Advances in Human Umbilical Vein Scaffolds for Vascular Tissue Engineering: Innovations, Challenges, and Future Directions

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Abstract

Tissue engineering and regenerative medicine have emerged as promising approaches for developing vascular grafts that mimic native blood vessels. The human umbilical vein (HUV) has been widely explored as a scaffold for vascular tissue engineering due to its biocompatibility, biodegradability, and ability to support endothelialization. This review explores the latest advancements in scaffold fabrication, including decellularization techniques, heparin modifications, and bioprinting strategies to enhance mechanical properties and endothelial cell adhesion. Induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) have shown potential in promoting vascularization and graft integration. Additionally, the role of extracellular matrix (ECM) remodeling and angiogenic factors in vascular graft performance is highlighted. Recent studies underscore the importance of hemodynamic factors in preventing intimal hyperplasia, a major challenge in graft longevity. Furthermore, vitrified umbilical arteries and tissue-engineered small-caliber grafts are being explored as alternatives for cardiovascular applications. This review provides insights into current strategies and future directions in vascular graft development, emphasizing precision personalized medicine approaches to optimize graft functionality and patient-specific therapies.

Keywords: Human umbilical vein, tissue engineering, vascular grafts, endothelialization, regenerative medicine

Significance | This review explores innovative human umbilical vein scaffolds, enhancing vascular tissue engineering for regenerative medicine and cardiovascular applications.

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1. Introduction

Vascular diseases remain the leading cause of mortality worldwide, with projections indicating that they will account for approximately 23.3 million deaths annually by 2030 (Daniel et al., 2005). These conditions commonly manifest as coronary artery disease, peripheral arterial disease, and aortic disease. In the United Kingdom, myocardial infarction alone results in the hospitalization of over 180,000 individuals each year (Thottappillil & Nair, 2015). To manage vascular diseases, various interventional strategies such as angioplasty, stenting, and bypass surgery are widely employed (Hoenicka et al., 2010).

A sedentary Western lifestyle is associated with an increased incidence of vascular diseases, including peripheral arterial occlusive disease and coronary artery disease (Luo et al., 2020). In many cases, revascularization procedures necessitate the use of autologous arteries as bypass grafts. However, in a subset of patients, vascular graft retrieval is not feasible due to prior removal, limb loss, or comorbid conditions that impair tissue availability (Fazal et al., 2021). The high morbidity and mortality associated with vascular diseases highlight the urgent need for alternative treatment strategies.

Tissue engineering has emerged as a promising approach to addressing vascular disease by developing bioengineered scaffolds that mimic native blood vessels. These scaffolds are designed to

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support cellular adhesion, proliferation, and differentiation, facilitating the formation of functional vascular tissues (Caracciolo et al., 2021). The extracellular matrix (ECM) of blood vessels plays a critical role in regulating vascular cell migration, attachment, and physiological function. It also serves as a structural foundation for vasculogenesis and angiogenesis, which are essential processes for vascular repair and regeneration (Costa-Almeida et al., 2014).

The primary objective of tissue-engineered vascular grafts is to develop functional vascular replacements capable of regenerating in vivo while replicating the mechanical and biological properties of native vessels (Jia et al., 2013). Ideally, these grafts should possess diameters and viscoelastic properties that match the recipient vessels while maintaining a non-thrombogenic, immune-inert luminal surface (Serbo & Gerecht, 2013). Human umbilical cord veins present a particularly attractive option for vascular graft development due to their accessibility, suitable diameter, and lack of major branches (Hoenicka et al., 2013). The umbilical cord contains two arteries and one vein, all encased in Wharton's jelly, which offers mechanical support and bioactive properties conducive to vascular regeneration (Mangold et al., 2015).

The use of human umbilical veins in peripheral revascularization has been well-documented (Hoenicka et al., 2008). However, traditional processing methods, such as glutaraldehyde fixation, impair the antithrombogenic and remodeling capacities of these grafts (Daniel et al., 2005). Current advances in vascular graft engineering aim to enhance these properties through biomaterial modifications and cell-seeding strategies (Schultz et al., 2011). Despite these innovations, prosthetic vascular grafts remain a significant financial burden, contributing approximately $25 billion annually to healthcare costs (Tissue Engineering and Regenerative Medicine, 2023). Endovascular treatment for aortic aneurysms constitutes nearly 87% of these interventions, with the remainder allocated to peripheral vascular grafts (10%), hemodialysis access (3%), and coronary artery bypass procedures (1%) (Olson et al., 2011).

The ability to construct, restore, and regulate the vascular system has vast therapeutic implications, particularly for ischemic conditions such as myocardial infarction, peripheral vascular disease, and chronic wounds (Chan & Leong, 2008). Ischemic tissues, which suffer from oxygen deprivation, experience extensive cell damage and death, necessitating urgent vascular repair strategies (Meng et al., 2021). Consequently, there is a pressing clinical need to promote angiogenesis—the formation of new blood vessels from preexisting ones—or vasculogenesis, the de novo formation of vessels, to restore perfusion in ischemic tissues (Kubis & Levy, 2003).

Vascular tissue engineering encompasses a multidisciplinary approach that integrates diverse cell sources, scaffolds, growth factors, cytokines, and mechanical stimuli to replicate the natural vascular environment (Chen et al., 2022). Specifically, long-platform scaffolds composed of biodegradable biomaterials offer precise control over vascular network formation by allowing the customization of scaffold composition, mechanical properties, degradation rate, and structural dimensions (Masson-Meyers & Tayebi, 2021). Researchers have increasingly focused on incorporating bioactive molecules and cellular components into scaffold designs to enhance their mechanical strength, biocompatibility, and antithrombogenic properties (Mallis et al., 2020).

This review explores biodegradable scaffold platforms that regulate vascular tissue formation and promote angiogenesis. Following an overview of the mechanisms underlying vascular tissue development and biomechanics, we discuss the primary principles and cell sources utilized in vascular tissue engineering (Pashneh-Tala et al., 2016). Special emphasis is placed on the potential of human umbilical cord veins as a scaffold source for small-caliber vascular grafts, considering their mechanical stability, biocompatibility, and potential for in vivo remodeling (Haruguchi & Teraoka, 2003).

2. Methodology

To ensure a comprehensive review of relevant literature, this study utilized two major academic databases: PubMed and Google Scholar. A systematic search was conducted using advanced search functions in both databases to identify studies related to the use of the human umbilical vein (HUV) as a source for vascular graft scaffolds.

The literature search in PubMed was performed using the Boolean search query ("Human" AND "Umbilical" AND "Vein" AND "Vascular" AND "Graft"), while in Google Scholar, the search was conducted using the keywords "Human umbilical vein as a source for vascular graft scaffold" and "Human umbilical vein for vascular graft". Given the evolving nature of research in vascular tissue engineering, a 20-year time frame (2003–2023) was applied to refine search results. Publications were initially screened based on relevance and publication year, yielding 20 articles from PubMed and 12 articles from Google Scholar. To further expand the scope of the review, reference lists from selected studies were examined to identify additional relevant articles.

Key information was systematically extracted from the selected studies, including author(s), research location, and publication year; study design (e.g., experimental, clinical, or review); key benefits and findings related to the application of HUV in vascular grafting; outcome measures (e.g., biocompatibility, mechanical properties, clinical success); and a summary of results. The extracted data were compiled and structured into Table 1 to facilitate comparative analysis.

Table 1. Characteristics of the literatures reviewed

Author	Study Design	Advantage	Outcome
Hoenicka, et al 2013	Experimental	• Tissue-engineered small-calibre vessel grafts may help to alleviate the lack of graft material for coronary and peripheral bypass grafting • This study explored the use of endothelium denuded human umbilical veins (HUVs) as scaffolds for vascular tissue engineering in a perfusion bioreactor.	• Denuded HUVs are preferable to decellularized blood vessels because they preserve the smooth muscle layer's functionality, retain proteins important for biomechanics and cell attachment, and serve as a suitable scaffold for the seeding of an autologous endothelium that is resistant to flow.
Hoenicka, et al., 2007	Experimental	• The purpose of this work was to determine whether the human umbilical vein (HUV) is a good scaffold for tissue engineering of small-caliber vascular grafts that may be stored.	• Vitrified vessels did not significantly increase platelet binding compared to fresh controls. HUV functions well as an antithrombogenic living scaffold that may be stored.
Mangold, et al., 2012	Experimental	• The current study looked examined how three distinct decellularization techniques affected the mechanical, seeding properties, and histological.	• Decellularization impacted the appearance of elastic fibers by causing a partial decrease of fibronectin and laminin staining in the subendothelial layer. • Decellularization may be a less effective method for making tissue-engineered blood arteries with non-immunogenic luminal contacts than endothelium replacement.
Hoenicka, et al., 2008	Experimental	• This study looked at how umbilical veins behave as scaffolds for vascular tissue engineering and if delivery and sample collection methods have an impact.	• The research offers proof that vessels from planned caesarean sections should be chosen over other types of vessels for tissue engineering applications because they can be extracted sterilely and exhibit superior vasoconstrictor responses and antithrombotic qualities. • The studies also suggest that umbilical cords can be picked up once day without the functional qualities degrading.
Daniel, et al., 2005	Experimental	• This study set out to assess the efficiency of the autodissection technique in producing an ex vivo biomaterial with greater consistency and lower variance. To investigate the suitability of the HUV scaffold for vascular tissue engineering applications, mechanical parameters such as burst pressure, compliance, uniaxial tension testing, and suture holding capacity were evaluated.	• Native cellular remodelling processes have showed a great deal of promise for HUV scaffold in terms of cellular integration. • This research has demonstrated that the HUV scaffold is homogeneous, mechanically strong, and retains its biphasic stress-strain relationship while the tissue is processed. The HUV scaffold could result in better grafts for vascular reconstruction procedures by preserving the original blood vessels' mechanical characteristics and promoting positive cellular connections.

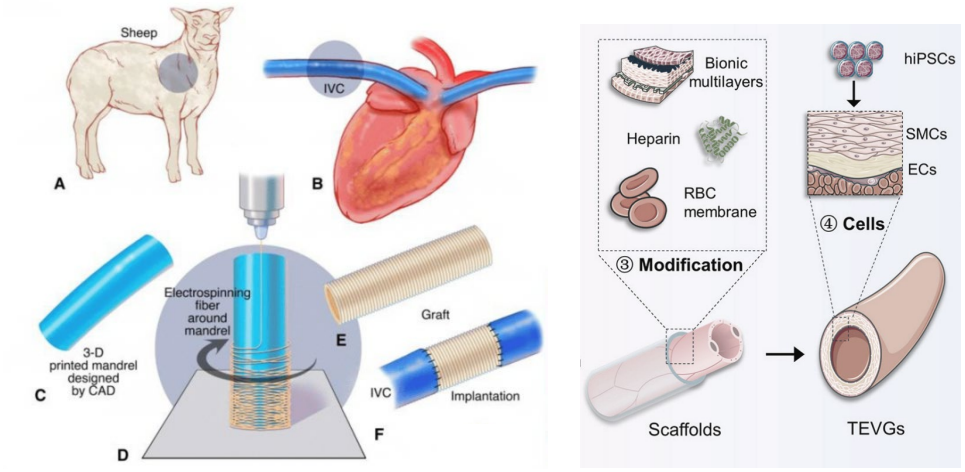

Figure 1. Strategies for Engineered Vascular Grafts and Vascularized Tissue Engineering. (a) Schematic representation of the study design for patient-specific, cell-free nanofiber tissue-engineered vascular grafts. (A, B) Extraction of vascular topographical data from a preoperative angiogram in a sheep model. (C) Design of a three-dimensional (3D)-printed mandrel using computer-aided design (CAD). (D) Electrospinning of nanofibers around the mandrel to fabricate the vascular graft. (E) Completed nanofiber vascular graft. (F) Surgical implantation of the fabricated graft. Tissue-engineered vascular grafts (TEVGs) provide a viable alternative capable of integrating, remodeling, and repairing host vessels, responding to mechanical and biochemical stimuli. (Image courtesy of Chen et al. 2023).

3. Vascular Graft Development and Engineering Strategies

The restoration of function in damaged or lost vascular tissue presents a significant challenge, particularly in adult blood vessels, due to the limited regenerative capacity of adult cells (Schultz et al., 2011). Histologically, tissue comprises multiple structures, including various cell types, leading to complex and highly organized interactions, particularly in the vascular system. When significant damage occurs, vascular tissue replacement becomes necessary, necessitating advancements in graft tissue engineering technology (Tissue Engineering and Regenerative Medicine, n.d.) (Figure 1).

Tissue engineering is an interdisciplinary field aimed at restoring, maintaining, or enhancing tissue function (Olson et al., 2011). While tissue engineering strives to generate sufficient tissue or even analogous organs, research on vascular grafts remains relatively limited. The most notable advancements have been observed in the application of grafts in skin and cartilage repair (Chan & Leong, 2008). The vascular network plays a crucial role in distributing signaling chemicals, hormones, and antibodies while facilitating the transport of gases, nutrients, and metabolites between tissues and organs (Meng et al., 2021). Initially, immature blood vessels are formed through angiogenesis or vasculogenesis, which further develop into the complex vascular tissue (Kubis & Levy, 2003).

Vascular development is directly regulated by angioblasts or endothelial progenitor cells (EPCs), facilitating the in-situ formation of blood vessels. This process is essential not only in embryonic development but also in physiological and pathological conditions in adults (Kubis & Levy, 2003). In contrast, angiogenesis, the formation of new blood vessels from pre-existing ones, involves specific proteases initiating the degradation of the extracellular matrix (ECM). This degradation allows endothelial cells (ECs) to infiltrate avascular tissue. As the ECM degrades, it migrates to distant locations, forms anastomoses, and establishes a lumen. The construction of the basement membrane and the adhesion of pericytes lead to the formation of new blood vessels. Fibroblasts and other stromal cells release growth factors and ECM components to promote neovessel development. Vasculogenesis, on the other hand, depends on circulating EPCs, which differentiate into functional ECs, attach to the vascular bud, and integrate into the newly formed vessel (Chen et al., 2022).

Several factors must be considered when reconstructing a vascular graft, including histological, anatomical, and physiological functions. The key steps in vascular graft development for tissue engineering involve three primary domains: (1) growth factor delivery through injection or infusion at supraphysiological concentrations, (2) cell transplantation via bolus cell injection, and (3) scaffold-based approaches, including chemical immobilization or physical encapsulation of biomolecules with optimized factor concentration (Masson-Meyers & Tayebi, 2021). These approaches are crucial for ensuring the successful integration and function of vascular grafts in clinical applications.

4. Challenges of Human Umbilical Vein as a Vessel Graft Scaffold

The human umbilical vein (HUV) is widely recognized as a promising and accessible material for vascular tissue engineering (Daniel et al., 2005). However, several challenges hinder its application as a scaffold for vascular grafts, primarily due to the complex nature of vascular tissue and its susceptibility to failure (Thottappillil & Nair, 2015).

One of the major limitations of HUV-based grafts is thrombosis, which occurs due to endothelial cell (EC) damage or absence, leading to protein adherence and clotting activation (Pashneh-Tala et al., 2016). Additionally, intimal hyperplasia—caused by the migration of vascular smooth muscle cells (SMCs) and excessive extracellular matrix (ECM) deposition—can lead to vessel occlusion, particularly at the anastomotic sites of grafted veins (Haruguchi & Teraoka, 2003). Mismatches in vessel diameter, EC damage, and seam line tension further contribute to blood flow disruption and graft failure (Hoenicka et al., 2010).

Atherosclerosis is another major complication in HUV grafts, occurring due to similar pathological mechanisms as in native arteries. Monocyte infiltration and the subsequent formation of foam cells and atherosclerotic plaques further compromise graft function (Costa-Almeida et al., 2014). Moreover, synthetic alternatives to HUV grafts exhibit increased susceptibility to bacterial colonization, leading to persistent inflammation, toxin release, and, ultimately, graft rupture or sepsis (Luo et al., 2020).

Overcoming these challenges requires advanced bioengineering strategies, including optimizing endothelialization, improving biomechanical properties, and reducing immunogenicity (Mallis et al., 2020). Innovations in scaffold modification and bioprinting techniques continue to enhance the clinical feasibility of HUV-based vascular grafts (Fazal et al., 2021).

5. Potential Use of Human Umbilical Vein for Vessel Grafts

In recent decades, various scaffolds have been explored for vascular tissue engineering, with varying degrees of success. Synthetic polymers often lack the necessary mechanical properties and antithrombotic characteristics, limiting their effectiveness (Thottappillil & Nair, 2015). Tubular organs derived from human or animal sources have gained interest due to their structural integrity, mechanical properties, and ability to avoid foreign body reactions after appropriate treatment (Caracciolo et al., 2021).

The human umbilical vein (HUV) has been evaluated for its potential as a vascular graft scaffold due to its unbranched structure and harvestable length (Hoenicka et al., 2013). Hoenicka et al. (2013) conducted tissue engineering research utilizing endothelium-free HUVs in a perfusion bioreactor. They assessed

parameters such as endothelial removal, blood vessel diameter adjustment, contractile function, reductive capacities, and histological characteristics. Their findings indicated that the smooth muscle layer retained its functionality, key proteins essential for biomechanics and cell attachment remained intact, and the scaffold supported autologous endothelial cell seeding resistant to flow, making denuded HUVs superior to decellularized blood vessels.

Despite these advantages, clinical applications of HUVs have been limited primarily to peripheral bypass grafting. Their use in small-caliber coronary bypass procedures remains challenging due to the absence of an antithrombotic surface and limited adaptability to higher pressures (Hoenicka et al., 2010). To overcome these limitations, Daniel et al. (2005) explored the potential of HUV matrices in tissue engineering. Their study assessed mechanical properties such as burst pressure, compliance, uniaxial tension, and suture-holding capacity. The results demonstrated that HUV scaffolds retained their biphasic stress-strain relationship, mechanical strength, and homogeneity throughout processing, suggesting their potential for vascular reconstruction while preserving the native vessel's mechanical properties and promoting cellular interactions.

A major challenge in vascular graft development is thrombogenicity. However, HUVs exhibit endothelium-independent antithrombotic properties, which help mitigate platelet adhesion to luminal surfaces (Mangold et al., 2015). One approach to enhancing these properties is vitrification, which preserves biomechanical integrity while preventing excessive platelet binding (Mallis et al., 2020). Research indicates that vitrified blood vessels do not significantly increase platelet adhesion compared to fresh controls, suggesting that conditioning through vitrification could enhance HUV's viability as a vascular graft scaffold (Mallis et al., 2020).

Overall, while challenges remain, advances in bioengineering and scaffold modification techniques continue to enhance the feasibility of HUV-based vascular grafts. Further studies focusing on optimizing endothelialization, reducing immunogenicity, and improving biomechanical properties will be critical in translating HUV scaffolds into clinical applications (Fazal et al., 2021).

6. Conclusion

Human umbilical vein (HUV) presents a promising alternative for vascular grafting due to its favorable mechanical properties, structural integrity, and potential for endothelialization. Studies highlight its suitability as a scaffold for tissue engineering, demonstrating its ability to retain biomechanical strength, support autologous endothelial seeding, and exhibit endothelium-independent antithrombotic properties. Challenges remain, particularly its thrombogenicity and limited adaptation to high-pressure environments. However, advancements such as vitrification may enhance its viability. Further research into optimizing HUV scaffolds could lead to improved vascular grafts, offering a viable solution for cardiovascular tissue engineering and regenerative medicine applications.

Author contributions

T.J. conceptualized and designed the study. D.H.L. conducted the experiments and collected data. Y.E.S. performed the data analysis and interpretation. All authors contributed to drafting the manuscript, reviewed, and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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