reported to consist of irregular bulks of connective tissue (poorly or not at all vascularized), and small fragments of bone graft used to fill the surgical site.

It is also reported that no inflammatory reaction or infiltrate was detected in any type of pseudoperiosteum.

As it was mentioned above, one of the main postulates of guided bone/tissue regeneration is the stabilization of the

blood clot. Bone graft material and application of a nonresorbable membrane in the site that needs augmenting are utilized to ensure that this criterion is met. The "pseudo periosteum" further stabilizes the bone substitute by coating it with a layer of connective tissue. Because of that phenomenon the titanium mesh is labeled as a "protective matrix" rather than an "occlusive membrane".[41]

Another aspect of the GBR procedure's success is the angiogenesis, in particular, the vascularization of the graft material. It is mainly ensured by the bone marrow's blood vessels which start creeping slowly through the fenestrations in the cortical plate. This nutrient supply is further enhanced by the addition of the fewer blood vessels in the pseudoperiosteum. It could also be hypothesized that pseudoperiosteum layer acts as a biological membrane, which prevents soft tissue in growth and compromising of the final result.

DISCUSSION

Barrier membranes suitable for GBR can be separated into two categories – resorbable and nonresorbable. Resorbable membranes are often favoured since their application does not require a second surgical procedure for the retrieval of the device. Despite that fact, some clinical situations such as vertical bone defects require the use of nonresorbable Ti and PTFE membranes because of their excellent space maintaining characteristics. Furthermore, after their use, a layer of connective tissue, which researchers call "pseudo periosteum" can be observed above the newly formed bone.[13] It could be hypothesized that its occurrence is related to the immunological response to the material due to the fibrous nature of the tissue.

The biocompatibility of the membrane materials has been extensively studied and the consensus is that they are bionert.[42] However, it has been stated that no material implanted in living tissue is truly inert because every biomaterial induces a tissue response[22] – the foreign body reaction. Anderson et al.[22] describes the FBR as the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis or a biomaterial. Its end result is the encapsulation of the material in a fibrous mesh. The present review was conducted to examine the immune response to two types of nonresorbable membranes used in GBR.

The PTFE membranes were initially developed as a vascular graft material and are used extensively in cardiovascular surgery.[43] The highly porous fibrous matrix of PTFE allows its incorporation into the host material. It is autoclavable and nonantigenic, and is said to be both biologically and chemically inert.[44] Korzinskas et al.[21] show that the PTFE membrane induced a tissue response including inflammatory cell types such as macrophages and granulocytes, up to day 30 post implantation. Furthermore, after histomorphometrical detection, the group found out prevalence of M1 macrophages at day 10 after implantation compared to macrophages expressing M2 phenotype. Even though the quantity of M1 macrophages was reduced later on and became comparable to the immune response to the collagen membrane, it was shown that PTFE is not fully bioinert. PTFE membranes are also used for nasal augmentation procedures.[45] Studies in that field also suggest that there is minimal tissue inflammatory response to the material. Histological findings presented in previous studies included fibrous tissue in growth through the membrane (pseudo periosteum) and low grade inflammatory reactions around the implanted device. Fibrous tissue in growth through the porous structure of the membrane has been accepted as a successful material host interaction in the literature.[44]

Titanium and titanium alloys have a long history of successful use in dental and orthopedic application and its excellent biocompatibility has been well documented.[46] However, studies show that no metal is completely inert in vivo and whenever an implant is introduced into the body, it will always generate an inflammatory response. The end stage of this process is the collagen capsule formation with thickness corresponding to the phagocytic activity.[47] Titanium alloys always show a thinner encapsulation when compared to other alloys (the cobalt-chrome alloy induces encapsulation with up to 2-μm thickness).

The presence of this fibrous tissue, occasionally referred to as "pseudo periosteum" was first noted by Dahlin et al.[39] and its formation is noted to take between 2 and 6 weeks[48]. Researchers label it "pseudo" because it only somewhat resembles the outer layer of the physiological periosteum tissue. Generally, this is a dense connective tissue layer with low cellularity, no mineralization[38] and scarcity of blood vessels. The role of this tissue may be associated with prevention of graft infection and resorption.[14] There are some that suggest that its formation could aid secondary intention healing should a membrane exposure occurs.[13] On the other hand, Eisig et al.[49] suggest that the fibers extending from the soft tissue flap to the bone through the pores might imply migration of fibroblasts and impeded bone regeneration, which may indicate that clot stability could be easily impaired before mineralization commences. In a research conducted by Cucchi et al.[40], two groups of patients were subjected to vertical and horizontal bone augmentation with different nonresorbable membranes – Ti mesh and dPTFE membrane. The group concluded that when the dPTFE device was used, denser bone was generated in comparison to the other group. Interestingly, the researchers stated that when the titanium lattice structure was used as a barrier membrane, larger quantities of pseudo-periosteum were observed which may be related to the quality of the newly formed bone.

CONCLUSIONS

In conclusion, there are little to no biomaterials that are truly bioinert and this makes no exception for the nonresorbable membranes used in GBR. The foreign body reac-

tion they elicit is related to the formation of the so called "pseudo periosteum". This iatrogenically made tissue is hypothesized to have a number of advantages and drawbacks, but further research is needed in that area in order to truly understand its nature and importance to the guided bone regeneration process.

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Иммунологический ответ на нерезорбируемые барьерные мембраны, используемые для направленной костной регенерации и формирования псевдонадкостницы: описательный обзор

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Дата получения: 9 ноября 2020 ♦ **Дата приемки:** 13 января 2021 ♦ **Дата публикации:** 28 февраля 2022

Образец цитирования: Giragosyan K, Chenchev I, Ivanova V, Zlatev S. Immunological response to nonresorbable barrier membranes used for guided bone regeneration and formation of pseudo periosteum: a narrative review. Folia Med (Plovdiv) 2022;64(1):13-20. doi: 10.3897/folmed.64.e60553.

Резюме

В этой статье мы рассматриваем информацию о локальном биологическом иммунном ответе (образование псевдонадкостницы гостеприимника) на два типа нерезорбируемых мембран, используемых для горизонтальной и вертикальной аугментации альвеолярного гребня: армированная титаном политетрафторэтиленовая мембрана и титановая сетчатая мембрана. Был сделан обзор литературы, который включал имеющиеся *in vitro, in vivo* и клинические исследования клеточного и молекулярного иммунологического ответа этих двух типов нерезорбируемых мембран, и в частности образования псевдонадкостницы.

Полученные данные показывают, что хотя барьерные мембраны считаются биоинертными, они вызывают иммунный ответ в организме. Результатом этой реакции является образование тонкой фиброзной капсулы, известной как «псевдо периост».

По-настоящему биоинертных биоматериалов практически не существует, и нерезорбируемые мембраны, используемые в направленной костной регенерации, не являются исключением. Считается, что эта ятрогенная ткань имеет определённые преимущества и недостатки. Тем не менее, необходимы дальнейшие исследования в этой области, чтобы действительно понять природу и важность направленной костной регенерации.

Ключевые слова

барьерная мембрана, биоматериалы, биосовместимость, воспаление, ГБР, гистология, иммунологический ответ, политетрафторэтилен, псевдонадкостница, ПТФЭ, реакция на инородное тело, титановая сетка, увеличение кости, формирование кости