Published in final edited form as:

Acta Biomater. 2018 April 01; 70: 25–34. doi:10.1016/j.actbio.2018.01.008.

Challenges in vascular tissue engineering for diabetic patients

Jhilmil Dhulekar and

Clemson University, Department of Bioengineering

Agneta Simionescu

Clemson University, Department of Bioengineering

Abstract

Hyperglycemia and dyslipidemia coexist in diabetes and result in inflammation, degeneration, and impaired tissue remodeling, processes which are not conducive to the desired integration of tissue engineered products into the surrounding tissues. There are several challenges for vascular tissue engineering such as non-thrombogenicity, adequate burst pressure and compliance, suturability, appropriate remodeling responses, and vasoactivity, but, under diabetic conditions, an additional challenge needs to be considered: the aggressive oxidative environment generated by the high glucose and lipid concentrations that lead to the formation of advanced glycation end products (AGEs) in the vascular wall. Extracellular matrix-based scaffolds have adequate physical properties and are biocompatible, however, these scaffolds are altered in diabetes by the formation AGEs and impaired collagen degradation, consequently increasing vascular wall stiffness. In addition, vascular cells detect and respond to altered stimuli from the matrix by pathological remodeling of the vascular wall. Due to the immunomodulatory effects of mesenchymal stem cells (MSCs), they are frequently used in tissue engineering in order to protect the scaffolds from inflammation. MSCs together with antioxidant treatments of the scaffolds are expected to protect the vascular grafts from diabetes-induced alterations. In conclusion, as one of the most daunting environments that could damage the ECM and its interaction with cells is progressively built in diabetes, we recommend that cells and scaffolds used in vascular tissue engineering for diabetic patients are tested in diabetic animal models, in order to obtain valuable results regarding their resistance to diabetic adversities.

Keywords

Biological scaffolds; Advanced glycation end products; Mesenchymal stem cells; Antioxidants

Corresponding author: Dr. Agneta Simionescu, Clemson University, Department of Bioengineering, 301 Rhodes Hall, Clemson, SC 29634, United States, Phone: +18646563729, Fax: +18646564466, agneta@clemson.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Diabetes, one of the major risk factors for cardiovascular diseases, is increasing to epidemic proportion worldwide[1], currently affecting 8% of the world's population and more than 29 million people in the United States alone[2]. Hyperglycemia, resulting from deficiency in insulin secretion (Type 1 Diabetes) or insulin resistance (Type 2 Diabetes), coexists with dyslipidemia, oxidative stress, and inflammation, significantly increasing the risk of cardiovascular diseases[3, 4]. One of the major complications of diabetes is associated with accelerated atherosclerosis and vascular wall stiffening, the hallmark of diabetes[5]. Despite extensive research and progress in the treatment of cardiovascular diseases, there are still numerous amputations and vascular related deaths associated with diabetes. AHA states that about 500,000 coronary artery bypass graft procedures are performed every year in the US. Additionally, about 12 million patients in the US have a form of peripheral arterial disease and the American Diabetes Association estimates that 20-50% of them are diabetic [6, 7].

Over the last several years, diabetic patients have not shared the same decline in arterial disease-related mortality as non-diabetic patients[8]. Patients with diabetes still have a high incidence of restenosis after receiving drug-eluting stents[9], and coronary artery bypass grafting occlusions are more common among diabetics versus non-diabetics at 1-year angiography[10]. The autologous arteries and veins are the "gold standard" for coronary artery bypass grafting, but 1/3 of patients (about 140,000 each year) do not have vessels suitable for grafting. Vascular synthetic grafts with medium and large diameters function well, but small-diameter grafts fail rapidly (50% patency rate by two years) and cryopreserved cadaveric veins have only 30% patency rates after 12 months[11-13]. Therefore, there is a major need for vascular grafts with long-term stability and patency for diabetic patients.

Progress has been made in tissue engineering that holds great promise to treat vascular diseases[14, 15]. A typical approach in tissue engineering is based on a biodegradable and biocompatible scaffold (based on natural or synthetic polymers, including promising elastomeric polymers[16, 17]) with mechanical properties similar to the target tissue, seeded with autologous stem cells, chemically and mechanically stimulated in a vascular bioreactor, followed by implantation, that leads to remodeling and maturation into fully functional vascular grafts[18, 19] (Fig. 1).

Challenges of vascular tissue engineering include non-thrombogenicity, adequate burst pressure and compliance, suturability, appropriate remodeling responses, and vasoactivity[20]. For diabetic patients though, the vascular tissue engineering products would face an additional challenge: an aggressive oxidative environment generated by the increased concentration of glucose and lipids and their altered metabolism. Indeed, hyperglycemia and dyslipidemia that coexist in diabetes would result in inflammation, degeneration, and impaired tissue remodeling, processes that are not conducive to the desired integration of tissue engineered constructs into the surrounding tissues.

Based on the current knowledge of pathological modifications induced by diabetes in the vascular wall, this review will focus on the likely modifications generated by the

glycooxidative and lipoxidative environment in the major extracellular matrix components and in the cells used in blood vessel tissue engineering. Strategies for maintaining a good patency and durability of the vascular grafts in a diabetic milieu will also be presented.

2. Effect of diabetes on extracellular matrix components

Vascular tissue engineered grafts require resilient porous scaffolds with controlled biodegradability and appropriate mechanical properties from the onset of implantation[21]. Therefore, there is an increased interest in extracellular matrix (ECM) -based scaffolds processed from xenogeneic or allogeneic blood vessels by complete removal of cells [22, 23]. These biological scaffolds have adequate physical properties and are biocompatible, biodegradable with safe byproducts[24, 25]. Plus, the 3D organization of the ECM components distinguishes them from synthetic scaffolds[22]. Particularly, elastin, the vascular wall component that reduces the cell proliferative response to arterial injury[26] and maintains tissue elasticity, is not regenerated experimentally; therefore, it's an advantage to use decellularized structures that preserve the entire matrix composition. Hyaluronic acid is a component of the ECM, considered a space filling macromolecule for a long time and responsible for tissue hydration. However, recently it has been shown that the hyaluronic acid chains in the glycocalyx are involved in regulating the functions and dysfunctions of vascular cells, linked to atherosclerosis and diabetes[27]. Low molecular weight hyaluronic acid fragments could promote endothelial cell dysfunction and smooth muscle cell migration, in atherosclerosis and restenosis after injury. Hyaluronidases start the fragmentation of hyaluronic acid macromolecules in the extracellular space, continuing the degradative process inside the cells. These enzymes, activated by hyperglycemic conditions, contribute to glycocalyx volume reduction, increased coagulation, endothelial cell dysfunction[28], and smooth muscle cell migration. However, due to the ability of hyaluronic acid to form hydrogel-based scaffolds that favor tissue repair processes, and especially due the pro-angiogenic properties of hyaluronic acid fragments, this ECM component is extensively used in tissue engineering, particularly in diabetic wound healing applications[29]. Indeed, stem cell-containing hyaluronic acid-based spongy hydrogels enhance diabetic wound healing by positively impacting re-epithelialization and by modulating the inflammatory response[30].

It is remarkable that these ECM-based scaffolds promote the transition from classically activated pro inflammatory M1 macrophage phenotype in favor of an alternatively activated pro healing M2 macrophage phenotype; the mechanism is unknown, but it has been suggested that specific peptide sequences present in the structure of matrix components interact and activate particular cells [31]. Indeed, amino acid sequences were identified in the matrix proteins or their degradation products, also referred to as matrikines[32] that might be involved in macrophage polarization; these peptides induce several biological activities, such as chemotaxis, MMP release, and modulation of cell phenotypes, via a 67-kD elastin laminin receptor present on the surface of fibroblasts, smooth muscle cells, and monocytes [33-36].

For acellular ECM-scaffold preparation, several cell removal methods have been published, that eliminate all epitopes associated with cells, including galactose alpha 1,3 galactose

(alpha-gal), expressed on the cell surface of all mammals, except humans and old world primates[37]. In the same time, these methods preserve not only the organization of the major matrix components (collagen, elastin) but also the basement membrane proteins (type IV collagen, laminin), essential for tissue regeneration[24, 38-47]. Therefore, acellular biological scaffolds have been used in regenerative medicine applications, for both preclinical animal studies and clinical purposes [23, 48]. Collagen and elastin-based scaffolds implanted sub-dermally in diabetic rats with very strict glycemic control revealed structural alterations caused by the formation of advanced glycation end products (AGEs) [39]. The non-enzymatic nucleophilic addition reaction between a free amino group and the reducing sugar carbonyl group forms a Schiff base, which rearranges into an Amadori product (the Maillard reaction) that generates irreversible cross links in long lived proteins, such as collagen and elastin, leading to vascular stiffening, the hallmark of diabetes. Glucose and lipid molecules also undergo a series of oxidant-induced fragmentation resulting in the formation of glyoxal and methylglyoxal, short-chain reactive compounds involved in protein oxidation and formation of AGEs[49, 50] (Fig. 2). Free radicals containing oxygen or nitrogen were identified among the key participants in glycoxidation and lipid peroxidation[50-52]. The spontaneous reaction of protein glycation is influenced by several variables such as pH, temperature, degree and duration of hyperglycemia, half-life and concentration of protein, duration of hyperglycemia, concentration of glucose, and permeability of the tissue to free glucose. In addition, by crosslinking the extracellular matrix molecules, AGEs can also trap unwanted plasma proteins in the vessel wall, such as lipoproteins, and accelerate atherosclerosis[53]. Besides crosslinking matrix proteins, the high glucose concentration reduces the matrix metalloproteinase activity, impairing collagen degradation and inducing fibrosis, ectopic calcification, and stiffness of the vascular wall[54]. In diabetic patients, these scaffolds could be modified by the high glucose and lipid concentrations. Therefore, clinically it is too early to speculate on the lifetime of these grafts, since there are no acellular heart valves, patches or sheets approved for implantation in human patients. Humacyte collagen vascular grafts are currently in clinical trials as A-V shunts for hemodialysis in diabetic and non-diabetic patients, but results are not yet available (clinicaltrials.gov). The only product we could find in the literature was the human acellular dermal matrix, which has been shown to be beneficial in treating dermal wounds in diabetic patients with no short term complications [55]. However, human acellular dermal matrix has been quite frequently used off-target; for example, when used for breast reconstruction, the total complication rate was almost 20% [56]. A meta-analysis of human acellular dermal matrix used in abdominal wall reconstruction in diabetic patients showed as high as 27% complications with hernia and bulging [57]. Polymeric vascular grafts implanted in diabetic animals also exhibited increased complications and adverse effects [58]. Regarding calcification, a recent Veterans Affairs Cooperative Study performed on a large number of persons with type 2 diabetes showed that subjects with coronary artery or abdominal artery calcification had a dramatically high prevalence of peripheral artery disease and coronary artery disease[59].

3. Effect of diabetes on tissue-specific cells

The endothelium, the semi-permeable membrane at the blood-tissue interface, which regulates thrombosis, thrombolysis, and platelet adherence, as well as inflammatory and immune reactions, is injured under insulin-resistance conditions; cells decrease their secretion of nitric oxide and increase the production of endothelin-1 and reactive oxidative species (ROS), leading to endoplasmic reticulum stress and apoptosis[60-62], processes that accelerate the early stage of atherosclerosis[63]. Smooth muscle cells in the media are also affected by diabetes. Hyperglycemia stimulates and sustains the inflammatory “synthetic” phenotype of smooth muscle cells and enhances their migration and proliferation[64, 65] during progression of atherosclerosis. Intimal and medial calcification is also a widespread feature of diabetes, associated with atherosclerosis, and elastin pathology[66-70]. The mechanism of diabetic vascular calcification *in vivo* is still not fully understood, however chronic inflammation and oxidative stress induced by the activation of the AGE–RAGE axis has been shown to be involved[71]. RAGE activation induces alkaline phosphatase expression, calcium deposition, and Msx2 expression, a crucial transcription factor for osteogenic differentiation in human vascular smooth muscle cells, via Notch/Msx2 induction[72]. Ca^{2+} -handling alterations in vascular smooth muscle cells play a key role in the development and progression of vascular complications in diabetes[73]. Biomarkers for this actively regulated and complex process are: Klotho/fibroblast growth factor-23, Runx-2, fetuin-A, matrix Gla protein, BMP-2, osteoprotegerin, osteopontin, osteonectin and osteocalcin[74, 75]. The calcium-sensing receptor, a G-protein coupled receptor, plays a pivotal role in the extracellular calcium homeostasis and is expressed in endothelial and smooth muscle cells[76, 77]. Also, by increasing the stiffness of the matrix, AGEs could induce osteoblastic differentiation in the intima and media[72, 78, 79]. The third type of cells in the vessel wall, the adventitial fibroblasts are known to be actively involved in blood vessel homeostasis[80]. Recently though, it has been shown that the adventitia is more than a passive supportive layer. Activated fibroblasts proliferate and migrate to the media and intima, contributing to medial smooth muscle hypertrophy, neointimal growth[81], plaque thickening and fibrous cap formation[82]. Adventitial fibroblasts play an active role in the arterial response to injury, cytokines, stretch, and matrikines, which stimulate their activation and differentiation into myofibroblasts, the contractile cells involved in wound healing and adventitial remodeling (first described by Gabbiani and Majno in 1971)[83, 84] (Fig. 3). Adhesion molecules, such as P-selectin and VCAM-1 are upregulated within the vasa vasorum contributing to homing and accumulation of additional inflammatory cells, recognizing the adventitia as a primary site of inflammation in the course of vascular disease[85]. As the matrix components are modified under diabetic conditions, the cells detect and respond to altered matrix stimuli by pathological remodeling and increased stiffness of the vascular wall; an example is the smooth muscle cell dedifferentiation and vessel wall thickening triggered by hyaluronan[27]. Undeniably, one of the most daunting environments that could damage the ECM and its interaction with cells is progressively built in diabetes. Pericytes, perivascular cells involved in the structural stabilization of the microvascular wall, regulation of blood flow, angiogenesis, and vascular permeability, are frequently used in tissue engineering[86], not only for their supportive role in the vascular wall, but also for their immunomodulatory and phagocytic properties, as well as their

multipotent capability and plasticity similar to mesenchymal stromal cells[87, 88]. However, these cells are also affected by diabetes and the related oxidative stress, leading to disruption of endothelial cell-pericyte interaction and apoptosis[89]. For example, muscular pericytes in diabetic patients have an imbalanced redox state due to the downregulation of the antioxidant enzymes superoxide dismutase 1 and catalase, and activation of the pro-oxidant PKC β II-dependent p66^{Shc} signaling pathway[90].

4. Effect of diabetes on mesenchymal stem cells

In vascular tissue engineering, mesenchymal stem cells (MSCs) are used [11, 91], due to their proliferative and growth potential, angiogenic activity, as well as ability to differentiate into target vascular cells[92, 93]. Autologous stem cells are seeded into scaffolds in order to induce tissue remodeling and maturation[94]. Healthy vascular cells with precise roles in maintaining the vascular wall homeostasis are needed to support the structural and functional integrity of the new blood vessel. Bone marrow mesenchymal stem cells have been used as a source for both endothelial and smooth muscle cells[95, 96], but adipose tissue - derived stem cells (ASCs) have also been identified as a promising stem cell source, due to their availability and ability to differentiate along desired cell lines [97-101]. However, mesenchymal stem cells of different origins could be affected by hyperglycemia that impairs their ability to adequately repair and regenerate the diabetes-injured vascular tissue[102, 103]. Particularly, type 2 diabetes-induced oxidative stress has been shown to impede the multipotency and proangiogenic activity of adipose tissue-derived stem cells isolated from diabetic patients with coronary artery disease[104] and bone marrow-derived stem cells, and reduce their capacity to increase neovascularization and blood flow recovery in a hindlimb ischemia small animal models[105, 106]. Although their regenerative abilities could be compromised by diabetes[107, 108], a great benefit of using MSCs in cell therapy and tissue engineering is conferred by their broad modulatory effect on the immune system[109]. They secrete a large range of anti-inflammatory factors, such as TGF- β , IL-6, and prostaglandin E2 in response to pro-inflammatory factors, such as IFN- γ , TNF- α , and IL-17A[110]. Consequently, mesenchymal stem cells affect the function of all immune cell types. Stem cells reduce the production of inflammatory cytokines by immune cells IL-6 and TNF- α , and suppress cytotoxic T-cell proliferation, and stimulate the secretion of anti-inflammatory cytokines such as IL-4 and IL-10 [24, 100, 111, 112] . Mesenchymal stem cells secrete indoleamine 2,3-dioxygenase (IDO), which depletes tryptophan from their environment, inhibiting lymphocyte proliferation and suppress the cytotoxic effect of NK cells. Though the mechanisms for inducing therapeutic effect still remain largely unknown, it is likely that MSCs regulate the adaptive and innate immune systems by soluble factors and cell-cell contacts, that suppress T cells and maturation of dendritic cells, reduce B-cell activation and proliferation, NK cell cytotoxicity, and promote generation of regulatory T cells[113]. Mesenchymal cells also regulate macrophage polarization, by reducing the number of classically activated pro inflammatory M1 macrophage phenotype in favor of the alternatively activated pro healing M2 macrophage phenotype[114-116]; therefore the polarization between M1 and M2 macrophages is of great interest for the field of tissue engineering and regenerative medicine[117].

The immunomodulatory properties of ASCs have been demonstrated in a variety of experimental models of diseases, including spinal cord injury, neurodegenerative diseases, and graft versus host disease[118, 119]. ASCs also secrete soluble factors that promote tissue regeneration at the injury site via a paracrine mechanism: angiogenic factors (VEGF), anti-apoptotic factors (IGF-1), hematopoietic factors (colony stimulating factors and interleukins), transforming growth factor- β 1 and hepatic growth factor. Results from clinical trials have confirmed the safety and efficacy of ASCs in reducing diabetes-related complications. Diabetic patients infused with bone marrow derived stem cells and ASCs had a 40% decrease in insulin requirements with no adverse effects in a 3 months follow-up period[120, 121]. Studies evaluating the therapeutic impact of ASC in patients with diabetic foot showed improved rest pain score, walking time, and evidence of increased vascular collateral networks within 6 months of intramuscular ASC injection[122]. Wound healing was accelerated in diabetic mice with skin ulcers when ASC were delivered [123, 124]. Inflammation is the central mechanism driving vascular complications in diabetes; therefore, its suppression is a key factor for tissue engineered construct survival and integration. ECM-based scaffolds seeded with autologous ASCs and implanted sub dermally in diabetic rats, revealed moderate diabetes-related inflammatory reactions, only 10.2% T-cells and 5% macrophages, compared to non-seeded scaffolds. Also, a 20% increase in the M2 cell number was noticed, in both control and diabetic conditions, resulting in constructive tissue remodeling[125] (Fig. 4). Injected or infiltrated cells stained positive for alpha-smooth muscle actin and vimentin positive cells, which indicated the presence of fibroblasts or myofibroblasts; they also secreted laminin, a basement membrane protein essential for cell adhesion [126], differentiation, and maturation [127, 128]. Due to the immunomodulation properties of MSC, it is expected that stem cell-seeded vascular scaffolds would moderate the diabetes- induced aggressive inflammation and promote constructive remodeling and integration of tissue engineered vascular tissues. However, it is possible that the aggressive inflammatory diabetic environment could decrease the beneficial immunomodulatory and anti-inflammatory effect of MSCs[129].

5. Reactive oxygen species and antioxidants in blood vessel tissue engineering

Hyperglycemia and dyslipidemia generate oxidative stress, initiated by mitochondrial overproduction of superoxide, the precursor of other ROS molecules that contribute to the development of diabetic complications in the cardiovascular system[130]. The excessive free fatty acid and glucose supplies exceed the buffering capacity of the cell endogenous antioxidant defense mechanisms. NADPH-oxidases, the only known enzyme family solely dedicated to producing ROS, are expressed and active in the diabetic aorta[131], in endothelial cells, as well as fibroblasts[132]. ROS and chemotactic molecules, in particular CCL2, CX3CL1, and CCL5TLR4, activate TLR4 on monocytes and macrophages, which infiltrate the diabetic injured tissues. TLR4, a pattern recognition receptor essential for initiating inflammatory responses associated with innate immunity, is highly expressed on the classically-activated, pro-inflammatory macrophages (M1 phenotype), whereas it is down regulated on the alternatively-activated, pro-healing macrophages (M2 phenotype) [133]. M1 macrophages also secrete free radicals containing oxygen and nitrogen [134,

135]. However, preconditioning by moderate mitochondrial ROS generation strongly increases in vivo adipose tissue-derived MSC proangiogenic properties in diabetic tissues[136].

Treatments with antioxidants for reducing diabetes-related damage have been investigated experimentally and clinically[137]. Sources of antioxidants include enzymatic and non-enzymatic compounds. Enzymes with antioxidative activity are superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Commonly known non-enzymatic compounds with antioxidant activity include vitamins A, C, and E, glutathione, α -lipoic acid, mixed carotenoids, coenzyme Q10 or ubiquinone, many bioflavonoids, minerals such as copper and zinc, and cofactors such as folic acid, uric acid, albumin and B vitamins. The fat-soluble vitamin E prevents lipid peroxidation in the vascular tissue of diabetic rats by strengthening the antioxidant defense system and reduces the progression of coronary atherosclerosis in diabetic mice[138]. Additionally, vitamin E also decreases the oxidative stress in macrophages[137]. Vitamin C plays an important role in several oxidative/inflammatory processes, including scavenging ROS, preventing initiation of chain reactions, increasing nitric oxide production in endothelial cells and protecting cell membranes against lipid peroxidation. Several publications report on the protection against diabetic complications by plant extracts containing bioflavonoids and polyphenols, such as quercetin, and resveratrol[139]. Plant polyphenols may influence different initial steps of atherosclerosis through inhibition of the endothelial NADPH oxidase and elevation of nitric oxide bioavailability and bioactivity[140]. Quercetin and resveratrol prevent the redox imbalance in endothelial cells in the presence of oxidized low-density lipoproteins[141].

Penta-galloyl glucose, (PGG) a well-characterized naturally-derived polyphenol based on gallic acid (3,4,5-trihydroxybenzoic acid) units bound to a polyol core[142], has been reported to have many beneficial effects based on its antioxidant, anti-diabetic, and anti-inflammatory properties[142]. The mechanism is not well understood, but it has been suggested that it may be based on the decrease of metal ions' uptake or the promoting of their excretion through chelating activities.

Scaffold pretreatments with antioxidants could improve the durability of vascular grafts in diabetes. PGG exhibits high affinity for proline-rich proteins, particularly collagen and elastin[143]; experiments on rat aorta[144] showed and increased stability of collagen and elastin and slow down degradation by a factor of about 50[145]. Pre-treatment of scaffolds with PGG demonstrated reduced accumulation of AGEs, T-cell and macrophage infiltration, as well as inhibited calcium deposition in the matrix-based scaffolds implanted subcutaneously in diabetic rats[39], correlated with significantly reduced stiffening. These results demonstrate the promising ability of polyphenols to stabilize matrix- based vascular scaffolds and protect them from diabetes-related damages, thereby increasing their durability (Fig. 5).

6. Diabetic animal models

To understand the effects of the pro-oxidant diabetic environment on scaffolds and cells used in blood vessel tissue engineering, as well as to test the efficacy of antioxidants, in vivo

diabetic models are critical. Mainly rodents are used to identify novel treatments for diabetes and its cardiovascular complications. For type I diabetes studies, the non-obese diabetic (NOD) mouse displaying spontaneous autoimmunity is the most commonly model, but experimentally induced diabetes models through surgical (pancreatectomy) and chemical methods (use of the β -cell toxic drugs alloxan and streptozotocin) are also highly preferable. Diet-induced models and monogenic obesity in mice and Zucker fatty rats that have a mutated leptin receptor leading to hyperphagia and obesity are used for type 2 diabetes studies[146]. Pigs are primarily chosen to model type 2 diabetes for determining the mechanisms of metabolic abnormalities that follow diabetes modifications. Swine models are relevant for investigation of cardiovascular complications of diabetes since they can develop coronary, aortic, iliac and carotid atherosclerotic lesions relevant to human condition, and they recapitulate the histopathology seen in humans[147]. Primates are preferentially used in translational safety and efficacy studies in gene-and cell-therapies[148], but they also present a major advantage for studies regarding development of atherosclerosis[147].

Conventionally, tissue engineered vascular grafts are routinely tested by implantation in healthy animals, however to better approximate clinical translation, we propose that these grafts should be also implanted in diabetic animals.

7. Conclusion

Diabetes is a major risk factor for vascular diseases. Changes induced at cellular and extracellular matrix level result in dysfunctional remodeling of the vascular wall, including stiffening, fibrosis, and calcification. There is a major need for vascular grafts with long-term potency and tissue engineering holds great potential for the treatment of vascular diseases. Grafts based on scaffolds and autologous stem cells are developed, but typically they are tested in healthy animals for preclinical evaluation, although most components of the graft could be affected by the aggressive diabetic conditions, in a similar manner to the native vascular structures. Anti-oxidant therapies and tissue engineered grafts implanted in the circulatory system of diabetic animals subjected to elevated circulating glucose and free fatty acids, combined with insulin resistance, could provide valuable knowledge for building blood vessels substitutes resistant to diabetic adversities.

Acknowledgments

The authors would like to acknowledge the financial support from NIGMS of the National Institutes of Health under award number 5P20GM103444-07 and a grant from the Competitiveness Operational Program 2014-2020, Targeted therapies for aortic valve disease in diabetes, THERAVALDIS, ID P_37_298, MySMIS code: 104362, contract number 115/13.09.2016.

References

1. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf
2. Beckman JA, Creager MA. Vascular Complications of Diabetes. Circulation research. 2016; 118(11):1771–85. [PubMed: 27230641]
3. Scherer PE, Hill JA. Obesity, Diabetes, and Cardiovascular Diseases: A Compendium. Circulation research. 2016; 118(11):1703–5. [PubMed: 27230636]

4. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001; 37(4):1053–9. [PubMed: 11304502]
5. Kanter JE, Bornfeldt KE. Inflammation and diabetes-accelerated atherosclerosis: myeloid cell mediators. *Trends in endocrinology and metabolism: TEM*. 2013; 24(3):137–44. [PubMed: 23153419]
6. Aiello A, Anichini R, Brocco E, Caravaggi C, Chiavetta A, Cioni R, Da Ros R, De Feo ME, Ferraresi R, Florio F, Gargiulo M, Galzerano G, Gandini R, Giurato L, Graziani L, Mancini L, Manzi M, Modugno P, Setacci C, Uccioli L. Treatment of peripheral arterial disease in diabetes: A consensus of the Italian Societies of Diabetes (SID, AMD), Radiology (SIRM) and Vascular Endovascular Surgery (SICVE), Nutrition. *Metabolism and Cardiovascular Diseases*. 2014; 24(4): 355–369.
7. A. American Diabetes. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003; 26(12):3333–41. [PubMed: 14633825]
8. Nguyen LL. Percutaneous treatment of peripheral vascular disease: the role of diabetes and inflammation. *J Vasc Surg*. 2007; 45(Suppl A):A149–57. [PubMed: 17544036]
9. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Keim E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolimus-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation*. 2004; 109(19):2273–8. [PubMed: 15123524]
10. Singh SK, Desai ND, Petroff SD, Deb S, Cohen EA, Radhakrishnan S, Schwartz L, Dubbin J, Fremes SE. The impact of diabetic status on coronary artery bypass graft patency: insights from the radial artery patency study. *Circulation*. 2008; 118(14 Suppl):S222–5. [PubMed: 18824758]
11. Kumar VA, Brewster LP, Caves JM, Chaikof EL. Tissue Engineering of Blood Vessels: Functional Requirements, Progress, and Future Challenges. *Cardiovasc Eng Technol*. 2011; 2(3):137–148. [PubMed: 23181145]
12. Ravi S, Chaikof EL. Biomaterials for vascular tissue engineering. *Regen Med*. 2010; 5(1):107–20. [PubMed: 20017698]
13. Jordan SW, Haller CA, Sallach RE, Apkarian RP, Hanson SR, Chaikof EL. The effect of a recombinant elastin-mimetic coating of an ePTFE prosthesis on acute thrombogenicity in a baboon arteriovenous shunt. *Biomaterials*. 2007; 28(6):1191–7. [PubMed: 17087991]
14. Mensah GA, Catravas JD, Engelgau MM, Hooper WC, Madeddu P, Ryan US, She JX, Reed E, Vinicor F, Yacoub MH. Vascular endothelium summary statement VI: Research directions for the 21st century. *Vascul Pharmacol*. 2007; 46(5):330–2. [PubMed: 17222586]
15. Pashneh-Tala S, MacNeil S, Claeysens F. The Tissue-Engineered Vascular Graft-Past, Present, and Future, *Tissue engineering*. Part B. Reviews. 2015
16. Guan J, Sacks MS, Beckman EJ, Wagner WR. Synthesis, characterization, and cytocompatibility of elastomeric, biodegradable poly(ester-urethane)ureas based on poly(caprolactone) and putrescine. *J Biomed Mater Res*. 2002; 61(3):493–503. [PubMed: 12115475]
17. Nieponice A, Maul TM, Cumer JM, Soletti L, Vorp DA. Mechanical stimulation induces morphological and phenotypic changes in bone marrow-derived progenitor cells within a three-dimensional fibrin matrix. *Journal of biomedical materials research Part A*. 2007; 81(3):523–30. [PubMed: 17133453]
18. L'Heureux N, Dusserre N, Konig G, Victor B, Keire P, Wight TN, Chronos NA, Kyles AE, Gregory CR, Hoyt G, Robbins RC, McAllister TN. Human tissue-engineered blood vessels for adult arterial revascularization. *Nat Med*. 2006; 12(3):361–5. [PubMed: 16491087]
19. Nieponice A, Soletti L, Guan J, Deasy BM, Huard J, Wagner WR, Vorp DA. Development of a tissue-engineered vascular graft combining a biodegradable scaffold, muscle-derived stem cells and a rotational vacuum seeding technique. *Biomaterials*. 2008; 29(7):825–33. [PubMed: 18035412]
20. Krawiec JT, Vorp DA. Adult stem cell-based tissue engineered blood vessels: a review. *Biomaterials*. 2012; 33(12):3388–400. [PubMed: 22306022]
21. Rabkin E, Schoen FJ. Cardiovascular tissue engineering. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*. 2002; 11(6):305–17. [PubMed: 12459430]

22. Badylak SF. The extracellular matrix as a biologic scaffold material. *Biomaterials*. 2007; 28(25): 3587–93. [PubMed: 17524477]
23. Badylak SF, Freytes DO, Gilbert TW. Extracellular matrix as a biological scaffold material: Structure and function. *Acta Biomater*. 2009; 5(1):1–13. [PubMed: 18938117]
24. Chuang TH, Stabler C, Simionescu A, Simionescu DT. Polyphenol-stabilized tubular elastin scaffolds for tissue engineered vascular grafts. *Tissue engineering Part A*. 2009; 15(10):2837–51. [PubMed: 19254115]
25. Moroni F, Mirabella T. Decellularized matrices for cardiovascular tissue engineering. *Am J Stem Cells*. 2014; 3(1):1–20. [PubMed: 24660110]
26. Karnik SK, Brooke BS, Bayes-Genis A, Sorensen L, Wythe JD, Schwartz RS, Keating MT, Li DY. A critical role for elastin signaling in vascular morphogenesis and disease. *Development*. 2003; 130(2):411–23. [PubMed: 12466207]
27. Moretto P, Karousou E, Viola M, Caon I, D'Angelo ML, De Luca G, Passi A, Vignetti D. Regulation of hyaluronan synthesis in vascular diseases and diabetes. *Journal of diabetes research*. 2015; 2015:167283. [PubMed: 25834831]
28. Dogne S, Rath G, Jouret F, Caron N, Dessy C, Flamion B. Hyaluronidase 1 Deficiency Preserves Endothelial Function and Glycocalyx Integrity in Early Streptozotocin-Induced Diabetes. *Diabetes*. 2016; 65(9):2742–53. [PubMed: 27246914]
29. Wang Y, Han G, Guo B, Huang J. Hyaluronan oligosaccharides promote diabetic wound healing by increasing angiogenesis. *Pharmacol Rep*. 2016; 68(6):1126–1132. [PubMed: 27588388]
30. da Silva LP, Santos TC, Rodrigues DB, Pirraco RP, Cerqueira MT, Reis RL, Correlo VM, Marques AP. Stem Cell-Containing Hyaluronic Acid-Based Spongy Hydrogels for Integrated Diabetic Wound Healing. *J Invest Dermatol*. 2017; 137(7):1541–1551. [PubMed: 28259681]
31. Brown BN, Ratner BD, Goodman SB, Amar S, Badylak SF. Macrophage polarization: an opportunity for improved outcomes in biomaterials and regenerative medicine. *Biomaterials*. 2012; 33(15):3792–802. [PubMed: 22386919]
32. Barallobre-Barreiro J, Lynch M, Yin X, Mayr M. Systems biology-opportunities and challenges: the application of proteomics to study the cardiovascular extracellular matrix. *Cardiovascular research*. 2016; 112(3):626–636. [PubMed: 27635058]
33. Jacobs E, Fuchte K, Bredt W. Amino acid sequence and antigenicity of the amino-terminus of the 168 kDa adherence protein of *Mycoplasma pneumoniae*. *Journal of general microbiology*. 1987; 133(8):2233–6. [PubMed: 3127540]
34. Duca L, Floquet N, Alix AJ, Haye B, Debelle L. Elastin as a matrikine. *Critical reviews in oncology/hematology*. 2004; 49(3):235–44. [PubMed: 15036263]
35. Hinek A, Rabinovitch M. 67-kD elastin-binding protein is a protective “companion” of extracellular insoluble elastin and intracellular tropoelastin. *The Journal of cell biology*. 1994; 126(2):563–74. [PubMed: 8034752]
36. Simionescu A, Philips K, Vyavahare N. Elastin-derived peptides and TGF-beta1 induce osteogenic responses in smooth muscle cells. *Biochemical and biophysical research communications*. 2005; 334(2):524–32. [PubMed: 16005428]
37. Badylak SF. Xenogeneic extracellular matrix as a scaffold for tissue reconstruction. *Transpl Immunol*. 2004; 12(3–4):367–77. [PubMed: 15157928]
38. Mercuri JJ, Patnaik S, Dion G, Gill SS, Liao J, Simionescu DT. Regenerative Potential of Decellularized Porcine Nucleus Pulposus Hydrogel Scaffolds: Stem Cell Differentiation, Matrix Remodeling, and Biocompatibility Studies. *Tissue Eng Part A*. 2013
39. Chow JP, Simionescu DT, Warner H, Wang B, Patnaik SS, Liao J, Simionescu A. Mitigation of diabetes-related complications in implanted collagen and elastin scaffolds using matrix-binding polyphenol. *Biomaterials*. 2013; 34(3):685–95. [PubMed: 23103157]
40. Wang B, Tedder ME, Perez CE, Wang G, de Jongh Curry AL, To F, Elder SH, Williams LN, Simionescu DT, Liao J. Structural and biomechanical characterizations of porcine myocardial extracellular matrix. *J Mater Sci Mater Med*. 2012; 23(8):1835–47. [PubMed: 22584822]
41. Tedder ME, Simionescu A, Chen J, Liao J, Simionescu DT. Assembly and testing of stem cell-seeded layered collagen constructs for heart valve tissue engineering. *Tissue Eng Part A*. 2011; 17(1–2):25–36. [PubMed: 20673028]

42. Mercuri JJ, Gill SS, Simionescu DT. Novel tissue-derived biomimetic scaffold for regenerating the human nucleus pulposus. *J Biomed Mater Res A*. 2011; 96(2):422–35. [PubMed: 21171162]
43. Ariganello MB, Simionescu DT, Labow RS, Lee JM. Macrophage differentiation and polarization on a decellularized pericardial biomaterial. *Biomaterials*. 2011; 32(2):439–49. [PubMed: 20933269]
44. Wang B, Borazjani A, Tahai M, Curry AL, Simionescu DT, Guan J, To F, Elder SH, Liao J. Fabrication of cardiac patch with decellularized porcine myocardial scaffold and bone marrow mononuclear cells. *J Biomed Mater Res A*. 2010; 94(4):1100–10. [PubMed: 20694977]
45. Sierad LN, Simionescu A, Albers C, Chen J, Maivelett J, Tedder ME, Liao J, Simionescu DT. Design and Testing of a Pulsatile Conditioning System for Dynamic Endothelialization of Polyphenol-Stabilized Tissue Engineered Heart Valves. *Cardiovasc Eng Technol*. 2010; 1(2):138–153. [PubMed: 21340043]
46. Tedder ME, Liao J, Weed B, Stabler C, Zhang H, Simionescu A, Simionescu DT. Stabilized collagen scaffolds for heart valve tissue engineering. *Tissue Eng Part A*. 2009; 15(6):1257–68. [PubMed: 18928400]
47. Lu Q, Ganesan K, Simionescu DT, Vyavahare NR. Novel porous aortic elastin and collagen scaffolds for tissue engineering. *Biomaterials*. 2004; 25(22):5227–37. [PubMed: 15110474]
48. Badylak SF, Weiss DJ, Caplan A, Macchiarini P. Engineered whole organs and complex tissues. *Lancet*. 2012; 379(9819):943–52. [PubMed: 22405797]
49. Rumble JR, Cooper ME, Soulis T, Cox A, Wu L, Youssef S, Jasik M, Jerums G, Gilbert RE. Vascular hypertrophy in experimental diabetes. Role of advanced glycation end products. *The Journal of clinical investigation*. 1997; 99(5):1016–27. [PubMed: 9062360]
50. Weiss MF, Erhard P, Kader-Attia FA, Wu YC, Deoreo PB, Araki A, Glomb MA, Monnier VM. Mechanisms for the formation of glycoxidation products in end-stage renal disease. *Kidney international*. 2000; 57(6):2571–85. [PubMed: 10844627]
51. Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovascular research*. 1998; 37(3):586–600. [PubMed: 9659442]
52. Nagai R, Murray DB, Metz TO, Baynes JW. Chelation: a fundamental mechanism of action of AGE inhibitors, AGE breakers, and other inhibitors of diabetes complications. *Diabetes*. 2012; 61(3):549–59. [PubMed: 22354928]
53. Cerami A, Vlassara H, Brownlee M. Role of nonenzymatic glycosylation in atherogenesis. *Journal of cellular biochemistry*. 1986; 30(2):111–20. [PubMed: 3517022]
54. Shah MS, Brownlee M. Molecular and Cellular Mechanisms of Cardiovascular Disorders in Diabetes. *Circ Res*. 2016; 118(11):1808–29. [PubMed: 27230643]
55. Rupert P. Human acellular dermal wound matrix for complex diabetic wounds. *J Wound Care*. 2016; 25(4):S17–8–S20–1.
56. Schnarrs RH, Carman CM, Tobin C, Chase SA, Rossmeier KA. Complication Rates With Human Acellular Dermal Matrices: Retrospective Review of 211 Consecutive Breast Reconstructions. *Plast Reconstr Surg Glob Open*. 2016; 4(11):e1118. [PubMed: 27975023]
57. Adetayo OA, Salcedo SE, Bahjri K, Gupta SC. A Meta-analysis of Outcomes Using Acellular Dermal Matrix in Breast and Abdominal Wall Reconstructions: Event Rates and Risk Factors Predictive of Complications. *Ann Plast Surg*. 2016; 77(2):e31–8. [PubMed: 22156884]
58. Wang Z, Zheng W, Wu Y, Wang J, Zhang X, Wang K, Zhao Q, Kong D, Ke T, Li C. Differences in the performance of PCL-based vascular grafts as abdominal aorta substitutes in healthy and diabetic rats. *Biomater Sci*. 2016; 4(10):1485–92. [PubMed: 27537499]
59. Reaven PD, Sacks J, V. Investigators. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia*. 2005; 48(2):379–85. [PubMed: 15688207]
60. Symons JD, Abel ED. Lipotoxicity contributes to endothelial dysfunction: a focus on the contribution from ceramide. *Rev Endocr Metab Disord*. 2013; 14(1):59–68. [PubMed: 23292334]
61. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006; 113(15):1888–904. [PubMed: 16618833]

62. Barrett EJ, Liu Z. The endothelial cell: an “early responder” in the development of insulin resistance. *Rev Endocr Metab Disord.* 2013; 14(1):21–7. [PubMed: 23306779]
63. Guerrero-Hernandez A, Leon-Aparicio D, Chavez-Reyes J, Olivares-Reyes JA, DeJesus S. Endoplasmic reticulum stress in insulin resistance and diabetes. *Cell Calcium.* 2014; 56(5):311–22. [PubMed: 25239386]
64. Di Marco E, Gray SP, Jandeleit-Dahm K. Diabetes alters activation and repression of pro- and anti-inflammatory signaling pathways in the vasculature. *Front Endocrinol (Lausanne).* 2013; 4:68. [PubMed: 23761786]
65. Chawla V, Simionescu A, Langan EM 3rd, LaBerge M. Influence of Clinically Relevant Mechanical Forces on Vascular Smooth Muscle Cells Under Chronic High Glucose: An In Vitro Dynamic Disease Model. *Ann Vasc Surg.* 2016; 34:212–26. [PubMed: 27126714]
66. Sakata N, Noma A, Yamamoto Y, Okamoto K, Meng J, Takebayashi S, Nagai R, Horiuchi S. Modification of elastin by pentosidine is associated with the calcification of aortic media in patients with end-stage renal disease. *Nephrol Dial Transplant.* 2003; 18(8):1601–9. [PubMed: 12897101]
67. Chen NX, Moe SM. Vascular calcification: pathophysiology and risk factors. *Curr Hypertens Rep.* 2012; 14(3):228–37. [PubMed: 22476974]
68. Proudfoot D, Shanahan CM. Biology of calcification in vascular cells: intima versus media. *Herz.* 2001; 26(4):245–51. [PubMed: 11479936]
69. Snell-Bergeon JK, Budoff MJ, Hokanson JE. Vascular calcification in diabetes: mechanisms and implications. *Curr Diab Rep.* 2013; 13(3):391–402. [PubMed: 23526400]
70. Kovacic JC, Fuster V. Vascular calcification, diabetes, and cardiovascular disease: connecting the dots. *JACC Cardiovasc Imaging.* 2012; 5(4):367–9. [PubMed: 22498325]
71. Barlovic DP, Soro-Paavonen A, Jandeleit-Dahm KA. RAGE biology, atherosclerosis and diabetes. *Clin Sci (Lond).* 2011; 121(2):43–55. [PubMed: 21457145]
72. Suga T, Iso T, Shimizu T, Tanaka T, Yamagishi S, Takeuchi M, Imaizumi T, Kurabayashi M. Activation of receptor for advanced glycation end products induces osteogenic differentiation of vascular smooth muscle cells. *J Atheroscler Thromb.* 2011; 18(8):670–83. [PubMed: 21512281]
73. Fernandez-Velasco M, Ruiz-Hurtado G, Gomez AM, Rueda A. Ca(2+) handling alterations and vascular dysfunction in diabetes. *Cell Calcium.* 2014; 56(5):397–407. [PubMed: 25218935]
74. Evrard S, Delanaye P, Kamel S, Cristol JP, Cavalier E. Vascular calcification: from pathophysiology to biomarkers. *Clin Chim Acta.* 2015; 438:401–14. [PubMed: 25236333]
75. Lin ME, Chen T, Leaf EM, Speer MY, Giachelli CM. Runx2 Expression in Smooth Muscle Cells Is Required for Arterial Medial Calcification in Mice. *Am J Pathol.* 2015; 185(7):1958–69. [PubMed: 25987250]
76. Loot AE, Pierson I, Syzonenko T, Elgheznawy A, Randriamboavonjy V, Zivkovic A, Stark H, Fleming I. Ca²⁺-sensing receptor cleavage by calpain partially accounts for altered vascular reactivity in mice fed a high-fat diet. *J Cardiovasc Pharmacol.* 2013; 61(6):528–35. [PubMed: 23429586]
77. Babinsky VN, Hannan FM, Youhanna SC, Marechal C, Jadoul M, Devuyst O, Thakker RV. Association studies of calcium-sensing receptor (CaSR) polymorphisms with serum concentrations of glucose and phosphate, and vascular calcification in renal transplant recipients. *PLoS One.* 2015; 10(3):e0119459. [PubMed: 25786244]
78. Yao Y, Jumabay M, Ly A, Radparvar M, Cubberly MR, Bostrom KI. A role for the endothelium in vascular calcification. *Circ Res.* 2013; 113(5):495–504. [PubMed: 23852538]
79. Wei Q, Ren X, Jiang Y, Jin H, Liu N, Li J. Advanced glycation end products accelerate rat vascular calcification through RAGE/oxidative stress. *BMC Cardiovasc Disord.* 2013; 13:13. [PubMed: 23497312]
80. Liu Y, Liang C, Liu X, Liao B, Pan X, Ren Y, Fan M, Li M, He Z, Wu J, Wu Z. AGEs increased migration and inflammatory responses of adventitial fibroblasts via RAGE, MAPK and NF-kappaB pathways. *Atherosclerosis.* 2010; 208(1):34–42. [PubMed: 19959167]
81. Haurani MJ, Pagano PJ. Adventitial fibroblast reactive oxygen species as autocrine and paracrine mediators of remodeling: bellwether for vascular disease? *Cardiovasc Res.* 2007; 75(4):679–89. [PubMed: 17689510]

82. Wilcox JN, Scott NA. Potential role of the adventitia in arteritis and atherosclerosis. *Int J Cardiol.* 1996; 54(Suppl):S21–35. [PubMed: 9119525]
83. Gabbiani G, Majno G. Dupuytren's contracture: fibroblast contraction? An ultrastructural study. *The American journal of pathology.* 1972; 66(1):131–46. [PubMed: 5009249]
84. Majno G. The story of the myofibroblasts. *Am J Surg Pathol.* 1979; 3(6):535–42. [PubMed: 534390]
85. Veerman KJ, Venegas-Pino DE, Shi Y, Khan MI, Gerstein HC, Werstuck GH. Hyperglycaemia is associated with impaired vasa vasorum neovascularization and accelerated atherosclerosis in apolipoprotein-E deficient mice. *Atherosclerosis.* 2013; 227(2):250–8. [PubMed: 23411040]
86. Schaefer JA, Guzman PA, Riemenschneider SB, Kamp TJ, Tranquillo RT. A cardiac patch from aligned microvessel and cardiomyocyte patches. *Journal of tissue engineering and regenerative medicine.* 2017
87. Caporali A, Martello A, Miscianinov V, Maselli D, Vono R, Spinetti G. Contribution of pericyte paracrine regulation of the endothelium to angiogenesis. *Pharmacol Ther.* 2017; 171:56–64. [PubMed: 27742570]
88. Crisan M, Deasy B, Gavina M, Zheng B, Huard J, Lazzari L, Peault B. Purification and long-term culture of multipotent progenitor cells affiliated with the walls of human blood vessels: myoendothelial cells and pericytes. *Methods Cell Biol.* 2008; 86:295–309. [PubMed: 18442653]
89. Ferland-McCollough D, Slater S, Richard J, Reni C, Mangialardi G. Pericytes, an overlooked player in vascular pathobiology. *Pharmacol Ther.* 2017; 171:30–42. [PubMed: 27916653]
90. Vono R, Fuoco C, Testa S, Pirro S, Maselli D, FerlMcCollough D, Sangalli E, Pintus G, Giordo R, Finzi G, Sessa F, Cardani R, Gotti A, Losa S, Cesareni G, Rizzi R, Bearzi C, Cannata S, Spinetti G, Gargioli C, Madeddu P. Activation of the Pro-Oxidant PKC β II-p66Shc Signaling Pathway Contributes to Pericyte Dysfunction in Skeletal Muscles of Patients With Diabetes With Critical Limb Ischemia. *Diabetes.* 2016; 65(12):3691–3704. [PubMed: 27600065]
91. Isenberg BC, Williams C, Tranquillo RT. Small-diameter artificial arteries engineered in vitro. *Circulation research.* 2006; 98(1):25–35. [PubMed: 16397155]
92. Riha GM, Lin PH, Lumsden AB, Yao Q, Chen C. Review: application of stem cells for vascular tissue engineering. *Tissue engineering.* 2005; 11(9–10):1535–52. [PubMed: 16259608]
93. Li S, Sengupta D, Chien S. Vascular tissue engineering: from in vitro to in situ. *Wiley Interdiscip Rev Syst Biol Med.* 2014; 6(1):61–76. [PubMed: 24151038]
94. Wu X, Rabkin-Aikawa E, Guleserian KJ, Perry TE, Masuda Y, Sutherland FW, Schoen FJ, Mayer JE Jr, Bischoff J. Tissue-engineered microvessels on three-dimensional biodegradable scaffolds using human endothelial progenitor cells. *American journal of physiology Heart and circulatory physiology.* 2004; 287(2):H480–7. [PubMed: 15277191]
95. Kurpinski K, Lam H, Chu J, Wang A, Kim A, Tsay E, Agrawal S, Schaffer DV, Li S. Transforming growth factor-beta and notch signaling mediate stem cell differentiation into smooth muscle cells. *Stem cells.* 2010; 28(4):734–42. [PubMed: 20146266]
96. Davani S, Marandin A, Mersin N, Royer B, Kantelip B, Herve P, Etievent JP, Kantelip JP. Mesenchymal progenitor cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a rat cellular cardiomyoplasty model. *Circulation.* 2003; 108(Suppl 1):II253–8. [PubMed: 12970242]
97. Harris LJ, Zhang P, Abdollahi H, Tarola NA, DiMatteo C, McIlhenny SE, Tulenko TN, DiMuzio PJ. Availability of Adipose-Derived Stem Cells in Patients Undergoing Vascular Surgical Procedures. *Journal of Surgical Research.* 2010; 163(2):e105–e112. [PubMed: 20638677]
98. Gimble JM, Guilak F. Adipose-derived adult stem cells: isolation, characterization, and differentiation potential. *Cytotherapy.* 2003; 5(5):362–369. [PubMed: 14578098]
99. Gimble JM, Katz AJ, Bunnell BA. Adipose-Derived Stem Cells for Regenerative Medicine. *Circulation Research.* 2007; 100(9):1249–1260. [PubMed: 17495232]
100. Kronsteiner B, Wolbank S, Peterbauer A, Hackl C, Redl H, van Griensven M, Gabriel C. Human Mesenchymal Stem Cells from Adipose Tissue and Amnion Influence T-Cells Depending on Stimulation Method and Presence of Other Immune Cells. *Stem Cells and Development.* 2011; 20(12):2115–2126. [PubMed: 21381973]

101. Krawiec JT, Liao HT, Kwan LL, D'Amore A, Weinbaum JS, Rubin JP, Wagner WR, Vorp DA. Evaluation of the stromal vascular fraction of adipose tissue as the basis for a stem cell-based tissue-engineered vascular graft. *Journal of vascular surgery*. 2017; 66(3):883–890 e1. [PubMed: 28017585]
102. Krawiec JT, Weinbaum JS, Liao HT, Ramaswamy AK, Pezzone DJ, Josowitz AD, D'Amore A, Rubin JP, Wagner WR, Vorp DA. In Vivo Functional Evaluation of Tissue-Engineered Vascular Grafts Fabricated Using Human Adipose-Derived Stem Cells from High Cardiovascular Risk Populations. *Tissue engineering Part A*. 2016; 22(9–10):765–75. [PubMed: 27079751]
103. Stolzing A, Sellers D, Llewelyn O, Scutt A. Diabetes induced changes in rat mesenchymal stem cells. *Cells, tissues, organs*. 2010; 191(6):453–65. [PubMed: 20130391]
104. Dzhoyashvili NA, Efimenko AY, Kochegura TN, Kalinina NI, Koptelova NV, Sukhareva OY, Shestakova MV, Akchurin RS, Tkachuk VA, Parfyonova YV. Disturbed angiogenic activity of adipose-derived stromal cells obtained from patients with coronary artery disease and diabetes mellitus type 2. *Journal of translational medicine*. 2014; 12:337. [PubMed: 25491476]
105. Kim HK, Kim YJ, Kim JT, Kwon CH, Kim YK, Bae YC, Kim DH, Jung JS. Alterations in the proangiogenic functions of adipose tissue-derived stromal cells isolated from diabetic rats. *Stem cells and development*. 2008; 17(4):669–80. [PubMed: 18788931]
106. Yan J, Tie G, Wang S, Messina KE, DiDato S, Guo S, Messina LM. Type 2 diabetes restricts multipotency of mesenchymal stem cells and impairs their capacity to augment postischemic neovascularization in db/db mice. *J Am Heart Assoc*. 2012; 1(6):e002238. [PubMed: 23316315]
107. DiMuzio P, Tulenko T. Tissue engineering applications to vascular bypass graft development: the use of adipose-derived stem cells. *Journal of vascular surgery*. 2007; 45(Suppl A):A99–103. [PubMed: 17544030]
108. Policha A, Zhang P, Chang L, Lamb K, Tulenko T, DiMuzio P. Endothelial differentiation of diabetic adipose-derived stem cells. *The Journal of surgical research*. 2014; 192(2):656–63. [PubMed: 25091340]
109. Molina ER, Smith BT, Shah SR, Shin H, Mikos AG. Immunomodulatory properties of stem cells and bioactive molecules for tissue engineering. *Journal of controlled release : official journal of the Controlled Release Society*. 2015; 219:107–18. [PubMed: 26307349]
110. de Witte SF, Franquesa M, Baan CC, Hoogduijn MJ. Toward Development of iMesenchymal Stem Cells for Immunomodulatory Therapy. *Front Immunol*. 2015; 6:648. [PubMed: 26779185]
111. DelaRosa O, Lombardo E, Beraza A, Mancheno-Corvo P, Ramirez C, Menta R, Rico L, Camarillo E, Garcia L, Abad JL, Trigueros C, Delgado M, Buscher D. Requirement of IFN-gamma-Mediated Indoleamine 2,3-Dioxygenase Expression in the Modulation of Lymphocyte Proliferation by Human Adipose-Derived Stem Cells. *Tissue Engineering Part A*. 2009; 15(10):2795–2806. [PubMed: 19231921]
112. Gonzalez-Rey E, Gonzalez MA, Varela N, O'Valle F, Hernandez-Cortes P, Rico L, Buscher D, Delgado M. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 2010; 69(1):241–248. [PubMed: 19124525]
113. Le Blanc K, Davies LC. Mesenchymal stromal cells and the innate immune response. *Immunol Lett*. 2015; 168(2):140–6. [PubMed: 25982165]
114. Anderson P, Souza-Moreira L, Morell M, Caro M, O'Valle F, Gonzalez-Rey E, Delgado M. Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. *Gut*. 2013; 62(8):1131–1141. [PubMed: 22637701]
115. Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM. A New Mesenchymal Stem Cell (MSC) Paradigm: Polarization into a Pro-Inflammatory MSC1 or an Immunosuppressive MSC2 Phenotype. *Plos One*. 2010; 5(4)
116. Ebrahimi B, Eirin A, Li ZL, Zhu XY, Zhang X, Lerman A, Textor SC, Lerman LO. Mesenchymal Stem Cells Improve Medullary Inflammation and Fibrosis after Revascularization of Swine Atherosclerotic Renal Artery Stenosis. *Plos One*. 2013; 8(7)
117. Huleihel L, Dziki JL, Bartolacci JG, Rausch T, Scarritt ME, Cramer MC, Vorobyov T, LoPresti ST, Swineheart IT, White LJ, Brown BN, Badyalak SF. Macrophage phenotype in response to ECM bioscaffolds. *Semin Immunol*. 2017; 29:2–13. [PubMed: 28736160]

118. McIntosh K, Zvonice S, Garrett S, Mitchell JB, Floyd ZE, Hammill L, Kloster A, Di Halvorsen Y, Ting JP, Storms RW, Goh B, Kilroy G, Wu X, Gimble JM. The immunogenicity of human adipose-derived cells: temporal changes in vitro. *Stem cells*. 2006; 24(5):1246–53. [PubMed: 16410391]
119. Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, Taureau C, Cousin B, Abbal M, Laharrague P, Penicaud L, Casteilla L, Blancher A. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol*. 2005; 129(1):118–29. [PubMed: 15801964]
120. Lindroos B, Suuronen R, Miettinen S. The potential of adipose stem cells in regenerative medicine. *Stem cell reviews*. 2011; 7(2):269–91. [PubMed: 20853072]
121. Trivedi HL, Vanikar AV, Thakker U, Firoze A, Dave SD, Patel CN, Patel JV, Bhargava AB, Shankar V. Human adipose tissue-derived mesenchymal stem cells combined with hematopoietic stem cell transplantation synthesize insulin. *Transplantation proceedings*. 2008; 40(4):1135–9. [PubMed: 18555133]
122. Hong SJ, Traktuev DO, March KL. Therapeutic potential of adipose-derived stem cells in vascular growth and tissue repair. *Curr Opin Organ Transplant*. 2010; 15(1):86–91. [PubMed: 19949335]
123. Nambu M, Kishimoto S, Nakamura S, Mizuno H, Yanagibayashi S, Yamamoto N, Azuma R, Nakamura S, Kiyosawa T, Ishihara M, Kanatani Y. Accelerated wound healing in healing-impaired db/db mice by autologous adipose tissue-derived stromal cells combined with atelocollagen matrix. *Annals of plastic surgery*. 2009; 62(3):317–21. [PubMed: 19240532]
124. Assi R, Foster TR, He H, Stamati K, Bai H, Huang Y, Hyder F, Rothman D, Shu C, Homer-Vanniasinkam S, Cheema U, Dardik A. Delivery of mesenchymal stem cells in biomimetic engineered scaffolds promotes healing of diabetic ulcers. *Regenerative medicine*. 2016; 11(3):245–60. [PubMed: 26986810]
125. Chow JP, Simionescu DT, Carter AL, Simionescu A. Immunomodulatory effects of adipose tissue-derived stem cells on elastin scaffold remodeling in diabetes. *Tissue Eng Regen Med*. 2016; 13(6):701–712.
126. Bouten CVC, Dankers PYW, Driessen-Mol A, Pedron S, Brizard AMA, Baaijens FPT. Substrates for cardiovascular tissue engineering. *Advanced Drug Delivery Reviews*. 2011; 63(4–5):221–241. [PubMed: 21277921]
127. Belkin AM, Stepp MA. Integrins as receptors for laminins. *Microsc Res Tech*. 2000; 51(3):280–301. [PubMed: 11054877]
128. LaNasa SM, Bryant SJ. Influence of ECM proteins and their analogs on cells cultured on 2-D hydrogels for cardiac muscle tissue engineering. *Acta biomaterialia*. 2009; 5(8):2929–38. [PubMed: 19457460]
129. Kizilay Mancini O, Shum-Tim D, Stochaj U, Correa JA, Colmegna I. Age, atherosclerosis and type 2 diabetes reduce human mesenchymal stromal cell-mediated T-cell suppression. *Stem cell research & therapy*. 2015; 6:140. [PubMed: 26253429]
130. Sachidanandam K, Fagan SC, Ergul A. Oxidative stress and cardiovascular disease: antioxidants and unresolved issues. *Cardiovasc Drug Rev*. 2005; 23(2):115–32. [PubMed: 16007229]
131. Konior A, Schramm A, Czesnikiewicz-Guzik M, Guzik TJ. NADPH oxidases in vascular pathology. *Antioxid Redox Signal*. 2014; 20(17):2794–814. [PubMed: 24180474]
132. Wingler K, Hermans JJ, Schiffrers P, Moens A, Paul M, Schmidt HH. NOX1, 2, 4, 5: counting out oxidative stress. *British journal of pharmacology*. 2011; 164(3):866–83. [PubMed: 21323893]
133. Vianello E, Dozio E, Arnaboldi F, Marazzi MG, Martinelli C, Lamont J, Tacchini L, Sigruner A, Schmitz G, Corsi Romanelli MM. Epicardial adipocyte hypertrophy: Association with M1-polarization and toll-like receptor pathways in coronary artery disease patients. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2016; 26(3):246–53.
134. Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology*. 2010; 298(5):R1173–R1187.

135. Badylak SF, Valentin JE, Ravindra AK, McCabe GP, Stewart-Akers AM. Macrophage Phenotype as a Determinant of Biologic Scaffold Remodeling. *Tissue Engineering Part A*. 2008; 14(11): 1835–1842. [PubMed: 18950271]
136. Carriere A, Ebrahimian TG, Dehez S, Auge N, Joffre C, Andre M, Arnal S, Duriez M, Barreau C, Arnaud E, Fernandez Y, Planat-Benard V, Levy B, Penicaud L, Silvestre JS, Casteilla L. Preconditioning by mitochondrial reactive oxygen species improves the proangiogenic potential of adipose-derived cells-based therapy. *Arteriosclerosis, thrombosis, and vascular biology*. 2009; 29(7):1093–9.
137. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos Univ Med J*. 2012; 12(1):5–18. [PubMed: 22375253]
138. Otero P, Bonet B, Herrera E, Rabano A. Development of atherosclerosis in the diabetic BALB/c mice. Prevention with Vitamin E administration. *Atherosclerosis*. 2005; 182(2):259–65. [PubMed: 16159598]
139. Karasu C. Glycooxidative stress and cardiovascular complications in experimentally-induced diabetes: effects of antioxidant treatment. *Open Cardiovasc Med J*. 2010; 4:240–56. [PubMed: 21270942]
140. Schewe T, Steffen Y, Sies H. How do dietary flavanols improve vascular function? A position paper. *Archives of biochemistry and biophysics*. 2008; 476(2):102–6. [PubMed: 18358827]
141. Korkina L, Kostyuk V, De Luca C, Pastore S. Plant phenylpropanoids as emerging anti-inflammatory agents. *Mini Rev Med Chem*. 2011; 11(10):823–35. [PubMed: 21762105]
142. Zhang J, Li L, Kim SH, Hagerman AE, Lu J. Anti-cancer, anti-diabetic and other pharmacologic and biological activities of penta-galloyl-glucose. *Pharm Res*. 2009; 26(9):2066–80. [PubMed: 19575286]
143. Isenburg JC, Simionescu DT, Vyavahare NR. Elastin stabilization in cardiovascular implants: improved resistance to enzymatic degradation by treatment with tannic acid. *Biomaterials*. 2004; 25(16):3293–302. [PubMed: 14980424]
144. Basalyga DM, Simionescu DT, Xiong W, Baxter BT, Starcher BC, Vyavahare NR. Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases. *Circulation*. 2004; 110(22):3480–7. [PubMed: 15545515]
145. Isenburg JC, Karamchandani NV, Simionescu DT, Vyavahare NR. Structural requirements for stabilization of vascular elastin by polyphenolic tannins. *Biomaterials*. 2006; 27(19):3645–51. [PubMed: 16527345]
146. King A, Bowe J. Animal models for diabetes: Understanding the pathogenesis and finding new treatments. *Biochemical pharmacology*. 2016; 99:1–10. [PubMed: 26432954]
147. Radenkovic M, Stojanovic M, Prostran M. Experimental diabetes induced by alloxan and streptozotocin: The current state of the art. *J Pharmacol Toxicol Methods*. 2016; 78:13–31. [PubMed: 26596652]
148. Graham ML, Schuurman HJ. Validity of animal models of type 1 diabetes, and strategies to enhance their utility in translational research. *Eur J Pharmacol*. 2015; 759:221–30. [PubMed: 25814249]

Almost 25 million Americans have diabetes, characterized by high levels of blood sugar that binds to tissues and disturbs the function of cardiovascular structures. Therefore, patients with diabetes have a high risk of cardiovascular diseases. Surgery is required to replace diseased arteries with implants, but these fail after 5–10 years because they are made of non-living materials, not resistant to diabetes. New tissue engineering materials are developed, based on the patients' own stem cells, isolated from fat, and added to extracellular matrix-based scaffolds. Our main concern is that diabetes could damage the tissue-like implants. Thus we review studies related to the effect of diabetes on tissue components and recommend antioxidant treatments to increase the resistance of implants to diabetes.

Fig. 1.

Fig. 2.

CELL TYPE	EFFECTS OF DIABETIC MILIEU	CELLULAR AND BIOCHEMICAL CHANGES	CLINICAL CONSEQUENCES
Vascular endothelial cells	<ul style="list-style-type: none"> • Activation and dysfunction 	<ul style="list-style-type: none"> • Low nitric oxide secretion • High endothelin-1 secretion • Increased reactive oxygen species production • Endoplasmic reticulum stress • Apoptosis 	<ul style="list-style-type: none"> • Prothrombotic luminal surfaces • Altered vasoactivity • Accelerated atherosclerosis
Vascular smooth muscle cells	<ul style="list-style-type: none"> • Activation and phenotypical modulation 	<ul style="list-style-type: none"> • Synthetic phenotype • High migration and proliferation • Activation of receptors for advanced glycation end products • Osteoblastic differentiation • Plaque maturation 	<ul style="list-style-type: none"> • Collagen deposition • Fibrosis and stiffness • Elastin pathology • Vascular calcification • Accelerated atherosclerosis
Adventitial fibroblasts	<ul style="list-style-type: none"> • Activation and phenotypical modulation 	<ul style="list-style-type: none"> • Migration into media • Differentiation into myofibroblasts • Stimulation of vascular smooth muscle activation 	<ul style="list-style-type: none"> • Fibrosis and stiffness • Plaque thickening • Accelerated atherosclerosis • Altered extracellular matrix homeostasis

Fig. 3.

Fig. 4.

Fig. 5.