Biological Analogs of Infrainguinal Arteries: Evolution and Development Prospects (Review)

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Currently, the gold standard of plastic material for infrainguinal artery replacement is still autovein, however, not infrequently the necessity for prostheses arises.

The review presents the characteristics of xeno- and allogenic prostheses for lower limb arteries, which have been used in vascular surgery worldwide since 1960-ies till the present.

There have been analyzed the clinical results with the bioprostheses, their advantages and disadvantages being discussed. We have shown that the approach based on chemically cross-linked human and animal tissues used for bioprostheses is limited in its further development.

We have studied the evolution of tissue engineering vascular grafts (TEVG), and carried out a critical review of current state of the issue, and presented further paths of its development.

Key words: lower limb arteries; arterial bioprostheses; vascular tissue engineering.

Relevancy of the problem

The main cause of the stenosis of lower limb arteries (infrainguinal arteries, IAr) is atherosclerosis, its incidence increasing annually [1]. Currently, a minimally invasive surgery like as balloon angioplasty and stent implantation is possible in most patients [2]. Nevertheless, the majority of patients underwent surgery procedures consisting in the replacement of a damaged artery by either prosthesis or an autogenous v. saphena magna, it still being a gold standard of efficiency in such reconstructions [3]. However, considering predominantly multifocal character of atherosclerotic damage, an autovein is used primarily for coronary artery bypass grafting. For this reason, as well as due to some anatomical peculiarities of v. saphena magna (disseminated vein type), it is a prosthesis that is used most frequently [4].

Prostheses made of synthetic materials — Dacron and polytetrafluorethylene (PTFE) — are known to demonstrate good long-term results, if the diameter of a reconstructed artery is over 6 mm; however, these prostheses are contraindicated for bypass grafting of the arteries with a diameter of less than 4 mm [5]. Lower limb arteries are somewhere between: the diameter of the femoral artery in the area of proximal anastomosis is 6–7 mm; the popliteal artery — 5 mm, if the anastomosis is above the knee joint space, and 4 mm — below the knee joint space; for tibial and peroneal arteries an optimal diameter of bypass should not exceed 3.5 mm.

Within several decades the question is still open: what prosthesis type and model should be regarded as optimal

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for IAr reconstruction? The key measure is primary patency rate: the absence of restenosis in a long-term (at least 5 years) postoperative period. In secondary patency rate, when the bypass function is restored by means of various procedures — angioplasty, stenting, anastomosis repair, etc. — the graft characteristics are less indicative. Needless to say, that the best primary patency rate is demonstrated by autogenous vein.

Concerning prostheses of different types, randomized studies are necessary, since it is extremely difficult to compare the findings of different vascular centers: patients’ composition on comorbidities, the state of inflow and outflow tracts differ dramatically. However, the patency rate of any bypasses including autovein are well known to be significantly higher in patients with persistent blood flow in three crural arteries compared to patients with two or even one arteries occluded.

Available literature covers insufficiently the effects of bioprostheses. Moreover, there are no data on large randomized studies. The authors of one meta-analysis published in 2017 have shown that generally, bioprostheses outperform the analogs made of PTFE in long-term patency, however, there is no information available for evidence-based opinion [6].

Current state of biomedical sciences holds out a hope of developing within the near decade clinically available tissue engineering constructions including those to substitute damaged vessels of various locations [7]. However, even now, breakthroughs in the development of tissue engineering analogs of low limb arteries and near-term prospects require analysis.

In this regard, our survey research aims at studying clinical consequences of using different biological prostheses of lower limb arteries, as well as estimating the prospects of tissue engineered vessels.

The evolution of bioprostheses of infrainguinal arteries

The first serious but though failed attempt to develop IAr bioprosthesis were the researches carried out in 50–60ies of the last century [8–10]. The authors used bovine carotid artery treated with proteolytic enzyme — ficin — with the following preservation in formaldehyde. Further variations of the artery treatment methods consisted in the substitution of a cross-linking agent for a glutaraldehyde, the treatment process being made more complex [11–13]. Bioprostheses Solcograft and Solcograft-P based on the ideas by Rosenberg were tested in patients [8, 11] including multicenter studies with the number of patients over 100 [12, 13]. The authors considered these bioprostheses to be a reasonable alternative to synthetic analogs; however, secondary patency rate was only 50–60% in 4 years, while the incidence of aneurysms was 36–42%. The studies by Holdsworth et al. [13] drew a line in clinical application of bioprostheses made of bovine carotid artery. It is most likely that failures were due to both: mismatch of the bioprosthesis and reconstructed artery diameters (bioprosthetic diameter was 7.5–14 mm [9], while the diameter of femoropopliteal arterial segment was 4–7 mm), and also the treatment method (dialdehydes impart rigidity and hydrophobic properties to biomaterial, that has an adverse effect on biomechanical and functional characteristics of a flow in the repair area).

Bioprosthesis made of human umbilical cord vein preserved in glutaraldehyde (HUV bioprosthesis, or BioGraft) developed by Dardick in 1974 has left a significant mark in the history of vascular surgery [14]. From 1975 to 1989 Meadox Medicals, Inc. (USA) was engaged in manufacturing the bioprosthesis [15]. BioGraft demonstrated good primary patency rate: 50–60% within a period up to 3 years, and 42–50% within the period up to 6 years [16–18]. Randomized studies involving over 200 patients have proved that primary patency rate of HUV bioprosthesis is significantly higher than that of synthetic prostheses made of PTFE [18–20]. The major drawback of BioGraft, according to different researchers [16, 21, 22] was high incidence rate of aneurysms and biodegradation: 8–17%. As a result, Dardick et al. carried out investigations to reveal the aneurysm causes [23], and invented external support in the form of total covering of biomaterial by Dacron mesh. The product is known as second generation HUV bioprosthesis, and in 1989 the rights to it were transferred to BioVascular Inc., which further realized its manufacture. Modifications made in the bioprosthesis design had a positive effect on clinical results: 6-year primary patency rate increased by 14% [24], while aneurysm incidence decreased up to 2.9–3.5% [24, 25].

In 2011 Ziegler et al. [26] published their analytical review summarizing the experience with infrainguinal reconstructions using various types of arterial prostheses. The data presented in the review shows an autovein to exhibit the best results (see the Table). Most worldwide PTFE prostheses show satisfactory results only in femoropopliteal above knee reconstructions. HUV bioprostheses are intermediate between an autovein and synthetic prostheses, and can be used for IAr reconstruction in case a patient has no adequate autovein. However, in 2005 FDA put a veto on manufacture and application of human tissue products [15].

Currently, in world market there are bioprostheses of two types. One of them — Omniflow II — is marketed as a biosynthetic prosthesis of sheep collagen, which is glutaraldehyde-treated. To obtain this prostheses, polyester mesh put on a silicone rod is placed under the skin in adult sheep for 12–14 weeks. During this period the donor animal collagen covers tightly and grows out of the polymer mesh, the implant is extracted and preserved by glutaric aldehyde [27]. The authors of this technology are Ketharanathan and Christie [28]. In 1983, after successful preclinical and clinical trials, Australian company BioNova began to produce Omniflow bioprostheses for vascular surgery [27].
There is very scanty data on clinical results with Omniflow II bioprosthesis. The considerable experience on its usage in 274 patients was presented by Koch et al. [29, 30]. The authors estimate the results as satisfactory, though 5-year primary patency rate even in persistent crural outflow paths was 45% in femoro-popliteal above knee bypass, and 40% — in femoro-popliteal below knee bypass, that is significantly worse of aggregate data (not specified by subgroups depending on crural outflow paths) obtained when implanting HUV bioprosthesis (see the Table). If one crural artery was retained, the patency rate was 27 and 17%, respectively. Most researchers believe Omniflow II application to be feasible only under the conditions of infected reconstructed area [31–33], since biomaterials due to no surgical porosity are more resistant to contamination compared to porous synthetic materials. However, other authors, who have obtained negative results, criticize harshly this arterial prosthesis, they consider its application to be unreasonable [34, 35].

ProCol bioprosthesis is the second presented at the market and less studied. It is made of bovine mesenteric vein and treated by glutaraldehyde. Schmidli et al. [36] used it for infrainguinal reconstructions in 32 patients, and received poor results: primary patency rate in a month was 16%; secondary (a year later) was 26%. Prosthetic aneurysms were found in 6% cases within a year and a half. Currently, the prosthesis is recommended only as an arterio-venous shunt for dialysis patients. However, LeMaitre Vascular (USA) accrued a right to Omniflow II (in 2014) and ProCol (in 2016) bioprostheses, and is extensively marketing them worldwide [37].

In Russia, a biological KemAngioprosthesis (NeoCor, Kemerovo, Russia) has been used in vascular surgery since 1993. It is made from bovine internal thoracic artery preserved by epoxy compound and modified with heparin.

The development of this bioprosthesis was based on the researches started in 1987 by Nojiri et al. [38], those progressed rapidly in the late 80-ies and early 90-ies of the last century. Epoxy compounds, used as an alternative to glutaraldehyde for cross linkage of xenogenic-artery collagen, have attracted close attention of researchers, since biomaterial treated with epoxides acquires hydrophilic and elastic properties, close to those natural arteries have, as well as high resistance to calcification [39]. In 1993 Baxter International (USA) announced the entry into market of novel arterial bioprosthesis Denaflex treated with polyepoxy preserving agent Denacol-313 [40]. However, the bioprosthesis has never entered the market. A failed attempt to implement Denaflex in clinical practice was probably due to the fact that all researchers worked with epoxy mixtures Denacol (Nagase Ltd., Japan) having many toxic impurities because of technical purification grade. In Russia, epoxy preserving agent ethylene glycol diglycidyl ether has 97.5–99% purity. It is synthesized as a commercial product by N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of Siberian Branch of Russian Academy of Sciences.

The experience accumulated by Russian vascular surgeons with epoxy-treated infrainguinal bioprostheses has been embodied in some works [41–49]. In general, the authors consider the findings as satisfactory and recognize KemAngioprosthesis to be a reasonable alternative to an autovein in femoro-popliteal above knee position, and a prosthesis of choice for femoro-popliteal below knee reconstruction, when an autovenous transplant is unavailable. So, the largest study [41] devoted to the 12-year results with 315 KemAngioprostheses showed that their 6-year patency rate in femoro-popliteal above knee position is 60.3% that is comparable with the results obtained with HUV bioprostheses (see the Table). In their later researches the authors showed that the results of IAr prosthetic reconstructions can be improved by two approaches. The first one is bioprosthetic treatment improving: namely, substitution of unfractionated heparin for low-molecular-weight enoxaparin [48]. The second approach is to influence such risk factors as platelet hyperaggregation and inflammatory response [49]. However, the problem of aneurysm formation arising when using all biological prostheses is typical for KemAngioprosthesis as well. The complication rate is 1.9–7.0% [41, 47].

Thus, in modern reconstructive surgery, autovenous transplants, synthetic and biological prostheses are used to replace affected infrainguinal arteries. None of these substitutes is an ideal alternative to a natural artery; all of them, to some extent, are susceptible to complications requiring redo surgery or limb amputation.

**Tissue-engineered arteries: an alternative to vascular prostheses?**

The use of regenerative medicine approaches, a tissue-engineering construction implanted in the compromised area in particular, could be an optimal decision for IAr substitution, and complete or partial recovery of a natural artery due to living self-renewing tissue in prospect.

For this purpose a tissue engineering vascular graft...
TEVG should meet a number of strong requirements [50, 51]:

1) at an initial stage: effectively withstand and compensate mechanical loading of a blood flow with minimal or no leakages through the wall; the relation between elasticity, extensibility and mechanical strength characteristics should be adjusted so that there would be no deformities and pressure gradients in the reconstruction area [52–56];

2) to cause no unfavorable reactions, primarily an immune response; when making a graft, the materials should be nontoxic for surrounding tissues and cells, since they participate in its filling [57, 59];

3) a graft inner layer, which is in direct contact with blood, should be thrombo-resistant [57];

4) to be easy-to-use: long maintenance of sterility, no specific transportation terms and storage conditions, ease handling of a product in surgical procedures when implanted. All these aspects will play an important role in the formation of commercial TEVG market [59];

5) it is crucial for tissue engineering constructions based on bioresorbable matrices to be completely substituted by living cellular and extracellular structures [60, 61].

**Approaches to the development of tissue engineering vessels.** There are two approaches to TEVG, which are similar in sequence: matrix creation → cellular filling of a matrix → self-organization of a structure in response to environmental and internal conditions into a viable graft, which closely resembles a replaced vessel in anatomical and functional characteristics. The first approach consists in filling a graft by cells in vitro before implantation, the second approach — the same process in a recipient’s body.

The key moment of the first approach efficiency is an adequate choice of cells for culturing; as a rule, stem cells are used [62]: mononuclear and mesenchymal bone marrow [63–68], muscular [69], induced pluripotent [70, 71], adipose-derived mesenchymal stem cells [72–74]. Some researchers also use fibroblasts [75, 76]; however, their regenerative potential is limited, and their usage is impeded, since it is difficult to match an appropriate tissue, which can be incised for further work with cells [77–79].

Two variants are possible: autacellular — acquisition of recipient’s cells; alloacellular [80] — donor cells meeting histocompatibility requirements. Cell cultures are placed in a bioreactor, where they gradually fill a porous matrix in conditions imitating blood flow.

Bioreactor approach is attractive for a surgeon and a recipient as it enables to avoid constructing a complex vessel, which is just to be implanted in an affected area. However, sampling and culture of stem cells (and in case of an allo-cell resource — search for a donor) are rather labor-intensive procedures and require heavy time and financial expenses [81]. The storage life of “bioreactor” TEVG is limited, and special conditions are needed to maintain cell viability [82–84]. Moreover, at the current stage of scientific development “bioreactor” TEVG fails to culture an adequately organized vessel even under controlled conditions of a bioreactor [85].

Another approach consists in the use of cell-free matrices, which are to be inhabited by cells in situ in a recipient’s body. Consequently, there is no need to look for a donor — cell resource is always autogenous. Moreover, acellular grafts require no cell culture — therefore, the fabrication technique is simplified, and a sterile storage period increases, so the prime cost reduces, and a product becomes available for clinical practice [86]. In such approach, all attempts of researchers are concentrated on creating an optimal matrix.

**Matrices for tissue engineering constructions.** The very first studies were devoted to synthetically non-degradable matrices. Zilla et al. in 1987 reported about successful human implantation of PTFE prostheses with an internal surface endothelialized in vitro [87]. Then the technique was improved [88], and in 2009 the authors in the study shared their 15-year experience of using such prostheses in 318 patients, who had been operated on a femoro-popliteal segment. 10-year patency generally was 61% [89] that seems to be as good as the results of autovenous reconstructions. However, despite proven efficiency, the current approach is not of high-priority, since non-degradable matrices are unlikely to have regeneration potential: they are unable to achieve the main goal — to create an adequate living artery in situ to substitute an affected segment [90].

In parallel with studying synthetic non-degradable matrices, decellularized allogeneic and xenogeneic arteries were being under study as well. Despite the variability of decellularization protocols, the approach consists in destroying and removing donor cells followed by chemical cross-linking of extracellular matrix, which prevents its degradation in the recipient’s body; after that the construction is exposed to cell filling. The supporters of the approach think the key advantage to be in the fact that it enables to avoid constructing a complex structure of extracellular matrix de novo [90]. A key disadvantage of the technique is the instability of non-resorbable matrix combined with high immunogenicity of xenomaterial: decellularized vascular grafts are proved to provoke acute and chronic inflammation [91, 92].

The next spiral of elaboration was a bioresorbable matrix. For its fabrication, synthetic and natural polymers are chosen, as when degrading they enable new tissue formation in course of time. The most frequently used synthetic polymers are polycaprolactone (PCL), polyglycolic acid (PGA), polyester of glycerol and sebacic acid (PGS), polyester of urethane–urea (PEUU); natural polymers are fibrin, silk fibroin, collagen, elastin, chitosane, alginate, and their various combinations [86, 93, 94]. The authors of some relatively recent studies have combined both polymer types in an attempt to achieve optimal properties of each tissue layer [60, 95–98].
There are several methods to fabricate bioresorbable matrices, which are based on porous polymers [99] or films, which are then rolled [100]. However, the most popular technique is still electrospinning. When using electrospinning, a polymer jet is exposed to electrostatic forces, and the setting solid polymer on the collector forms an amorphous three-dimensional filament net, which resembles an extracellular matrix [101].

With time “frameless” techniques for TEVG formation have appeared. The so-called “self-assembly” was the first method historically: a two-dimension cell layer is folded around the core forming a tube of a future graft [102]. When the approach appeared, new methods started emerging, such as: cell printing [103] and the formation of “micro-tissue aggregates” — cell groups placed in a form where they eventually form the tubular structure of a vessel.

Currently, most studies are carried out on model animals: mice, pigs, sheep, dogs [104]. Only some tissue engineering constructions have accomplished clinical testing. In particular, a research team — the pioneers in the field (Dahl et al.) — improved the initial “synthetic matrices/bioreactor” approach by exposing a developed graft to decellularization, the cells being selectively destroyed, but the extracellular matrix they formed remained. The technique was clinically approved in 2012; TEVG were implanted to 10 patients, their primary patency was 78% in a month, and 60% — 6 months later [59]. The long-term results are still pending.

Unsolved problems of vascular tissue engineering. Natural vessels are known to consist of three layers and the membranes, which separate them, while current models are confined to one- or two-layer grafts. In itself it limits the graft capacity to adapt to micro-environment and reproduce de novo three-layer architectonics.

The more complex problem is a selective cell filling of the implanted scaffold — i.e., the occupation of each functional vascular layer by a required cell type: intima should be inhabited by endotheliocytes, and media and adventitium — by smooth muscular cells and fibroblasts. Up to now, no area of medicine has directional simulation of regeneration, and vascular tissue engineering is no exception. The trend, which is called “matrix functionalization”, is being rapidly developed now; however, there are still more questions rather than answers.

One more problem is the absence of an adequate model for TEVG testing. Currently, none of the model organisms under use has been found to be optimal due to variations from human in many parameters — from physiological and to the composition and structure of signal molecules [105–107].

Conclusion

An autologous vena saphena magna is considered to be a gold standard of flexible material to repair infrainguinal arteries for vascular surgeons in everyday practice. However, frequently, it is necessary to use prostheses. Bioprostheses show better patency efficiency compared to synthetic ones, but it does not solve the problem of adequate arterial substitution. The invention of tissue engineering constructions which are able to transform in a natural artery can become a comprehensive solution.

Still, there has been found no method to create tissue engineering vessels suited for practice, despite the abundance of researches and suggested approaches. We are to comprehend how an ideal graft ready for widespread practical use looks like. Most probably, adequate cost of a graft, its usability and safety for patients, as well as a minimized number of possible side effects are sure to be the main competitive advantages at a stage of tissue engineering vessel market formation [59].

Now it is evident that the developments in tissue engineering will gradually become everyday medical practice [108, 109]. Therefore, it is necessary to monitor continuously changing data on clinical and preclinical trials, review the demands placed on tissue engineering grafts, take into consideration economical and ethical factors when implementing novel developments. It is very important even now to remember about a notable approach in personalized medicine: a patient should be involved in decision making when choosing an implant. The role of such “personalization” factor will play the more and more notable role in the future [110, 111].

Foreign researchers are developing various approaches to TEVG creation. In Russia the trend is still underdeveloped. And due to this fact the quality-price ratio of most tissue engineering products are likely to exceed the threshold of availability. However, some developments have been started, and it is hoped that with time researchers will overcome the difficulties [112, 113].

Future belongs to modern developments in regenerative medicine. Now it is unclear which of them will become everyday practice. But one thing is practically assured: tissue engineering is the field of medicine, which is steadily transferring from a world of ideas into a world of real, tangible and promising results.

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