The role of angiogenesis in implant dentistry part II: The effect of bone-grafting and barrier membrane materials on angiogenesis

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Abstract
Background: In implant dentistry, bone substitute materials and barrier membranes are used in different treatments including guided bone regeneration (GBR), socket preservation, alveolar ridge augmentation, maxillary sinus elevation, and filling bony defects around the inserted dental implant. One of the most important factors in prognosis of treatments using these materials is the growth of new blood vessels in applied areas. Present review was performed to evaluate the effect of the bone-grafting and barrier membrane materials on angiogenesis events.

Material and Methods: An electronic search was performed in PubMed, MEDLINE, and EMBASE databases via OVID using the keywords mentioned in the PubMed and MeSH headings regarding the role of angiogenesis in implant dentistry from January 2000-April 2014.

Results: Of the 5,622 articles identified in our initial search results, only 33 met the inclusion criteria set for this review. Among bone substitute materials the autogenous bone-grafts, and among the barrier membranes the colagenous membranes, had the highest angiogenic potentials. Other bone-grafting materials or membranes were mostly used with pro-angiogenic factors to enhance their angiogenic properties.

Conclusions: Angiogenesis is one of the key factors, which plays a critical role in success rate of GBR technique and is seriously considered in manufacturing bone-grafting and barrier membrane materials. However, there is still lack of clinical and in-vivo studies addressing the effect of angiogenesis in treatments using bone-grafting and barrier membrane materials.

Key words: Angiogenesis, bone-grafting materials, GBR, ridge augmentation, sinus elevation, socket preservation.
Introduction
In the field of implant dentistry, bone-grafting and barrier membrane materials can be used in different situations such as the socket preservation (1), alveolar ridge horizontal and/or vertical augmentation, maxillary sinus elevation, and filling the bony defects or exposed threads of implants in order to maintain the required space and provide the necessary time period for migration of regenerative cells to the applied sites (2). The main purpose of using these materials is to prohibit the migration of epithelial or fibroblast cells, and only permit the migration of osteogenic cells into the applied site to regenerate the hard tissue in deficient areas (3,4).

The most important principles for increasing the success rate of treatments using these materials is the space maintaining, exclusion of epithelial and connective tissue cells migration to the site, the stabilization of blood clot, and the tight closure of surgical site (5).

Besides these primary surgical principles, blood supply is another crucial factor that provide the required nutritional elements, oxygen, immune system cells, mesenchymal stem cells, and growth factors (6-9). This blood supply is accomplished through angiogenesis, which includes the formation of new blood vessels from pre-existing vascular network present in adjacent soft and supraperiosteal tissues (6,10,11). It was shown that the formation of blood vessels through angiogenesis process is an undeniable factor in regenerative procedures such as dentin-pulp complex and dental pulp regeneration (12).

In bone regenerations, angiogenesis plays a central role by providing the functional connection between the grafting-material and surrounding host tissues. The well established and mature vascular networks can assist and accelerate the regenerative processes. In order to promote angiogenesis events, it is suggested to decoricate the surrounding bone to assist with the connection between blood vessels in the bone marrow of adjacent bone and bone substitute materials (6,13).

According to the facts, the present review intended to discuss the angiogenic potential of bone-grafting and barrier membrane materials used in bone regeneration procedures. It was hypothesis that whether bone-grafting and barrier membrane materials promote the angiogenesis event in regeneration and what are the current methods for enhancing the pro-angiogenic effect of these materials.

Material and Methods
1- The Review Purpose:
Present study was performed to evaluate the effect of different bone-grafting and barrier membrane materials on angiogenesis events during bone regeneration processes in the alveolar bone. The main aspects pursued in this review include: 1) the angiogenic potential of different bone-grafting materials including autogenous, allogenic, xenogeneic, and alloplastic bone materials; 2) the mechanism of action by which these materials can present pro- or anti-angiogenic effects; 3) which one of the bone materials has the highest pro-angiogenic potential; 4) what are the current approaches to enhance the pro-angiogenic effects of these materials; 5) The angiogenic potential of different barrier membranes including collagenous, polymeric, e-PTFE, d-PTFE, titanium-reinforced, and titanium Mesh membranes; 6) which one of these barrier membranes has the highest angiogenic property; and 7) what are the current approaches to enhance the pro-angiogenic effects of resorbable or non-resorbable membranes materials.

2- Inclusion and Exclusion Criteria:
The inclusion criteria were: 1) studies published in English; 2) studies accepted and published between January 2000-April 2014; 3) the scientific in-vitro, in-vivo, or ex-vivo articles, reviews, systematic reviews, case reports with controlled study design; 4) studies that had evaluated the effect of autogenous, allogenic, xenogeneic, or alloplastic bone-grafting materials on angiogenesis processes in the applied area; 5) studies that had utilized different pro-angiogenic substances in combination with these bone materials; 6) studies that had evaluated the impact of collagenous, polymeric, e-PTFE, d-PTFE, titanium-reinforced, or titanium Mesh membranes on angiogenesis processes in the applied area; and 7) studies that have used different pro-angiogenic agents to enhance angiogenic potential of these membranes.

The exclusion criteria were: 1) studies that were published before January 2000 or after April 2014; 2) studies that had not evaluated the angiogenic potentials of the bone-grafting or barrier membrane materials in GBR procedures.

3- Search Methodology:
The searching methodology included electronic searches performed in the PubMed, MEDLINE, and EMBASE databases via OVID using keywords mentioned in the PubMed and MeSH headings including the effects of bone substitute and barrier membranes materials on angiogenesis events occurring in surgical sites after insertion of the dental implant.

4- Search Strategy:
In the electronic search of scientific papers in the PubMed, MEDLINE, and EMBASE databases, the following keywords were used in combination with angiogenesis: “guided bone regeneration”, “autogenous bone graft”, “autogenous bone graft stem cells”, “autogenous bone graft osteoblast”, “autogenous bone graft osteoclast”, “autogenous bone graft endothelial cells”, “allogenic bone graft”, “freeze-dried bone allograft (DFDBA)”, “demineralized freeze-dried bone allograft (DFDBA)”, “xenogeneic bone graft”, “alloplastic bone graft”, “resorbable membranes”, “collagenous membra-
Bone-grafting or bone substitute materials are bio-ma-

Discussion
Of the 2,691 articles identified in the initial search re-

Results
Of the 2,691 articles identified in the initial search re-

Discussion
1 Effect of bone-grafting materials on angiogenesis
Bone-grafting or bone substitute materials are bio-ma-

mandibular symphysis, maxillary tuberosity, and tori

tines”, “polymeric membranes”, “non-resorbable mem-

branes”, “e-PTFE membranes”, “d-PTFE membranes”,

“titanium-reinforced membranes”, and “titanium mesh

membranes”.

Results
Of the 2,691 articles identified in the initial search re-

Besides, a number of non-resorbable membranes were

These bone-grafting materials are provided in block or

particulate forms from other locations in the body of the

same individual who is subjected to dental implant sur-

surgery. These donor sites can be intraoral such as ramus,
Table 1. The list of included studies that are directly related to the effect of bone-grafting and barrier membrane materials on angiogenesis process.

| Study                          | Main aspect                                                                 | Conclusion                                                                 |
|--------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bexell et al. (24) Davani et al. (25) | The angiogenic property of bone marrow multipotent mesenchymal cells | The BM-MSCs can differentiate into vascular endothelial and/or pericyte-like cells |
| Oswald et al. (29)             | The angiogenic potential of mesenchymal progenitor cells                    | The BM-MSCs in the presence of 2% fetal calf serum and 50 ng/ml VEGF, can express specific markers of endothelial cells such as KDR and FLT-1      |
| Chim et al. (30)               | The angiogenic factors in bone                                             | The osteoblasts can produce angiogenic factors such as VEGF, FGF-2, BMP-7, receptor activator of NF-κB ligand (RANKL), and EGF-like family members |
| Prasadam et al. (31)           | Osteocyte-induced angiogenesis                                             | The osteocytes can promote angiogenesis process through the VEGF-MAPK-dependent signaling pathways in endothelial cells |
| Wang et al. (32)               | Oxygen sensing and osteogenesis                                           | The VEGF production due to the hypoxia-inducible factor alpha pathway can promote bone formation indirectly by its effect on angiogenesis |
| Kanczler & Oreffo (35)         | Osteogenesis and angiogenesis                                             | The bone endothelial cells might control the differentiation rate of human bone marrow stromal cells (HBMSC) to osteoblasts. These endothelial cells can recruit the bone progenitor cells, and maintain them in standby status |
| Bouletreau et al. (36)         | Contributions of endothelial cells in osteogenesis                         | Endothelial cells are in close relationship with bone formation or remodeling, and osteogenic cells such as osteoblasts. The Hypoxia and VEGF up-regulate BMP-2 mRNA and protein expression in microvascular endothelial cells |
| Larsen et al. (40)             | The effect of combination of VEGF and FGF-2 with autograft bone materials on neoangiogenesis | The addition of FGF-2 to the autologous bone materials had superior pro-angiogenic effects in neoangiogenesis process in recipient site in compared with VEGF |
| Moreira et al. (41)            | Angiogenesis and osteogenesis at incorporation of onlay bone graft         | The onlay grafts, which included autologous and allogeneic bone grafts in combination with PRP as a modifier promoted the angiogenesis and osteogenesis events in rabbit mandibles |
| Nevins & Reynold (42)          | The recombinant human platelet-derived growth factor BB for implant site development | The PDGF-BB in combination with allograft bone materials can be used for bone regeneration at implant sites |
| Rosen et al. (43)              | The use of autograft combined with recombinant human platelet-derived growth factor BB to treat moderate to severe osseous lesions | The combination of FDBA and PDGF-BB is effective treating in major periodontal intraosseous defects |
| Boéck-Neto et al. (44)         | The angiogenic effect of autologous bone and several graft materials       | The hydroxyapatite and calcium phosphate induced higher VEGF expression and MVD in compared with DFBBA and polymeric grafts |
| Degidi et al. (45)             | The effect of Bio-Oss on VEGF expression and microvessel density in sinus augmentation | The Bio-Oss xenogenic bone material can significantly induce the VEGF expression and MVD |
| Canuto et al. (46)             | The effect of hydroxyapatite paste on alveolar healing                     | The nanocrystalline hydroxyapatite can promote the osteogenesis and angiogenesis by increasing the expression of BMP-4, BMP-7, and VEGF |
| Laschke et al. (47)            | Injectable nanocrystalline hydroxyapatite paste for bone substitution      | The injectable nanocrystalline HA has enhancing effect on microvessel density and pro-angiogenic property |
| Pezzatini et al. (48), (49)    | The effect of hydroxyapatite nanocrystals on microvascular endothelial cell viability and functions | The HA nanocrystals are effective on viability of endothelial cells of microvessel by inducing these cells to keep their healthy status and functional properties |
| Nakamura et al. (50)           | Endothelial cell migration and morphogenesis on silk fibroin scaffolds containing hydroxyapatite electret | The polarized HA present on silk fibroin scaffolds can positively affect endothelial cells migration and morphogenesis that can promote the angiogenesis process |

Endothelial cells are the other viable cells present in autogenous grafts. Authors indicated that bone marrow stromal cells have specific characteristics such as responding to angiogenesis (32). It was reported that the VEGF production due to the hypoxia-inducible factor alpha (HIF-1α) pathway can promote bone formation indirectly by its effect on angiogenesis (31).
Table 1 continue. The list of included studies that are directly related to the effect of bone-grafting and barrier membrane materials on angiogenesis process.

| Authors          | Description                                                                 | Result                                                                                           |
|------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Wu et al. (51)   | Promoting of angiogenesis and osteogenesis in radial critical bone defect regions of rabbits with nano-hydroxyapatite/collagen/PLA scaffolds | The nano-hydroxyapatite/collagen/PLA (nHAC/PLA) can be used as bone substitute material in new bone formation in segmental bone defects |
| Castaño et al. (52) | Angiogenesis in bone regeneration: tailored calcium release in hybrid fibrous scaffolds | The silicon-based calcium phosphate glasses (Bioglasses), due to their calcium ion release, can play a significant role in promotion of angiogenesis events |
| Smiler et al. (53) | Bone grafts augmented with adult stem cells                                  | The bone marrow aspirate including adult stem cells in combination with xenogeneic and alloplastic scaffold can promote the proliferation, differentiation, and maturation of stem cells and enhance the angiogenesis events |
| Gunda et al. (61) | Collagen derived endogenous angiinhibitors                                   | The collagen has a component known as non-collagenous domains (NC1), which imposes anti-angiogenic effects on surrounding tissues |
| Shen et al. (62) | Prolyl hydroxylase inhibitors increase neoangiogenesis                       | The PHD inhibitors such as L-MIM and DMOG can effectively activate HIF-1α, which resulted in VEGF production |
| Simion et al. (64) | Evaluation of a resorbable collagen matrix infused with rhPDGF-BB in peri-implant soft tissue augmentation | The recombinant human PDGF-BB in combination with resorbable collagen matrix and showed promising results in soft tissue regenerative procedures |
| Azzarello et al. (68) | Assessment of angiogenic properties of biomaterials                          | The polyglycolic acid (PGA) and PGA modified with poly(lactic-co-glycolic acid) (PLGA) compared with one-layer porcine small intestinal submucosa (SIS) or two-layer SIS, have lower pro-angiogenic effects |
| Perets et al. (69) | Enhancing the vascularization of three-dimensional porous alginate scaffolds | The PLGA microspheres are capable of controlled release of pro-angiogenic factors such as FGF-2 |
| Shah et al. (70) | Adaptive growth factor delivery from a polyelectrolyte coating promotes synergetic bone tissue repair and reconstruction | The PDGF-BB as a pro-angiogenic factor can be coated on PLGA for adaptive release in bone regenerative procedures |
| Yonamine et al. (71) | Effectable application of vascular endothelial growth factor to critical sized rat calvaria defects | The VEGF165 on PLGA membranes can effectively promote bone regeneration procedures |
| Song et al. (79) | The effect on angiogenesis in guided tissue regeneration procedure using expanded polytetrafluoroethylene membranes in dogs | The e-PTFE non-resorbable membrane was effective in rebuilding the supraalveolar vascular network |
| Kid & Williams (80) | Laminin-5-enriched extracellular matrix accelerates angiogenesis and neovascularization | The laminin-5-enriched e-PTFE can promote angiogenesis |
| Kidd et al. (81) | Stimulated endothelial cell adhesion and angiogenesis with laminin-5 modification of e-PTFE | The modified e-PTFE with laminin-5 increased the endothelial cells adhesion and promoted neovascularization process of the peri-implant tissues |
| Funato et al. (83) | Alveolar ridge augmentation with titanium mesh, resorbable membrane, and rhPDGF-BB | The rhPDGF-BB can be used in combination with titanium mesh membranes to enhance bone regenerative |
that endothelial cells might control the differentiation rate of human bone marrow stromal cells (HBMSC) to osteoblasts (35). Investigators showed that endothelial cells can recruit the bone progenitor cells, and maintain them in a standby status before their migration to required site, and promote their differentiation into functional osteoblasts after migration from blood vessels (35). The hypoxia induced pro-angiogenic factors such as VEGF can promote the expression of BMP-2 in endothelial cells. These results indicate that endothelial cells are in close relationship with bone formation or remodeling, and osteogenic cells such as osteoblasts (36) (Tables 1 and 1 continue, 2).

2.2- Allogenic bone materials

Generally the allogenic grafting materials are tissues derived from one individual and used as graft in another individual with different genetic traits. These materials are mostly considered to be osteoinductive and osteoconductive and do not express any osteogenic characteristic, as autogenous bone grafts do (6). In order to eliminate the risk of cross contamination, two methods of freeze-drying and the Tutoplast® processing are utilized to prepare allogenic bone grafts (37,38). The materials provided by freeze-drying technique include the demineralized freeze-dried bone allograft (DFDBA), which is osteoinductive and osteoconductive with faster resorption rate; and the freeze-dried bone allograft (FDBA) that is osteoconductive with slower resorption rate (39).

Larsen et al. reported that the neoangiogenesis at a recipient site is critical for survival of vascularized allogenic bone grafts (Fig. 1). These authors evaluated the effects of VEGF, FGF-2, and the combination of these pro-angiogenic factors as an additive to allogenic bone materials, on the angiogenesis events occurring at grafting site (40). They showed that FGF-2 had superior pro-angiogenic effects in neoangiogenesis process at the recipient site compared with VEGF (40). Moreira et al. indicated that onlay grafts, which included autogenous and allogenic bone grafts in combination with platelet-rich plasma (PRP) as a modifier, promoted the angiogenesis and osteogenesis events in rabbit mandibles (41) (Table 1 and 1 continue).

Angiogenesis plays a significant role in osteoblast differentiation and bone matrix formation at grafted sites (41). Nevins, Reynolds showed that platelet derived growth factor-BB (PDGF-BB) in combination with allograft bone materials can be used for bone regeneration at implant sites (42). It was indicated that the PDGF-BB, which is a pro-angiogenic factor, with FDBA or DFDBA as a scaffold, can be utilized for alveolar bone augmentation (42). Similar results were reported by Rosen et al. that showed in a retrospective case series report, of the effective combination of FDBA and PDGF-BB in major periodontal intraosseous defects (43). Boeck-Neto et al. evaluated the VEGF expression and microvessel density (MVD) after maxillary sinus augmentation with different allograft, alloplastic grafting materials (44). It was indicated that DFDBA and polymeric grafts induced the lowest level of VEGF expression and MVD, while the hydroxyapatite (HA) and calcium phosphate (CP) showed the highest values (44) (Tables 1 and 1 continue, 2).

The combination of other pro-angiogenic factors such as BMPs, angiopoietins, matrix metalloproteinase (MMP), or stem cell factors (SCF) with allogenic grafts can be taken into consideration in future studies.

2.3- Xenogeneic and alloplastic bone materials

Xenogeneic bone substitute materials are grafting materials obtained from other non-human species such as bovine. These substances are natural HA or anorganic bone matrix (ABM), which are obtained from the natural bone of bovine or other animal sources (6). The other grafting materials are the alloplastic substances, which are synthetic graft materials and include bioactive glass polymers, calcium carbonate, calcium sulfate, and synthetic ceramic materials like tricalcium phosphate (TCP) and HA (6). Both xenogeneic and alloplastic materials are considered as osteoconductive substances (Fig. 1), which only provide a physical matrix for recipient cells to infiltrate into the graft and form the new hard tissue (16).

Degidi et al. showed that a xenogeneic bone substitute material could significantly increase the MVD after six months. This grafting material could also induce VEGF expression when is used for sinus augmentation (45) (Tables 1 and 1 continue, 2).
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Mechanisms of Action

| Type of Bone Material/Barrier Membrane | Angiogenic Potential | Mechanisms of Action |
|--------------------------------------|----------------------|----------------------|
| Autogenous Bone Materials            | Pro-angiogenic       | 1) BM-MSCs           |
|                                      |                      | A: Differentiation into vascular endothelial and/or pericyte-like cells |
|                                      |                      | B: Inducing VEGF and FGF-2 expression |
|                                      |                      | 2) Osteocytes producing angiogenic factors such as VEGF, FGF-2, BMP-7, receptor activator of NF-κB ligand (RANKL), and EGF-like family members |
|                                      |                      | 3) Endothelial cells recruiting the bone progenitor cells and promote their differentiation into functional osteoblasts |
| Allogeneic Bone Materials (FDBA or DFDBA) | Pro-angiogenic       | Loaded with pro-angiogenic factors such as VEGF, FGF-2, PRP, and PDGF-BB |
| Xenogeneic Bone Materials (Bio-Oss)   | Pro-angiogenic       | Inducing VEGF expression |
| Alloplastic Bone Materials (HA & CP)   | Pro-angiogenic       | Increasing the VEGF expression and MVD |
| Nanocrystalline Hydroxyapatite        | Pro-angiogenic       | 1) Production of BMP-4, BMP-7, VEGF, MMP-2, focal adhesion kinase (FAK), eNOS, FGF-2 |
|                                      |                      | 2) Promoting the viability, migration and functionality of endothelial cells |
| Collagenous Membranes                 | Pro-angiogenic & Anti-angiogenic | 1) Due to containing prolyl hydroxylases inhibitors such as dimethyloxalylglycine (DMOG) and L-mimosine (L-MIM) |
|                                      |                      | 2) Loaded with pro-angiogenic factors such as bioactive glass particles (n-BG), or PDGF-BB |
|                                      |                      | Due to containing non-collagenous domains (NC1) |
| Polymeric Membranes (PLGA)            | Pro-angiogenic       | 1) Controlled release of pro-angiogenic factors such as VEGF165, PDGF-BB, and FGF-2, which were coated on PLGA |
|                                      |                      | 2) PLGA hollow fibremembrane can promote angiogenesis by providing the micro channels or neoangiogenesis |
| E-PTFE Membranes                      | Pro-angiogenic       | Enriched with laminin-5 |
| Titanium Mesh Membranes               | Pro-angiogenic       | Coated with rhPDGF-BB |
As previously mentioned, Boëck-Neto et al. showed that the alloplastic ceramic materials like HA and calcium phosphate induce the highest amount of VEGF expression and (MVD) in maxillary sinus lifting surgery compared with DFDBA and other alloplastic materials such as polymers (44). Canuto et al. indicated that nanocrystalline hydroxyapatite can promote the osteogenesis and angiogenesis by increasing the expression of BMP-4, BMP-7, and VEGF (46). Laschke et al. suggested that injectable nanocrystalline HA bone grafting materials such as Ostim due to their enhancing effect on microvessel density and pro-angiogenic property, can be used for guided vascularization procedures (47) (Tables 1 and 1 continue, 2). Pezzatini et al. demonstrated that HA nanocrystals can enhance angiogenesis by inducing the migration of endothelial cells and increasing the secretion of matrix metalloproteinase-2 (MMP-2), activation of focal adhesion kinase (FAK), endothelial nitric oxide synthase (eNOS), and FGF-2 expression (48). In another study, Pezzatini et al. indicated that HA nanocrystals are effective on viability of endothelial cells of microvessel by inducing these cells to keep their healthy status and functional properties (49). Nakamura et al. reported that polarized HA present on silk fibroin scaffolds can positively affect endothelial cells migration and morphogenesis, which results in promotion of angiogenesis events (50). Wu et al. demonstrated that nano-hydroxyapatite/collagen/PLA (nHAC/PLA) can be used as bone substitute material in new bone formation in segmental bone defects, due to its enhancing effect on angiogenesis and osteogenesis processes (51).

Castañó et al. indicated that silicon-based calcium phosphate glasses (Bioglasses), due to their calcium ion release, can play a significant role in promotion of angiogenesis events (52). Smiler et al. used bone marrow aspirate including adult stem cells in combination with xenogeneic and alloplastic scaffold in bone regeneration. These authors showed that these combinations can promote the proliferation, differentiation, and maturation of stem cells and enhance the angiogenesis events (53).

2.4- Effect of barrier membranes on angiogenesis
In 1988, Dahlin et al. proposed the GBR procedure protocol, which included the surgical placement of a barrier membrane on the subjected bony area to seal and provide the required space for bone regeneration (54). This study apparently showed the importance of using barrier membranes and their functional role in bone regenerative procedures. The most important purpose for using barrier membranes is to create a space on defect-ed bone in order to only permit the bone progenitor cells to migrate into this space, and prevent the in-growth of soft tissue cells into the defective area (54).

Barrier membranes are basically divided into two categories of resorbable and non-resorbable membranes. In the following sections the angiogenic properties of these membranes are overviewed.

2.5- Resorbable membranes
Resorbable membranes are barrier membranes, which after a short time are resorbed by hydrolysis or catabolic reactions, and do not need to be removed from the grafted site (55). However, these membranes, due to the fast biodegradation, might not be useful for regeneration procedures that require the physical space maintenance for more than one month (56). Resorbable membranes are categorized under two main groups of collagenous and polymeric membranes.

2.6- Collagenous membranes
Collagenous membranes are provided from type I or combination of type I and III collagens, which is obtained from pericardium, skin, or tendons of human, procine, or bovine (57). Collagen membranes are considered as one of the ideal membranes for regenerative procedures due to their superior biocompatibility and bioactivities such as direct effect on bone formation (58), and chemotactic effects on periodontal ligament (PDL) or gingival fibroblasts (59,60). Gunda et al. indicated that collagen has a component known as non-collagenous domains (NC1), which imposes anti-angiogenic effects on surrounding tissues (61). Shen et al. reported that prolyl hydroxylase enzyme (PHD) is a key enzyme with central role in degradation of hypoxia inducible factor alpha (HIF-1α), which is an angiogenic initiating factor in tissue development, regenerations, and reparations (62). These authors showed that PHD inhibitors such as L-MIM and DMOG can effectively activate HIF-1α, which resulted in VEGF production (62).

Vargas et al. indicated that addition of 10 wt% nanosized (20-30 nm) bioactive glass particles (n-BG) to the bovine type I collagen can promote the angiogenic characteristics of collagenous composites, which are used in tissue engineering procedures (63). Simion et al. used the pro-angiogenic factor, recombinant human PDGF-BB, on resorbable collagen matrix and reported promising results in soft tissue regenerative procedures (64) (Tables 1 and 1 continue, 2).

2.7- Polymeric membranes
Polymeric membranes are the second category of resorbable membranes, which are synthetic membranes composed of polyglycolides (PGAs), polyactides (PLAs), polyesters, and co-polymers (65). One of the disadvantages of polymeric membranes compared to collagenous membranes is the provocation of host inflammatory responses, which is much higher in case of polymeric membranes (66). However, polymeric membranes are mostly degraded by hydrolysis reaction that reduces the pH value and produces an acidic condition, which negatively impacts bone regeneration process (67).
Azzarello et al. indicated that polyglycolic acid (PGA) and PGA modified with poly(lactic-co-glycolic acid) (PLGA) compared with one-layer porcine small intestine submucosa (SIS) or two-layer SIS, have lower pro-angiogenic effects (68). Perets et al. suggested that PLGA microspheres are capable of controlled release of pro-angiogenic factors such as FGF-2. By incorporating this angiogenic factor, the PLGA membrane promoted the angiogenesis processes at grafted areas (69). Shah et al. showed that PDGF-BB as a pro-angiogenic factor can be coated on PLGA for adaptive release in bone regeneration procedures (70). Yonamine et al. reported that the incorporation of VEGF165 on PLGA membranes can effectively promote bone regeneration procedures (71). Ellis, Chaudhuri demonstrated that the PLGA hollow fiber membrane can promote angiogenesis by providing the micro channels inside its structure that permit angiogenesis to occur in these channels (72) (Tables 1 and 1 continue), 2).

2.8- Non-resorbable membranes:
Non-resorbable membranes are other types of membranes, which require the clinician to remove them after application at grafted areas. These membranes are mostly contaminated with bacteria and must be removed within 4-6 weeks after surgical application. Non-resorbable membranes include different types such as expanded polytetrafluoroethylene (e-PTFE), high-density polytetrafluoroethylene (d-PTFE), titanium-reinforced PTFE, and titanium mesh membranes (73). In the following section the angiogenic properties of these membranes are discussed.

2.9- E-PTFE, d-PTFE, and titanium-reinforced PTFE membranes
E-PTFE membranes have become a standard membrane for GBR procedures since 1990s (74-76). Becker et al. indicated that e-PTFE membranes can be successfully used for bone regeneration procedures around dental implants (76). The other type of PTFE membranes, is the d-PTFE membrane, which has higher density and smaller pore size (> 0.3 µμ) compared to e-PTFE membranes with larger pore sized (5-20 µμ) (77,78). D-PTFE membranes beside their higher density, have another advantage over e-PTFE membranes, which is their use in situations that the primary soft closure is not possible. In bone regeneration procedure such as socket preservation or other conditions, which due to tissue tension the primary closure is not affordable, the d-PTFE membranes can be used safely (78). Titanium-reinforced PTFE membranes contain a titanium framework embedded in e-PTFE or d-PTFE membranes, which enable them to be shaped easily and maintain their shape at surgical site. These membranes can be used in larger bony defects without rebounding or collapsing into the defective areas (6).

Song et al. used the e-PTFE membrane for regeneration of mandibular bony defects and evaluated its effects on angiogenesis processes at 2, 3, 4, and 8 weeks. These authors noticed that the presence of e-PTFE non-resorbable membrane was effective in rebuilding the supralveolar vascular network. However, it did not affect vascular anastomosing between new connective tissue and gingival flap, while 2-4 weeks after removal of membranes the vascularization between the gingival flap and new connective tissue became normal (79) (Table 1 and 1 continue).

Kid, Williams showed that laminin-5-enriched extracellular matrix can promote angiogenesis. These authors used e-PTFE samples, which were modified with cell matrices that were enriched with laminin-5. They noticed that the density of blood vessels was increased significantly (80). In another study Kid et al. indicated that the modified e-PTFE with laminin-5 increased the endothelial cells adhesion and promoted neovascularization process of the peri-implant tissues (81) (Table 1 and 1 continue).

2.10- Titanium Mesh membranes
Titanium mesh membranes are another type of non-resorbable membranes, which have a great ability to maintain the space required for alveolar bone augmentation. These membranes can perfectly withstand the pressure of overlying soft tissue and keep a large space for bone regeneration without collapsing (82). Funato et al. reported that rhPDGF-BB can be used in combination with titanium mesh membranes to enhance bone regenerative procedures in vertical ridge augmentation (83) (Table 1 and 1 continue).

Conclusions
In this review the effects of bone-grafting and barrier membrane materials on the angiogenesis processes at recipient sites were overviewed. According to the reviewed studies the following conclusions were drawn: Autogenous grafting materials have the highest potential for inducing angiogenesis events at the recipient site. The angiogenic properties of these materials are closely related to the viable cells such as BM-MSCs, osteocytes, and endothelial cells. The angiogenic properties of allogeneic bone materials are lower than other grafting bone substitutes. The addition of different pro-angiogenic factors such as VEGF, FGF-2, and PDGF can be promising in increasing the angiogenic activity of these materials. Among the xenogeneic and alloplastic bone materials, the HA and calcium phosphate have the highest pro-angiogenic effects. The modifications such as nano-sized HA crystals or the combination of calcium phosphate and Bioactive glass might enhance the pro-angiogenic activity in grafted areas. Resorbable collagenous membranes had pro-angiogenic effects due to release of prolyl hydroxylase inhibitors.
(L-MIM and DMGO), while the NCI component in these membranes act as an anti-angiogenic agent. The recent trend includes the enrichment of collagenous membranes and scaffolds with PDGF-BB or nano-sized bioactive glass to enhance their angiogenic properties. The polymeric membranes do not have any remarkable inherent pro-angiogenic effects and are mostly used as scaffolds for delivering and controlled release of pro-angiogenic factors.

The angiogenic properties of e-PTFE, d-PTFE, titanium-reinforced PTFE, and titanium mesh membranes have not been well-discussed in the literature. However, these non-resorbable membranes might have some angiogenic potential, but most of the pro-angiogenic effects of these membranes are related to the incorporated pro-angiogenic agents, which are used to enhance the angiogenic activity.

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Conflict of Interest
The authors hereby declare that they have actively participated in this work and preparation of the manuscript and have read the contents of this manuscript. We affirm that we have no financial affiliation or involvement with any commercial organization with direct financial interest in the subject or materials discussed in this manuscript.