Review Article

Using Polymeric Scaffolds for Vascular Tissue Engineering

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With the high occurrence of cardiovascular disease and increasing numbers of patients requiring vascular access, there is a significant need for small-diameter (<6 mm inner diameter) vascular graft that can provide long-term patency. Despite the technological improvements, restenosis and graft thrombosis continue to hamper the success of the implants. Vascular tissue engineering is a new field that has undergone enormous growth over the last decade and has proposed valid solutions for blood vessels repair. The goal of vascular tissue engineering is to produce neovessels and neoorgan tissue from autologous cells using a biodegradable polymer as a scaffold. The most important advantage of tissue-engineered implants is that these tissues can grow, remodel, rebuild, and respond to injury. This review describes the development of polymeric materials over the years and current tissue engineering strategies for the improvement of vascular conduits.

1. Introduction

Each year there is a strong demand for vascular grafts due to arteriosclerosis and other cardiovascular diseases that are the main cause of mortality in the western countries [1–4]. Nowadays, autotransplantation of blood vessels is usually performed; however, the possible presence of vein diseases and a limited availability of autologous blood vessels make this procedure often impracticable [5, 6]. This necessity has led to the use of nonbiodegradable synthetic prostheses and, more recently, to the approach of tissue engineering. Vascular tissue engineering has been described as "an interdisciplinary field that applies the principles and methods of engineering and the life sciences towards the development of biological substitutes that restore, maintain, and improve tissue function" [7]. Its aim is to develop biocompatible scaffolds that mimic the mechanical properties of autogenous conduits, while providing a framework for guided cell repopulation

creating a functional cardiovascular conduit [8]. The tissue engineering approach starts from the isolation of specific cells, their growth on a three-dimensional biomimetic scaffold under controlled culture conditions, the delivery of the construct to the desired site, and the direction of new tissue formation into the scaffold while it is degraded [9]. Thus, tissue engineering usually uses three components to achieve its outcomes: (a) cells, (b) scaffolds or matrices to provide a template for tissue ingrowth, and often with the addition of (c) environmental factors (such as compression, shear stresses, and a pulsatile flow in the case of arterial tissue engineering) and/or growth factors or morphogens (physical or chemical factors inducing tissue healing and cell differentiation) [10, 11].

Clearly, the scaffold must be produced on the basis of morphological, physiologic, and mechanical properties of the tissue that need to be regenerated which has to be studied from the anatomical point of view [12]. The wall of a blood

vessel is constituted by three main layers called tunica adventitia, tunica media, and tunica intima. The outermost layer is the tunica adventitia which is mainly composed by fibroblast and elastin and supply mechanical strength and integrity.

Tunica media is composed mainly by smooth muscle cells and elastin and is responsible for the viscoelastic behavior of the vessel. Tunica intima is the inner part of the vessel in contact with the circulating blood and is composed of a single layer of endothelial cells mounted on a basement membrane [2, 13]. Synthetic scaffolds which are intended to mimic the structure of a blood vessel must promote the correct orientation of the different cell types as well as the maintenance of the structural integrity and the long-term patency [14]. In this review, the developments made in the field of replacement of damaged blood vessels from the early surgical approaches to the innovative approach of tissue engineering will be discussed. Particular attention will be given to the use of polymeric materials and to the techniques of production of biomaterials that allow to mimic the morphological characteristics of the blood vessels.

2. From the Early Surgical Approaches to the Nonbiodegradable Grafts

The gold standard material for blood vessels replacement, because of the complex histological structure of this particular tissue, is represented by blood vessels themselves. For this reason the first surgical approaches were oriented to the autologous vessels transplantation [15]. The first approach to the problem of replacing a damaged vascular tract was dated in 1906, when for the first time a venous autograft was used as replacement of a section of an artery. It was José Goyanes who, on the occasion of a popliteal aneurysm, removed the damaged part of the artery and connected the cut ends using a section of the autologous popliteal vein. The patient showed an infection after the operation, but this must be probably caused by the injection of gelatin in the popliteal cavity before the operation, rather than implanting the graft. The subject was hospitalized and did not revealcirculation problems [16, 17]. In 1915, Bernheim provided another approach to repair popliteal aneurysm. The patient in this case had to undergo the removal of about 15 cm popliteal artery, replaced by 12 cm of the saphenous vein [18].

Other case studies were followed, but the two previous cases had considerable importance, as it was from here that came the idea of reconstructing a damaged tissue [19]. The major example of autologous implant is the saphenous vein, which consists of one of the two larger ducts venous lower limb together with the femoral vein and has a diameter generally between 4 and 6 mm. The clear advantage of using this vessel is that it evokes no rejection and shows mechanical characteristics comparable to arteries [20]. In 1948 Kunlin created a femoropopliteal bypass with a system consisting of the reversed saphenous vein, laying the foundation for a practice that is still to be established. In the same year early arterial systems began to spread consisting of foreign tissue but deriving from subjects of the same species [21]. Unfortunately, this approach is burdened by high failure rates,

as in the case of saphenous vein graft, due to atherosclerosis and intimal hyperplasia of the transplanted vessels [22]. Furthermore, it was showed that almost 30–40% of patients lack an appropriate saphenous vein [23, 24] due to previous phlebitis, vessel removal, varicosities, hypoplasia, or anatomical unsuitability [25]. There has been also an experimentation of homologous saphenous vein grafts (homograft), but there were no encouraging results in terms of physical and mechanical characteristics. In addition, there were frequent phenomena of rejection and deterioration, and it is supposed that the patency of the conduit remains unaltered only for vessels of diameter greater than 5 mm. For these reasons, in 1960 the homograft was abandoned [26]. Autologous arteries (internal and external iliac, superficial femoral, and internal mammary) were ideal artery bypass in the cardiac and the peripheral arteries but both had a limited availability of sites donors [27]. Because of the excellent long-term patency, the internal mammary artery was considered to be the best choice for coronary artery bypass graft in younger patients. For other patients, when the internal mammary was not available or not indicated, the alternative was represented by the right gastric or intercostal arteries [28]. The possible presence of vein diseases and a limited availability of autologous blood vessels represent the major limitation to the autologous transplantation that has led to the necessity to develop artificial blood vessels [29].

Currently expanded polytetrafluoroethylene (ePTFE) and Dacron (polyethylene terephthalate fibre) have been the most widely used synthetic materials for realizing grafts [30]. Dacron is one of the trade names of PET (polyethylene terephthalate) polymer belonging to the family of thermoplastic polyesters. The Dacron is resistant, deformable, and biostable and is present in different forms. It is used in cardiovascular surgery to achieve large-diameter vascular prostheses, for arterial sutures and for the construction of the valve rings. The highly crystalline and hydrophobic natures of Dacron both prevent hydrolysis of a graft, leading to a potential of residing inside the human body for decades. PET is usually transformed fibers, from its linear macromolecules with an average weight of about 20000 Da. Each wire that constitutes the prosthesis is composed by the association of monofilaments obtained by passage of polymers fused of PET in a supply chain. These wires are then elongated by heat treatment capable of conferring aspect ring. Subsequently, the individual filaments are gathered (spiral or helix) in a single fiber. The fact of being multifilament makes the fiber elastic and manageable. The wire weaved is used to fabricate woven or knitted prosthesis [31]. Teflon is a polymer of tetrafluoroethylene and is identified also as polytetrafluoroethylene (PTFE). It is the most important and used between polymers composed of fluorine and carbon. In the 60's, deriving from Teflon technolgy, PTFE foam (ePTFE), also known as Gore-tex,was developed. It has found application in vascular prostheses in the second half of the 70's. Again, just like in Dacron, the highly crystalline and hydrophobic nature yields a stable product by preventing hydrolysis. Tubular grafts made from ePTFE are produced by an extrusion, drawing, and sintering process and consist of fibrils and nodules, controllable to different pore sizes. The

Gore-Tex is therefore a nondegradable porous polymer with a surface electronegative, which limits the reaction with the components of the blood. It is biostable and in fact has a lesser tendency, for example, to deteriorate in a biological environment compared to PTFE. In general, however, the behavior that it has in a biological environment is influenced by the type of processing to which it is subjected.

In previous experiments it was found that the larger the porosity of the material, the better is its integration with the physiological environment. However, it was found that an implant characterized by high porosity resulted to be also fragile and therefore cannot be used clinically. In a significant study conducted by Isaka et al. [32] a highly porous graft was achieved but it was biocompatible and with the ability to integrate in host tissues. The graft was inserted in the abdominal aorta of eleven purebred dogs of both sexes with a weight between 10 and 12 kg. In the graft used the average internodal distance was 60 m and the structure showed tortuous channels formed by the nodes and fibrils of PTFE. The implant was 30–40 mm long; its inside diameter measured 6 mm and was reinforced by a filament fluoroethylene propylene. The eleven grafts were then inserted into the animals and extracted at intervals of 2 weeks (4 grafts), 4 weeks (4 other grafts), and 80 weeks (3 graft). On the implants removed an evaluation of the resistance to radial tension, longitudinal tension, the retention force of the suture, and the rate of deformation was performed. The results showed that there was no sign of any problems or occlusion at the level of anastomosis. The rate of deformation demonstrates a certain stability of the two properties considered. Furthermore, as regards the retention force of the suture, there was no substantial difference between before and after graftings. Additional experiments demonstrated that ePTFE and Dacron were successful in large-diameter (>5 mm) high-flow vessels, but in low flow or smaller diameter sites they are compromised by thrombogenicity and compliance mismatch [33]. In the 80's and 90's, however, the performance of grafts was evaluated with porosity gradually higher, starting from the assumption that large pores permit a fast growth of tissue from the outside of the graft up within its interstices, allowing a large integration of the prosthesis with the biological environment. Another category of polymers with large diffusion is represented by polyurethanes. Polyurethanes were originally developed commercially in Germany in the 1930s as surface coatings, foams, and adhesives. Segmented PUs are copolymers comprising 3 different monomers, a hard domain derived from a diisocyanate, a chain extender, and a soft domain, most commonly polyol. The soft domain is mainly responsible for flexibility, whereas the hard domain imparts strength. Polyether urethane was relatively insensitive to hydrolysis but susceptible to oxidative degradation.

Polyurethane grafts which have been available for the last 40 years have characteristics that would be ideal for use in bypass procedures, namely, similar compliance to native arteries with a surface that is conducive for seeding [34–37]. Unfortunately, polyurethane grafts have had variable results clinically with a tendency to degrade causing aneurysm formation [38]. Data obtained showed that when compared with ePTFE grafts, the PU graft overall showed no appreciable

difference in interval patency in canine aortic model. Furthermore, in a small study, the grafts were implanted in aortoiliac arteries of 4 dogs for 6 months evidencing that luminal thrombus affected 59% of polyurethane graft surfaces compared to 22% of ePTFE graft [39]. Anyhow, tissue reactions to PU grafts are discrepant in the literature because factors such as different compositions of polymers, graft fabrication, porosity, and surface modifications all affect the results. On the basis of these evidences no conclusion can be made as to whether PU grafts may be functionally superior to ePTFE or Dacron grafts until more data become available.

3. Synthetic Prosthetic Grafts Disadvantages and Diffusion of Tissue Engineering

It has been tested that currently available vascular grafts show satisfactory long-term patency rates only in large-caliber arteries (>8 mm), where a massive blood flow may overcome the risk of thrombogenicity. In medium-caliber replacements (6–8 mm), for example, in carotid or common femoral arteries [40], a little difference between prosthetic and autogenous material has been reported.

However, in small-caliber vessels (<6 mm), such as coronary arteries, infrainguinal arteries (below the inguinal ligament), and particularly in low-flow infrageniculate arteries, the outcomes of vascular prostheses are unsatisfactory.

Several methods have been developed to enhance the patency rates. The major example is the linking of heparin to graft surfaces in order to obtain a reduction of the thrombogenic activity [37, 41]. Nevertheless this strategy is associated with the problem of the duration of heparin activity due to premature release of the compound or the presence of a physical barrier, created by adherent blood components. Other modifications are the coating of the luminal surface with carbon so that electronegativity is improved and thus thrombus formation reduced [42]. Another widely used coating material is fibrin glue, which is able to improve endothelialization and other physical and chemical variations [43, 44]. Additionally, synthetic grafts are usually rejected within few months by the immune system of the body if the diameter of the vessel is smaller than 6 mm. This rejection arises from the consequent reocclusion caused by thrombosis, aneurysm, and intimal hyperplasia due to mismatch of compliance (compliance is the opposite of stiffness, measured as the strain/expansion or contraction of the graft with force) [45–50]. Thrombogenicity could be associated with the deposition of fibrin and platelets on the surface of an implanted material or with the proliferation of smooth muscle cells, which migrate from native vessel, invade the intima by growing instead of endothelial cells, and produce extracellular matrix [51]. Intimal hyperplasia (IH) is located at distal anastomosis of prosthetic grafts and generally developed 2–24 months after implantation and includes a variety of factors: a compliance mismatch between a relatively rigid prosthesis and the more elastic native artery [52], graft/artery diameter mismatch, lack of endothelial cells, surgical trauma and flow disturbances resulting in adaptive changes in the subendothelial tissue, characterized by proliferation and migration of vascular smooth muscle

cells from media to intima, and synthesis of extracellular matrix (ECM) proteins. To overcome these issues, novel biomaterials research [53] and particularly tissue engineering modalities are increasingly being adopted [54]. Tissue engineering opened the way to the creation of devices with an adequate mechanical strength and compliance in order to withstand long-term hemodynamic stresses; furthermore, these devices should be nontoxic, nonimmunogenic, biocompatible, available in various sizes for emergency care, resistant to *in vivo* thrombosis, and able to withstand infection and to incorporate into the host tissue with satisfactory graft healing [55], related with reasonable manufacturing costs [27].

It is thought that tissue engineering would be particularly valuable in the production of vascular grafts because of the massive need and precarious supply of natural graft material for clinical use.

The challenges faced by the approach of tissue engineering for replacing blood vessels are substantial. They include providing an elastic vessel wall that can withstand cyclic loading, matching the compliance of the graft with the adjacent host vessel, and a lining for the lumen that is antithrombotic [56]. From the first production of completely biological tissue-engineered blood vessels, composed of intima, media, and an adventitia, using cultured mature smooth muscle cells and endothelial cells in bovine collagen gels by Weinberg and Bell [57], there have been many attempts for successful blood vessel construction through tissue engineering approach.

Various strategies including *in vitro* endothelization of the graft have been used to overcome these problems but few *in vivo* results have been obtained [58, 59]. It is now clear that an intact luminal EC monolayer imparts resistance to thrombus formation and reduces the extent of intimal hyperplasia [60].

Several studies revealed that when blood comes into contact with another surface than the endothelium, there is an elevated risk of thrombosis. These conditions can be related also with loosely attached ECs that can detach right after implantation due to blood flow related shear stress [61]. The EC layer is also able to inhibit actively thrombosis. This is achieved by thrombomodulin receptors, heparin sulfate, proteoglycans, and the secretion of NO, prostacyclin, protein S, and t-PA, all of which inhibit the clotting process. Aside from these features, the endothelium has a primary role in blood pressure regulation, angiogenesis, and adhesion and transmigration of inflammatory cells. It is therefore considered a vital component for maintaining good long-term patency. ECs, however, have limited capacity for regeneration and exhaust their renewal after approximately 70 cell cycles, leading to the hypothesis that endothelialization of vascular grafts occurs via one of four mechanisms: (i) by seeding ECs, (ii) via EC migration from adjacent native vessel, (iii) through deposition of circulating endothelial progenitor cells onto the luminal surface, or (iv) via ingrowth of capillaries through porous grafts [62]. Since Herring proposed a method of seeding ECs onto the luminal surface of synthetic conduits back in 1978 [63, 64], many studies have attempted to improve clinical rates of patency by optimizing EC attachment. Parallel to this, in scaffold-based blood vessel engineering, bioreactors and pulsatile flow systems, designed by many scientists,

have been found to progress the mechanical property of the engineered blood vessels by augmenting the deposition and remodeling of extracellular matrix as well as the maturation and differentiation of self-assembled microtissues [65–68].

4. Tissue-Engineered Vascular Grafts

According to the tissue engineering approach a bioengineered tissue should be able to act as a temporary prosthesis that replace a particular damaged tissue for the time necessary to the cells, seeded in it or coming from the sites proximal to the implant, to synthesize a new extracellular matrix contributing to the production of a new tissue. The choice of the starting biomaterial is crucial as it influences the rate of degradation *in vivo*, the structural and functional integrity of the bio engineered tissue, and its gradual elimination from the body. The starting biomaterial also influences the mechanical properties of bioengineered tissue as well as its ability to be recognized as "self" by the body. This last feature is particularly important and can be completed only if the biomaterial carries biological signals that represent a stimulus for the adhesion and proliferation of the cells as well as for the production of new extracellular matrix. In other words, the physical-chemical characteristics of the biomaterial are able to influence the biochemical gap between living tissue and bioengineered ones. In some cases the biomaterial itself can represent a stimulus for the cellular functions (especially when natural components of the extracellular matrix are employed), while in most cases molecules such as growth factors, adhesion moieties, or even drugs of various nature have to be incorporated into bioengineered tissue by physical mixing or covalent bond. In this last case the biomaterial must have free functional groups to be exploited for the functionalization with one or more bioactive molecules. In blood vessels tissue engineering heparin and vascular endothelial growth factor (VEGF) are widely used. Both are in fact able to avoid the formation of thrombotic phenomena due to blood clotting. Heparin has anticoagulant activity and is crucial in the early stages after implantation, whereas VEGF, promoting endothelial cell proliferation, permits the formation of an intact endothelium on the surface of the scaffold in contact with the circulating blood avoiding the creation of turbulent motions responsible of the formation of thrombi. Moreover the presence of a confluent monolayer of endothelial cells prevents the development of pseudointimal hyperplasia by inhibition of bioactive substances responsible for SMC migration, proliferation, and production of ECM [69]. Since the early vascular tissue engineering has spreading, natural or synthetic polymers (or combination of the two classes) have been used as starting materials. Polyesters are a class of synthetic macromolecules widely used in tissue engineering because of their optimal mechanical properties, biocompatibility, and biodegradability.

These polymers have been used as sutures [70] plates and fixtures for fracture fixation devices [71] and scaffolds for cell transplantation [72, 73].

Polyesters such as poly(ε-caprolactone) (PCL), polylactic acid (PLA), and polyglycolic acid have been approved by FDA and extensively employed in experimental trials.
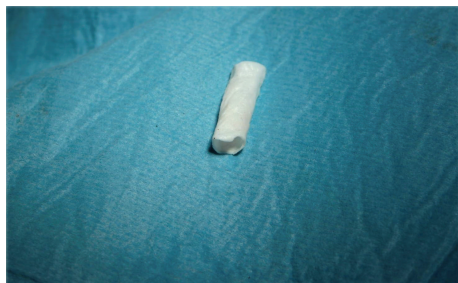
Figure 1: Tubular PHEA-PLA-PCL scaffold.

Concerning the vascular tissue engineering polyesters have been chosen as starting material very often thanks also to their good processability. Among the manipulation techniques electrospinning has gained great attention because it offers the possibility to obtain scaffolds with a defined shape and a complex porous architecture that can mimic the three-dimensional structure of extracellular matrix offering a good support for cell attachment and proliferation [74, 75]. Through electrospinning it is possible to prepare nonwoven mats of polymer fibers with diameters ranging from several microns down to less than 100 nm [76, 77]. Spun mats show amazing characteristics such as very large surface area to volume ratio, flexibility in surface functionalities, and superior mechanical performance (e.g., stiffness and tensile strength) compared with any other known form of the material [78]. These outstanding properties make the polymer fibers be optimal candidates in tissue engineering as substitutes of several tissues [79]. Nottelet et al. [80] developed a PCL-based vascular graft with an internal diameter of 2 or 4 mm. They implanted the cell-free scaffolds to Sprague-Dawley rats in substitution of an infrarenal abdominal aorta portion to evaluate the resistance and the patency of the implanted scaffolds over a period of 12 weeks. Scaffolds showed good surgical handling and suture retention properties and led to successful implantations without thrombosis or aneurysm formation at the three different time points. Authors observed also an almost complete endothelial coverage to the endoluminal graft surface after 6 weeks of implantation but some intima hyperplasia formation was observed in all grafts after 12 weeks.

Infiltration of fibroblast and macrophages was observed through all the scheduled times indicating the presence of an inflammation process even if no chronic lymphocytic reaction was observed.

The *in vivo* result of this study was even encouraging and has outlined the outstanding properties of PCL even if it is clear that some drawbacks are still present to be solved. As mentioned above, an ideal bioengineered tissue should optimally integrate with native tissues exploiting the possibility to be functionalized with bioactive molecules. The lack of functional groups in the starting biomaterial able to promote this type of functionalization could represent a major limitation. The small number of functional groups in the chemical structure of the polyesters limits the possibility to bind significant amounts of most of the bioactive agents and only molecules able to perform their biological function even at very low concentrations could be used.

Zheng et al. [81] produce a nanofibrous vascular graft by electrospinning of PCL functionalized with an arginine-glycine-aspartic acid-(RGD-) containing molecule named Nap-FFGRGD.

They also produce RGD free PCL grafts and compared results obtained from the implantation of the obtained vascular scaffolds in rabbit. Both grafts implanted in rabbit carotid arteries for 2 and 4 weeks showed endothelial cell adhesion in the lumen of the scaffold even if on the RGD-PCL cells were confluent and highly aligned, whereas those on the RGD free PCL graft were randomly aligned.

The endothelialization rates for RGD-PCL grafts were faster than those of the PCL grafts demonstrating the importance to incorporate the active molecule in the vascular graft.

Polyesters could be employed also in combination with bioactive macromolecules (mostly of natural origin) having a direct effect on the cells or with polymers having functional groups exploitable for the binding with the molecules of interest.

Pitarresi et al. [82] electrospun a mixture of PCL and α,β-poly(N-2-hydroxyethyl) (2-aminoethylcarbamate)-D,L-aspartamide-graft-polylactic acid (PHEA-EDA-g-PLA), a synthetic graft copolymer having in its chemical structure several free primary hydroxyl and amino groups coming from the hydrophilic backbone of PHEA-EDA, a biocompatible polymer derived from PHEA which is widely employed for several biomedical application [83–88] (Figures 1 and 2).

PHEA-EDA-g-PLA functional groups were exploited to covalently link a significant amount of heparin (36 μg per mg of scaffold) which has been employed to control the release of fibroblast growth factor. Authors demonstrate that the presence of both heparin and growth factor influences the ability of endothelial cells cultured *in vitro* upon the scaffold to produce an intact endothelial layer. Jia et al. [89] electrospun poly(L-lactic acid) (PLLA) in combination with collagen in order to obtain a scaffold with the optimal mechanical characteristic, due to the presence of the polyester, and able to represent an optimum substratum for cell adhesion and spreading thanks to the presence of collagen. They seeded bone marrow derived mesenchymal stem cells (MSCs) on the obtained nanofibers to investigate the capability of these cells to differentiate into vascular endothelial cells when cultivated with differentiating medium. Authors demonstrated that cells grown on PLLA/Coll nanofibrous scaffolds differentiated in endothelial cells showing cobblestone phenotype with expression of vascular specific proteins such as the platelet endothelial cell adhesion molecule-1 and Von Willebrand factor. The use of stem cells in tissue engineering is becoming increasingly popular because these cells can be extracted from various sources and can proliferate *in vitro* and differentiate into a series of mesodermal lineages, including osteoblasts, chondrocytes, adipocytes, myocytes, and vascular cells [90–93].

Among the polymers of natural origin, silk fibroin has certainly attracted a lot of attention in the field of vascular tissue engineering. Silk fibroin of silkworms is a commonly available natural polypeptidic biopolymer with a long history
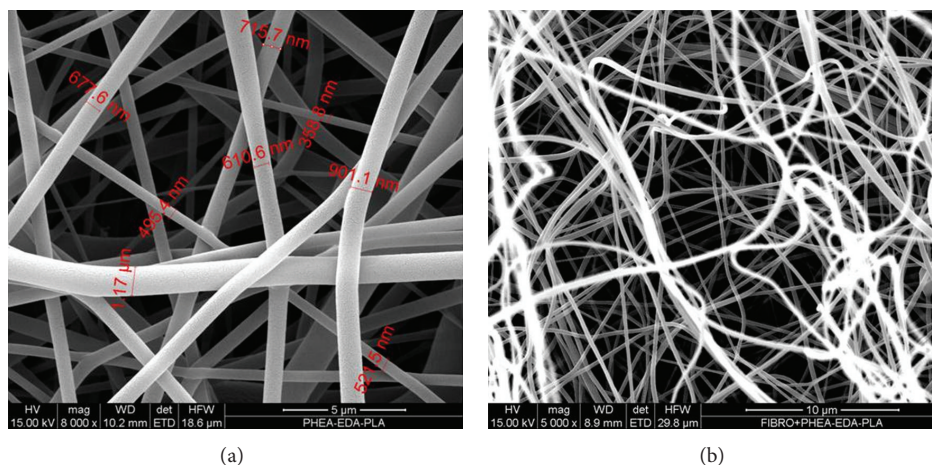
(a)

(b)

Figure 2: PHEA-PLA-PCL scaffold. (a) SEM, 8000x, (b) SEM, 5000x.

of applications in the human body as sutures. Increasingly, silk fibroin is exploited in other areas of biomedical science, as a result of new knowledge of its processing and properties like mechanical strength, elasticity, biocompatibility, and controllable biodegradability [94]. Silk based regenerated vascular tissues are clinically used as flow diverting devices and stents and in general [95, 96] the properties of silk fibroin are particularly useful for tissue engineering [97]. The implantation of vascular graft of silk fibroin composites of B. mori and transgenic silkworm into rat abdominal aorta results in excellent patency (about 85%) after a year [98]. Wang et al. produced a fibroin scaffold consisting of silk braided tubes coated (on both inside and outside surfaces) by a film of fibroin cross-linked with poly(ethylene glycol) diglycidyl ether (PEG-DE). Through freeze drying technique authors were able to obtain micro- and nanoscale pores distributed throughout the inner surface of the scaffold.

They tested the biocompatibility *in vitro* on fibroblasts and human umbilical vein endothelial cells demonstrating that the biomaterial causes no inhibitory effect on DNA replication, cell adhesion, or proliferative activity. Cells in fact were able to fully spread on the internal surface and formed an interconnected network [99]. Liu et al. produced sulfated silk fibroin (S-silk) by reaction with chlorosulphonic acid in pyridine and used the obtained biomaterial to form a scaffold by electrospinning technique. They found that the anticoagulant activity of S-silk scaffolds was significantly enhanced compared with silk fibroin nanofibrous scaffolds. Also they demonstrated that both endothelial cells and smooth muscle cells strongly attached to S-silk scaffolds and proliferated well expressing some phenotype-related marker genes and proteins [100].

Several other studies have been conducted by employing natural derived polymers (also in combination with synthetic polymers) for the development of tissue-engineered blood vessels.

Zhu et al. developed a 3D scaffold for vascular tissue engineering by employing hyaluronic acid (HA) and human like collagen (HLC). A tubular structure was obtained by cross-linking the polymers with glutaraldehyde and then by freeze drying the obtained product previously placed in a tubular mold. Authors demonstrated that the presence of HA promotes endothelial cell proliferation and maintains their viability. Furthermore, HA enhances the mechanical properties of vascular hybrid scaffold [101].

5. Conclusions

Despite numerous *in vitro* and *in vivo* results obtained by different research groups in the production of bioengineered blood vessels, to the best of our knowledge, there are no clinical applications of any of these devices.

This denotes a real difficulty of the transposition of the implant from the animal model to humans and thus there is still a need to develop devices able to recreate entirely the functional properties of native blood vessels following the principles of tissue engineering.

There are still many aspects to be explained before a real clinical translation of vascular implants.

Further studies can help to clarify the mechanisms of regeneration and may address towards the choice of a more efficient strategy for scaffold production and cells seeding.

Understanding the role of inflammatory cells in blood vessel regeneration, for example, could be of great importance for the future development of innovative grafts.

It is also desirable to overcome the problem of thrombogenicity in humans, finding a new approach that can retain endothelial cells on grafts for a sufficient period of time under flow conditions *in vivo*.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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