

Next-Generation Tissue Engineering for Diabetes: Biomaterials, Bioprinting, and Regenerative Strategies

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ABSTRACT

Diabetes mellitus remains a leading cause of kidney failure, lower-limb amputation, and blindness. Current management strategies, including insulin injections, pumps, and artificial pancreas systems, address glycemic symptoms but do not restore the underlying β -cell populations responsible for glucose-responsive insulin secretion. Tissue engineering offers a regenerative alternative by combining living cells, biomaterial scaffolds, and biochemical cues to replicate pancreatic function. This narrative review synthesizes findings from 82 peer-reviewed articles identified through PubMed and ScienceDirect to evaluate five tissue engineering strategies for diabetes: biomaterial scaffolds, hydrogels, encapsulation devices, 3D bioprinting-based cell replacement, and organ-on-a-chip platforms. Each strategy is assessed for mechanism of action, diabetic application, and key limitations. Biomaterial scaffolds support islet engraftment and wound repair but face immune rejection and degradation challenges. Hydrogels enable immunoisolation and wound healing but suffer from diffusion constraints and mechanical fragility. Encapsulation devices protect transplanted β -cells but are limited by fibrotic overgrowth and oxygenation failure. Three-dimensional bioprinting allows precise spatial arrangement of cell types in islet-like constructs, though vascularization and scale-up remain unresolved. Organ-on-a-chip platforms provide physiologically controlled environments for β -cell screening. Critically, these technologies are evaluated in isolation: a gap this review addresses by proposing a four-stage integrated preclinical and clinical pipeline to accelerate translation.

INTRODUCTION

1.1: Epidemiology and Burden of Diabetes

In the United States alone, about 38 million adults have some form of diabetes, roughly 1 in 10 people [1]. Diabetes is a chronic, often long-lasting health condition that affects the way humans metabolize food. It can be broken down into Type 1 diabetes, Type 2 diabetes, and gestational diabetes [2,3]. It has been known to further result in cardiovascular disease and kidney dysfunction. Studies have shown that it is the leading cause of kidney failure, lower-limb amputations, and blindness [1].

1.2: Contributing Factors

The prevalence of diabetes across the United States is unevenly distributed and varies widely based on socioeconomic status, racial/ethnic factors, gender, and age [4]. Native American and Alaska Native adults have the highest prevalence of diabetes (13.6%), followed by African American adults (12.1%), adults of Hispanic origin (11.7%), Asian adults (9.1%), and White adults (6.9%) [4]. This is due in part to genetic predisposition, in which certain populations carry genetic variations that make them more prone to insulin resistance and the development of Type 2 Diabetes [5]. Diabetes prevalence is also linked to education levels, income, and location. Adults with family income 500% above the federal poverty line had the lowest prevalence, while those below 100% of the poverty line had the highest at 13.1% [4]. With the general trend of life expectancy increasing, people are living sick longer due to the early onset of metabolic conditions [4].

1.3: Physiology of Diabetes

Insulin is a vital hormone that regulates the body's cellular energy supply and macronutrient balance. It is vital to the intracellular transport of glucose, the human body's main source of energy [6]. Insulin transports glucose throughout the body to feed insulin-dependent tissues, an important one being muscle tissue [7]. In Type 1 diabetes, autoimmune destruction of pancreatic β -cells eliminates endogenous insulin production entirely [2,8,9]. In Type 2 diabetes, progressive insulin resistance in peripheral tissues is compounded by β -cell dysfunction, reducing the capacity for compensatory insulin secretion [3,10].

1.4: Current Treatment Methods and Limitations

Various current solutions exist to combat diabetic problems for managing glucose levels. These insulin injection methods are widely available, such as needle and syringe injection, insulin pen, insulin pumps, and jet injectors. Other modern solutions include the artificial pancreas, which mimics the pancreas's functions of insulin production, often used for those with Type 1 Diabetes [11]. These traditional methods have their own drawbacks, such as extreme pain from constant injection, needle phobia, noncompliance, and peripheral hyperinsulinemia [11,12].

1.5: Emerging Solutions: Tissue Engineering Approaches

Due to the drawbacks of these current solutions, there is an increased need to find long-term solutions that new research and technology can bring. Tissue engineering is defined as the application of engineering and life science principles to restore or advance tissue function [13]. It describes the revolutionary approach in regenerative medicine, offering new alternatives to traditional forms of various clinical practices. Some baseline examples include artificial organs, biomaterials, and their use in cell therapy [13]. Tissue engineering has been used for a multitude of diseases, such as rheumatic diseases, cartilage defects, and liver diseases. Tissue engineering approaches in rheumatic diseases, such as mesenchymal stem cell therapy and scaffold-based techniques, show considerable promise for cartilage regeneration in arthritis; however, drawbacks of this include inflammation and remain largely experimental [14]. Similarly, tissue engineering has made an impact in repairing cartilage defects by combining cultured

cells with biocompatible scaffolds and growth factors to generate functional cartilage-like tissue that integrates into defect sites [15].

1.6: Scope of Review

While tissue engineering has shown significant impact in various areas, it has also demonstrated potential in addressing diabetic issues. New developments such as biomaterial scaffolds, organ-on-a-chip platforms, hydrogels, and cell replacement have changed the future of diabetes [13,16,17,18,19]. An overview of current and emerging therapeutic strategies is presented in Figure 1.

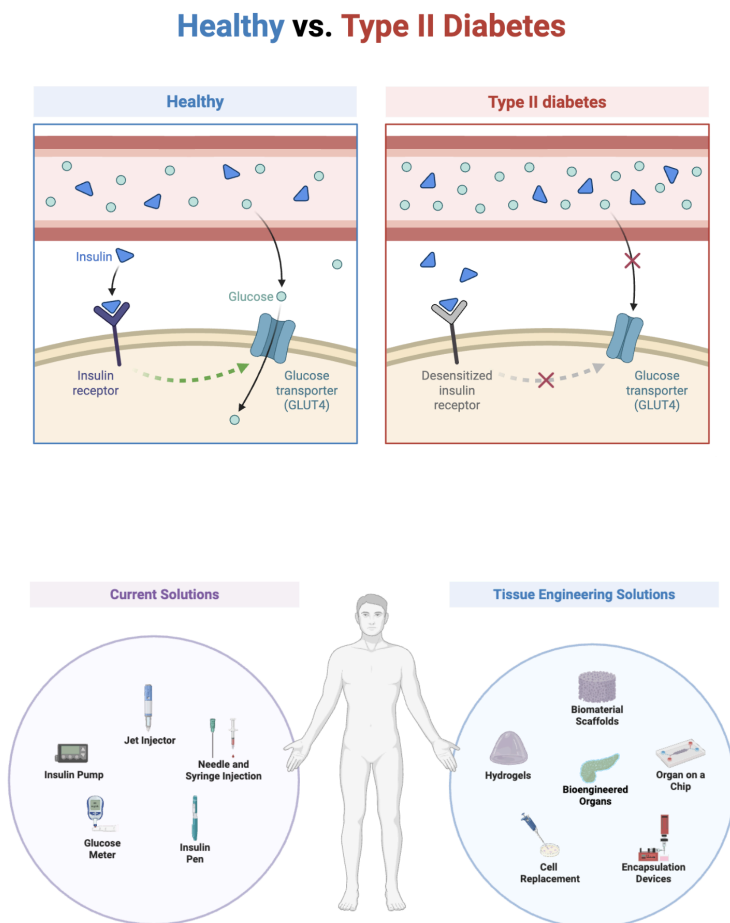


Figure 1. Comparison of Glucose Regulation in Health and Type II Diabetes: Insulin–GLUT4 Signaling, Receptor Desensitization, and Current and Emerging Therapeutic Strategies. Schematic comparison of glucose regulation in a healthy individual and in type II diabetes, highlighting normal insulin–GLUT4 signaling versus receptor desensitization and impaired glucose uptake, alongside an overview of current clinical diabetes management tools (insulin pump, jet injector, needle and syringe injection, insulin pen, glucose meter) and emerging tissue engineering strategies (hydrogels, biomaterial scaffolds,

bioengineered organs, cell replacement, organ-on-a-chip platforms, and encapsulation devices). Made with BioRender.Com.

METHODOLOGY

This narrative review was conducted through a structured search of peer-reviewed literature related to diabetes mellitus, tissue engineering, and emerging regenerative medicine strategies. Two primary biomedical databases were searched: PubMed and ScienceDirect. The primary search term "tissue engineering diabetes" was applied to both databases with review article and meta-analysis article type filters applied and no date restriction (search conducted June 2026), yielding 1,433 records from PubMed and 18,165 records from ScienceDirect, for a combined total of 19,598 records identified. Supplemental category-specific searches were conducted on PubMed using targeted terms including "biomaterial scaffold diabetes" (n = 146), "hydrogel diabetes" (n = 570), "encapsulation beta cell diabetes" (n = 149), "3D bioprinting pancreas diabetes" (n = 17), and "islet on a chip diabetes" (n = 21) to ensure comprehensive coverage across each of the five tissue engineering strategies reviewed. Additional relevant studies beyond those identified through the primary and supplemental database searches were identified through manual reference tracking of included articles and supplemental ScienceDirect searches using more specific search terms.

Studies were considered for inclusion if they met all of the following criteria: published in a peer-reviewed, indexed journal or, where no peer-reviewed equivalent existed, as an explicitly flagged preprint; written in English; and directly relevant to at least one of the five tissue engineering strategies reviewed: biomaterial scaffolds, hydrogels, encapsulation devices, cell replacement and 3D bioprinting, or organ-on-a-chip platforms. Alongside relevance to one of these strategies, studies were also required to address diabetes, pancreatic islet biology, diabetic wound healing, or β -cell replacement as a primary application. Review articles, original research studies, meta-analyses, and clinical trial reports were all eligible for inclusion.

Studies were excluded if they were non-peer-reviewed sources, conference abstracts, gray literature, or addressed tissue engineering applications entirely unrelated to diabetes or pancreatic function. Preference was given to studies published between 2012 and 2025 to reflect current advances; however, foundational studies published prior to this window were included where necessary to establish key mechanistic concepts or provide historical context, including seminal contributions to tissue engineering published as early as 1993.

Following title and abstract screening and full-text eligibility review against the above criteria, 82 studies were included in the final review. These comprised 63 tissue engineering strategy references which were categorized as biomaterial scaffolds (n = 23), hydrogels (n = 8), encapsulation devices (n = 8), cell replacement and 3D bioprinting (n = 11), and organ-on-a-chip platforms (n = 15) and 19 background references addressing epidemiology, diabetes physiology, current clinical treatment limitations, and

healthcare equity considerations. Findings from included studies were synthesized qualitatively to summarize mechanisms, diabetic applications, clinical translation status, and key limitations for each strategy. Cross-cutting themes, shared barriers, and gaps identified across strategies were analyzed with an emphasis on proposing an integrated preclinical and clinical research framework applicable to the field as a whole.

AI-assisted tools were used to support reference verification and editorial review of this manuscript; all citations were individually verified by the author against primary sources. The literature search and selection process is summarized in Figure 2.

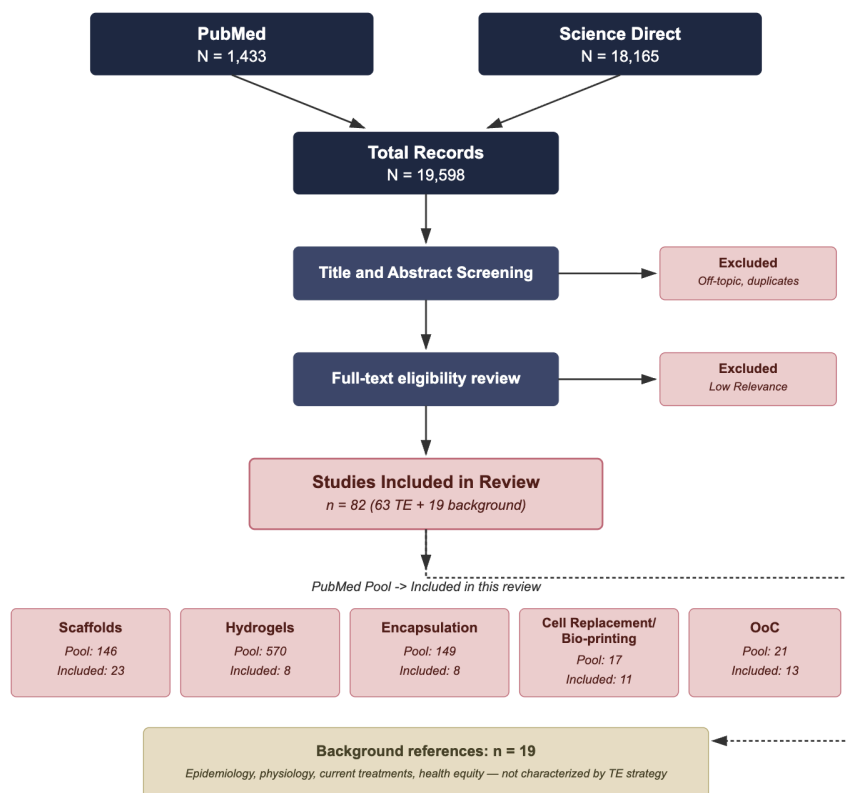


Figure 2: Literature search and selection process for this narrative review.

A two-database search of PubMed (N = 1,433) and ScienceDirect (N = 18,165) using the primary search term "tissue engineering diabetes" with review and meta-analysis article type filters applied and no date restriction (search conducted June 2026) yielded a combined total of 19,598 records. Records were screened at the title and abstract level for relevance to diabetes, pancreatic islet biology, or diabetic wound care, with records excluded for being off-topic, duplicated across databases, or addressing tissue engineering applications unrelated to diabetes. Remaining records underwent full-text eligibility review against predefined inclusion criteria requiring peer-reviewed publication in an indexed journal, English language, and direct relevance to at least one of the five tissue engineering strategies reviewed. A total of

82 studies were included in the final review, comprising 63 tissue engineering strategy references and 19 background references.

RESULTS

Biomaterial Scaffolds

3.1: Definition and General Principles

Scaffolds are three-dimensional biomaterials created for the purpose of permitting transport of body liquids and gases, allowing for cell interaction and tissue regeneration. They are made up of biomaterials, or biocompatible components. It is an artificial temporary platform applied to support and improve and restore the function of an organ [13]. Biomaterial scaffolds allow for the support of new tissue growth, a guided tissue response, the improvement of cell connection and consequent cellular activation, and prevention of adverse biological responses [13,20].

3.2: Natural vs. Synthetic Scaffolds

Natural biomaterials used for scaffolds include collagen, chitosan, and alginate. Collagen scaffolds are biomaterials primarily made up of collagen, an abundant protein found in the human body [21]. They support tissue engineering through improving and mimicking the functions and benefits of native extracellular matrices [22]. Collagen has an advanced biochemistry, composed of protein molecules made up of amino acids with 3 amino acid chains wound together to form a triple helix [23]. Used as a scaffold in wound healing, particularly in skin substitutes, Integra LifeSciences developed the Dermal Regeneration Template (DRT), an FDA-approved skin substitute for third-degree burns made up of bioengineered collagen [24]. The scaffolds promote re-epithelialization and dermal regeneration [25]. Collagen scaffolds are also used in bone regeneration, corneal disorder treatment, and cartilage tissue engineering by delivering chondrocytes in 3D matrices [25,26]. Chitosan, a copolymer molecule made up of N-acetyl-D-glucosamine, has one amino group and 2 hydroxyl groups in the repeating glucosidic residue [27]. Used in nerve regeneration as a conduit scaffold supporting axonal growth in peripheral nerves. Its antimicrobial properties and biocompatibility make it effective in wound dressing scaffolds. In tissue engineering, chitosan scaffolds are utilized for cartilage regeneration and drug delivery due to their porous structure and modifiable surface [27]. Alginate, a natural polysaccharide, is commonly used for three-dimensional scaffolding [28]. Employed as a scaffold in wound healing dressings, especially for exudative wounds and burns. Alginate beads and hydrogels are used for the encapsulation of pancreatic islet cells for diabetes treatment. In cartilage repair, alginate scaffolds are used to encapsulate and support the growth of chondrocytes for matrix production [28,29]. Synthetic materials include polylactic acid (PLA), a synthetic biopolymer that can be combined with various other polymers to produce new biomaterials suitable for creating tissue-engineered solutions [30]. Polyglycolic acid (PGA), a bioabsorbable polymer metabolized to glycine, has a higher inflammatory tissue response compared to polylactic acid [31]. Polyglycolic acid has been used in scaffolds for tissue engineering applications in spinal regeneration of the bone, tendon, cartilage, and tooth [31,32]. When polylactic acid and polyglycolic acid are both used in a scaffold, the combination is known as poly(lactic-co-glycolic acid)

(PLGA), which exhibits improved properties such as low crystallinity and reduced melting temperature [31].

3.3: Application of Scaffolds in Diabetes

Scaffolds have assisted in various fields of medicine and also made an impact in diabetes. A notable study tested a bilaminar composite scaffold made from a fast-degrading porous collagen layer combined with mechanically robust porcine pericardium. This was designed to assist in islet transportation in diabetic mice. It enables strong engraftment and glucose control recovery in mouse models of Type 1 Diabetes, indicating the possibilities of future β -cell replacement therapies in humans [16,33,34]. Scaffolds have also aided in healing diabetic foot ulcers. A diabetic foot ulcer (DFU) is a severe complication of diabetes, resulting in an open wound developing on the foot, increasing the chance for infection and amputation [35]. It is caused by poor blood sugar control, neuropathy, ischemia, nutritional dysfunction, trauma, and local infection.

Current treatments for diabetic foot ulcers, including debridement, wound dressing, hyperbaric oxygen therapy, and offloading, can only temporarily provide basic relief rather than treating damaged blood vessels and nerves [35]. The use of mesenchymal stem cells plays an important role in modern developments of treating diabetic foot ulcers. They address the underlying causes of poor healing such as inflammation, ischemia, infection, and faulty tissue regeneration, and can be used as a topical application in hydrogels or dressings [36,37,38,39,40].

3.4: Challenges and Limitations

Although scaffolds have provided remarkable techniques within the realm of healthcare and diabetes, they are prone to various challenges. Synthetic biodegradable scaffolds continue to face persistent challenges for sustainable, long-term tissue engineering applications [20]. Scaffolds applied for clinical translation with skin, cartilage, bladder, trachea, spinal cord, and cardiovascular repair have presented challenges for implementation, or have been shown to yield better results with alternative biomaterials or solutions [20]. Immune rejection and foreign-body responses remain persistent barriers, and controlling long-term degradation kinetics to match tissue regeneration timelines continues to challenge scaffold-based approaches in clinical settings [20,33].

Hydrogels

4.1: Composition and Types

Injectable hydrogels are usually based on natural polymers, synthetic polymers, or hybrid systems. Natural hydrogels include alginate, gelatin, hyaluronic acid, and chitosan, often combined to optimize mechanical properties and biocompatibility. Alginate is widely used because it undergoes ionic gelation (e.g., with Ca^{2+}) and can be blended with other polymers to adjust stiffness, porosity, and cell compatibility [41,42]. Synthetic hydrogels, such as polyethylene glycol (PEG) and methacrylated gelatin (GelMA), can be photo- or thermo-crosslinked in situ, allowing minimally invasive injection and stable gel formation [43,44]. Extracellular matrix (ECM)-derived hydrogels are also explored, as they form gels at body temperature and retain natural bioactive molecules, enabling them to act both as scaffolds and

drug delivery systems [45]. A schematic comparison of standard and glucose-responsive hydrogel systems is shown in Figure 3.

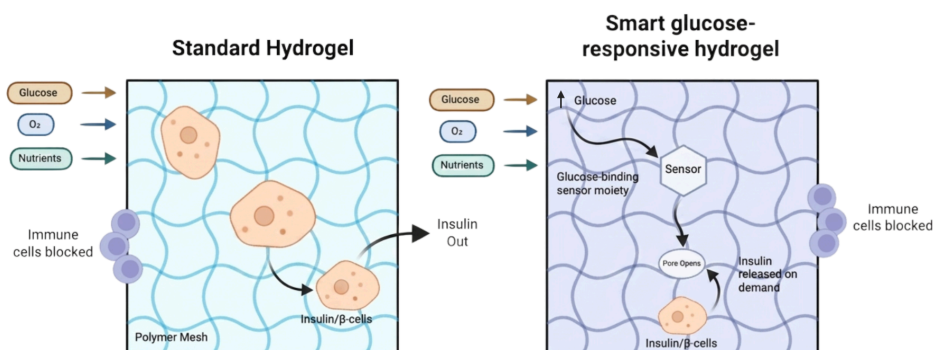


Figure 3: *Cross-sectional schematic of injectable hydrogel systems for diabetes therapy.*

Two-panel illustration comparing passive and glucose-responsive hydrogel platforms for β -cell immunoisolation and diabetic wound healing. The left panel depicts a standard alginate or hybrid hydrogel construct in which a polymer mesh network encapsulates pancreatic islets and β -cell clusters. The semipermeable mesh permits inward diffusion of glucose, oxygen, and nutrients while enabling outward insulin secretion, simultaneously blocking immune cell infiltration through size-exclusion. The right panel depicts a glucose-responsive smart hydrogel incorporating glucose-binding sensor moieties distributed throughout the polymer network. Elevated extracellular glucose triggers conformational changes in the sensor elements, driving localized pore opening and controlled on-demand insulin release. Created with BioRender.com.

4.2: Other Biomedical Applications

Hydrogels have found influential ways to advance medicine. A notable instance is cardiac tissue regeneration, where hydrogels act as a promising tool for regenerating damaged heart tissue after myocardial infarction. Hydrogels can mimic aspects of the heart's extracellular matrix, support cell survival, deliver therapeutic cells or molecules, and be used as injectable materials, cardiac patches, or bioprinting "bioinks" [42].

4.3: Application to Diabetes

Hydrogels can be applied to diabetes in two major ways. First, islet cell encapsulation uses alginate or hybrid hydrogels to immunoisolate transplanted pancreatic islets. This allows diffusion of oxygen, nutrients, and insulin while shielding the islets from direct immune attack, potentially reducing or eliminating the need for immunosuppression [41,42]. Second, hydrogels are being investigated for diabetic wound healing. Injectable hydrogels can fill irregular wound spaces, provide a moist healing

environment, and deliver therapeutic factors in a sustained manner [43,44,46]. Extracellular matrix or methacrylated gelatin (GelMA) hydrogels loaded with mesenchymal stem cell-derived exosomes have been shown to accelerate diabetic wound repair by reducing inflammation, stimulating angiogenesis, and promoting collagen deposition [45]. More recently, smart hydrogels responsive to glucose, pH, or external stimuli (light, magnetic fields) have been designed to achieve controlled release of drugs or bioactive molecules in the diabetic wound microenvironment [44,47,48].

4.4: Challenges and Limitations

Despite progress, injectable hydrogels for diabetes therapy face several challenges. Immune rejection and foreign-body responses remain significant issues, particularly for cell-based or exosome-loaded hydrogels [45]. In islet encapsulation, oxygen and nutrient diffusion limitations can impair cell survival and function if the hydrogel is too dense or thick [41,42]. In drug delivery, problems such as burst release and loss of therapeutic bioactivity reduce efficacy, although extracellular matrix and methacrylated gelatin (GelMA) hydrogels can improve sustained release [45]. Mechanical weaknesses, difficulties balancing injectability with final gel stiffness, and risks of photoinitiator toxicity in photocrosslinkable gels are also concerns [44]. Shear stress during injection or bioprinting can damage encapsulated cells [41]. Additionally, most hydrogels used clinically do not adapt dynamically to wound conditions, which motivates development of responsive systems: but these increase complexity and face translational barriers [47,48]. Manufacturing variability, sterilization, and regulatory approval of biologic-device combination products are further hurdles [43,45].

Encapsulation Devices

5.1: Definition and Types

Encapsulation devices are biomaterial constructs that enclose living cells or tissues inside a semi-permeable matrix or chamber designed to provide a supportive microenvironment while controlling molecular exchange with the host [17,41]. Microencapsulation refers to small, often spherical beads or droplets in which individual islets or small clusters of cells are embedded within hydrogel microspheres, usually alginate-based. Microcapsules maximize surface area for diffusion and are typically delivered by injection or implantation [41]. Macroencapsulation denotes larger, engineered chambers or pouches (millimeters to centimeters) that house many cells or cell aggregates within a single retrievable device; these devices often incorporate controlled porosity membranes, oxygenation strategies, or vascularization features to support larger graft volumes [49,50]. Both classes aim to be permselective: permitting nutrients, oxygen, glucose, and insulin to diffuse while limiting immune-mediated cell destruction [49,50,51,52]. The two primary encapsulation strategies are illustrated in Figure 4.

5.2: Other Biomedical Applications

Microencapsulation of probiotic bacteria or genetically engineered cells for sustained therapeutic protein secretion illustrates the general concept outside diabetes: probiotic or engineered cells are trapped in alginate microspheres that protect against gastric acidity and modulate release kinetics, allowing oral or localized delivery while improving cell survival and function [41]. Macroencapsulation has also been explored in other fields for cell-based delivery of therapeutic proteins, where larger, retrievable devices

facilitate dosing control and device retrieval if adverse events occur, illustrating the versatility of the macroencapsulation approach beyond islet transplantation [17,50]. These translated use cases demonstrate how scale, material choice, and device geometry are tailored to clinical requirements [17,41].

5.3: Diabetic Application

Encapsulation strategies for diabetes focus primarily on restoring glucose-responsive insulin secretion while aiming to reduce or eliminate lifelong immunosuppression [17,49,50]. The microencapsulation strategy utilizes alginate-derived microspheres to encapsulate donor pancreatic islets (or insulin-secreting cell lines), enabling metabolic exchange while providing immune isolation [17,41,53]. The macroencapsulation strategy uses semipermeable chambers, such as pouches, to contain either mature islets or stem-cell-derived pancreatic progenitors that subsequently mature in place [49,50]. Recent advances pair encapsulation with stem-cell-derived β cells placed inside devices engineered to improve oxygenation and membrane permeability. Early clinical and preclinical reports indicate measurable C-peptide production and partial glycemic benefit in some cohorts, showing early evidence for cell replacement with systemic immunosuppression [49,54].

The choice for implementation depends on tradeoffs between diffusion distance, retrievability, scale of cell dose, and device-host interactions [17,49,50].

5.4: Limitations and Engineering Challenges

Despite promise, encapsulation faces several key limitations that have slowed clinical translation [49,55]. Oxygen and nutrient diffusion limit viable graft thickness and cell density; hypoxia is a central cause of early graft failure, especially in macro devices where diffusion distances are larger [49,50]. Fibrotic overgrowth and foreign-body reactions have significantly slowed clinical translation. Host immune/fibrotic responses can form a collagenous capsule on device surfaces that further impedes diffusion and function; material purity and surface chemistry strongly affect this outcome [17,55]. Achieving insulin independence requires large numbers of functional β cells; microcapsules can provide high surface area but are harder to retrieve, while macrodevices are retrievable but must solve oxygenation and vascularization for large grafts [49,50,55]. Polymer degradation, mechanical failure, or loss of permselectivity over time can reduce efficacy; additionally, encapsulated cells may de-differentiate or lose function if the microenvironment is suboptimal [41,55]. Producing uniformly sized, sterile, and functionally consistent encapsulation products at scale poses complex good manufacturing practice (GMP), storage, and distribution challenges [17,41,55]. Encapsulation devices remain one of the most promising strategies to achieve cell-based, insulin-producing therapy for diabetes while aiming to reduce or eliminate systemic immunosuppression. Continued progress depends on engineering solutions for oxygenation/vascularization, surface chemistry to prevent fibrosis, scalable manufacturing of cells and matrices, and well-designed clinical trials to demonstrate durable, clinically meaningful glycemic control [17,49,55].

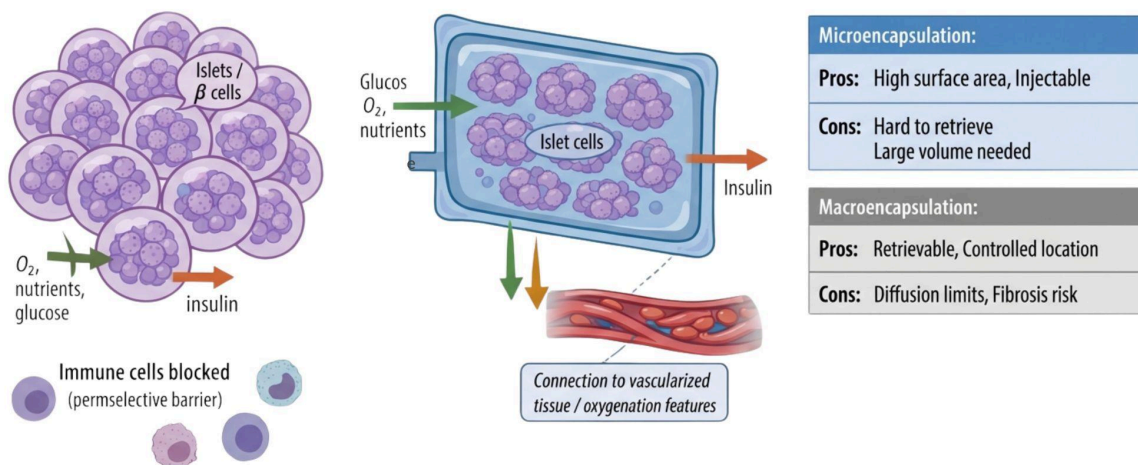


Figure 4: Schematic of islet cell encapsulation strategies using alginate or hydrogel systems.

Microencapsulation surrounds individual islets or β -cells with semipermeable hydrogel capsules that allow diffusion of glucose, oxygen, and nutrients while blocking immune cells and enabling insulin release. In contrast, macroencapsulation houses multiple islets within a larger device connected to vascularized tissue for oxygenation. Each approach presents trade-offs between injectability and surface area (microencapsulation) versus retrievability and controlled placement (macroencapsulation). Created with BioRender.com.

Cell Replacement and 3D Bioprinting

6.1: Concept of Cell Replacement

Cell replacement is the process of restoring lost, damaged, or dysfunctional cells in a tissue or organ to regain physiological function [56,57]. In tissue engineering, cell replacement aims to repopulate damaged tissues with functional cells, often combined with biomaterials and supportive scaffolds to improve survival, integration, and function [57,58]. For example, in diabetes, the pancreatic β -cells responsible for insulin production are destroyed or failing. Cell replacement strategies seek to restore β -cell populations to reestablish glucose regulation [2,18,58,59].

6.2: Traditional Tissue Engineering Approaches

Tissue engineering has traditionally combined cell therapy with three-dimensional biomaterials that provide structural support, mechanical stability, and a microenvironment conducive to cell growth, differentiation, and survival [57,60]. Scaffolds can be seeded with cells before implantation, allowing cells to adhere, proliferate, and begin forming functional tissue [61,62]. This traditional approach improves cell retention, function, and integration compared to direct cell injection, however often results in cell loss and poor survival [57,60].

6.3: Introduction to 3D Bioprinting

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3D bioprinting is an advanced tissue fabrication method that allows for the construction of tissue-like models layer by layer through the precise deposition of living cells and biomaterials [18,56,63]. Instead of using pre-fabricated scaffolds seeded with cells, 3D bioprinting uses bioinks, such as hydrogels, to arrange cells in a desired structure that mimics their native organization [56,62]. This enables the development of structures, including artificial islets or organoids, where optimal cell placement facilitates critical functions like nutrient diffusion, signaling, and overall performance [18,56,61,64,65].

6.4: Benefits of Bioprinting for Cell Replacement

Engineered constructs created via bioprinting can maintain cell function, offer a supportive microenvironment, and enhance cell survival and integration following implantation [18,60,61]. In diabetes, bioprinted pancreatic tissue constructs can imitate the architecture of native islets, thereby improving insulin secretion dynamics and responsiveness to glucose [18,56,62,66]. Compared to simple cell injection, bioprinting improves functional outcomes by enabling the recreation of complex tissue niches through the arrangement of multiple cell types [57,60,61].

6.5: Challenges and Future Directions

Despite its advantages, 3D bioprinting faces challenges that limit widespread clinical application [58,60]. Vascularization remains critical, printed constructs require sufficient nutrient and oxygen supply, particularly for thicker tissues [58,60,61]. Immune rejection and long-term cell survival are ongoing hurdles [57,58]. Additionally, scaling up from small tissue models to therapeutically relevant sizes is still a major technical challenge [61,65]. Nevertheless, combining bioprinting with scaffold-based strategies and traditional cell therapies shows promise for improving the efficacy of cell replacement approaches across multiple tissue types, such as pancreatic islets, cardiac tissue, and neural tissues [18,57,60]. Overall, 3D bioprinting represents a powerful tool in tissue engineering for cell replacement, offering precise control over cell placement, architecture, and microenvironment [18,56,61]. By complementing existing scaffold and injection-based approaches, it enhances cell survival, function, and integration while addressing some of the limitations of traditional cell therapies [57,60,62]. However, successful clinical translation will require addressing vascularization, immune compatibility, and scaling challenges [58,60,61].

Organ-on-a-Chip

7.1: Definition and Key Principles

An organ-on-a-chip (OoC) is a microengineered, microfluidic device designed to recreate key structural and functional aspects of human organs. These are maintained *in vitro* by integrating living cells within precisely controlled 3D microenvironments [19]. OoC systems generally incorporate microscale channels, porous membranes, and compartments based on the extracellular matrix, essential for maintaining tissue-specific architecture, fluid flow, and biomechanical stimulation [19,67]. OoC platforms offer a more physiologically accurate alternative to traditional dish-based cell culture by incorporating dynamic perfusion, mechanical stimuli, and controlled biochemical gradients [67,68].

7.2: Microfabrication and Device Design

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OoC systems are fabricated using microfluidic technologies such as soft lithography, photolithography, or 3D microprinting to create microchannels in biocompatible polymers like polydimethylsiloxane [19,69]. These channels allow laminar fluid flow that delivers nutrients, oxygen, hormones, and drugs while removing waste, enabling continuous dynamic culture conditions [69]. Cells are seeded within designated compartments or embedded in extracellular matrix (ECM) hydrogels, where they organize into functional tissue-like structures under precisely controlled flow, mechanical stretch, and environmental conditions [19,68]. Many modern chips also include integrated sensors, optical windows, electrodes, and oxygen sensors, allowing for real-time monitoring of cell behaviour, metabolism, and secreted factors [68,70].

7.3: Islet-on-a-Chip for Diabetes

In diabetes research, OoC platforms have been adapted into "islet-on-a-chip" systems: microfluidic devices engineered to culture pancreatic islets or stem-cell-derived β -cell clusters under controlled flow and nutrient delivery [71,72,73]. These chips mimic the in vivo microenvironment by regulating glucose concentration, oxygen levels, and shear stress, allowing researchers to measure insulin secretion dynamics with high temporal precision [71,74]. Because type 1 diabetes involves the destruction of β -cells and type 2 diabetes involves dysfunction of islet signalling, islet-on-a-chip systems provide a powerful tool to study β -cell physiology, stress responses, immune interactions, and drug or therapy effects [72,75]. They are also used to evaluate cell-replacement strategies such as stem-cell-derived β -cells and encapsulated islets before animal or clinical testing [71,75,76].

7.4: Role in Diabetes Modeling and Therapy Development

Organ-on-a-chip technology provides a physiologically relevant and highly controlled platform for studying human tissues in microengineered environments [19,67]. In diabetes research, islet-on-a-chip systems offer enhanced insight into β -cell behaviour, therapeutic responses, and cell-replacement strategies, bridging the gap between traditional culture models and in vivo studies [71,72,75]. Continued advancements in microfabrication, sensors, and stem-cell technologies are expected to further expand their role in therapy development and disease modelling [67,68,69,77].

FUTURE RESEARCH

A critical and underappreciated limitation across the tissue engineering strategies reviewed here is that each is developed, tested, and evaluated largely in isolation. Biomaterial scaffolds are assessed for engraftment efficiency, encapsulation devices are evaluated for immune protection, and islet-on-a-chip systems are used to study β -cell physiology, but these platforms are rarely combined into a coherent preclinical workflow before animal or clinical testing [77,78]. This fragmentation represents a non-obvious gap in the field: the assumption that technologies optimized independently will perform equivalently when integrated is largely untested, and may help explain the persistent high failure rate of tissue-engineered constructs in translation from bench to clinic [49,50,77].

Consider the specific case of encapsulated stem-cell-derived β -cells: one of the most clinically advanced

approaches currently in development [49,54]. These constructs must simultaneously satisfy multiple requirements: the encapsulation material must permit sufficient oxygen and glucose diffusion, the β -cells must retain glucose-responsive insulin secretion under the mechanical and chemical conditions imposed by the device, and the construct as a whole must resist fibrotic overgrowth in the host environment [17,49,55]. Currently, each of these variables is typically tested in separate experimental systems: diffusion in static hydrogel assays, β -cell function in standard culture, and fibrosis in animal implantation models. No standardized intermediate platform exists to screen construct candidates across all three parameters before committing to costly and ethically intensive animal studies [77,78,79].

Islet-on-a-chip technology, as reviewed in Section 7.3, is well-positioned to serve as exactly this kind of intermediate screening platform, yet its use for evaluating encapsulated constructs, rather than bare islets, has received minimal attention in the literature [71,72,73,75]. A chip-based system that incorporates controlled perfusion, tunable oxygen gradients, and immune cell co-culture could allow researchers to simultaneously assess diffusion kinetics, insulin secretion dynamics, and immune response for a given encapsulation candidate under physiologically relevant conditions [68,73,74]. This would generate directly comparable, standardized data across candidate materials before any animal work is conducted: a step currently absent from most reported translational workflows [77,79].

Before describing this framework in detail, it is important to distinguish clearly between what is evidence-based and what is proposed here as a future direction. The clinical and preclinical findings referenced throughout this section, including the encapsulated stem cell-derived β -cell results reported by Keymeulen et al. [49] and the polymer-encapsulation work of Vegas et al. [54], are drawn from published, peer-reviewed studies. The four-stage pipeline itself, by contrast, is a conceptual framework advanced by the author. It has not been validated as an integrated workflow, and each proposed transition between stages rests on the untested assumption that performance on an upstream platform predicts performance downstream. That assumption is plausible but currently unproven, and confirming it would itself require prospective study.

This proposed pipeline would proceed in three stages. First, candidate encapsulation materials would be screened using islet-on-a-chip platforms modified to simulate the post-implantation microenvironment, including relevant oxygen tension, glucose oscillations, and macrophage co-culture to model early immune responses [68,71,73]. Second, constructs passing chip-based screening would advance to 3D bioprinted tissue models incorporating vascular-like channels, allowing assessment of nutrient supply and insulin secretion at a tissue scale before in vivo implantation [60,61,63,66]. Third, only constructs demonstrating sustained function across both platforms would progress to animal studies, reducing the number of animal experiments required and improving the predictive value of preclinical data [77,78,79]. Such a pipeline would directly address the vascularization, immune response, and diffusion limitations identified across Sections 3 through 7 of this review, not by solving any one of them individually, but by ensuring that candidate constructs are evaluated against all of them in sequence before clinical translation is attempted [17,49,55,60,71].

Implementing this pipeline would require standardization of chip geometries and oxygen parameters across research groups, development of shared protocols for immune cell co-culture in microfluidic environments, and closer collaboration between biomaterials scientists, microfluidic engineers, and transplant immunologists, fields that currently publish largely independently of one another [77,78]. These are organizational and methodological challenges as much as they are technical ones, and addressing them represents a tractable, near-term research direction that does not require new scientific breakthroughs, only the integration of tools that already exist [78,79]. It should be emphasized that the predictive validity of this staged approach is a hypothesis rather than an established result. No study to date has evaluated whether chip-level or bioprinted-tissue benchmarks reliably forecast in vivo or clinical outcomes for encapsulated β -cell constructs, and establishing such correlations is a prerequisite to adopting the framework rather than a consequence of it.

The three-stage preclinical pipeline described above is intended to precede, not replace, formal clinical investigation. Stage 4 of the proposed framework therefore focuses on a structured transition into clinical trials, modeled on regulatory pathways already established for cell-based combination products. The phase 1/2 open-label multicenter trial conducted by Keymeulen et al. (ClinicalTrials.gov identifier: NCT03163511) provides the closest existing precedent, showing that encapsulated stem cell-derived β cells can produce measurable glucose control in patients with type 1 diabetes. In this study, the device was perforated to allow host vascularization, which likely improved oxygen and nutrient delivery and supported cell survival. Because the device allowed direct interaction with the host immune system, participants received immunosuppressive therapy with antithymocyte globulin (ATG) induction followed by tacrolimus and mycophenolate mofetil. This highlights a key tradeoff: designs that support vascular integration can improve graft function but require systemic immunosuppression. Three of ten patients achieved C-peptide levels associated with improved continuous glucose monitoring outcomes and reduced insulin dosing at one year. These results show that partial glycemic benefit is possible, but insulin independence has not yet been achieved at scale.

A Stage 4 clinical trial emerging from the proposed pipeline would differ from prior studies in one important way. Constructs advancing to human testing would already be screened using standardized organ-on-chip and bioprinted tissue platforms, with defined benchmarks for insulin secretion, oxygen consumption, and macrophage activation before implantation. This would allow trial design to include biologically grounded go or no-go criteria at the device level, rather than relying only on clinical outcomes measured months later. It could also reduce the number of patients exposed to ineffective constructs in early-phase trials. Prior clinical results show the risks of limited preclinical screening. A trial using a fully encapsulated device without vascular integration reported highly variable outcomes, likely due to poor oxygenation and inadequate cell survival after 12 weeks. These are the exact failure modes that Stages 1 and 2 of the proposed pipeline aim to identify before clinical use. Regulatory engagement with the FDA Center for Biologics Evaluation and Research and alignment with guidance for combination products would be required before initiating Stage 4. Long-term follow-up would also be necessary to assess durability of glycemic control, fibrotic encapsulation, and device retrievability at 12, 24, and 60 months after implantation. The proposed pipeline is illustrated in Figure 5.

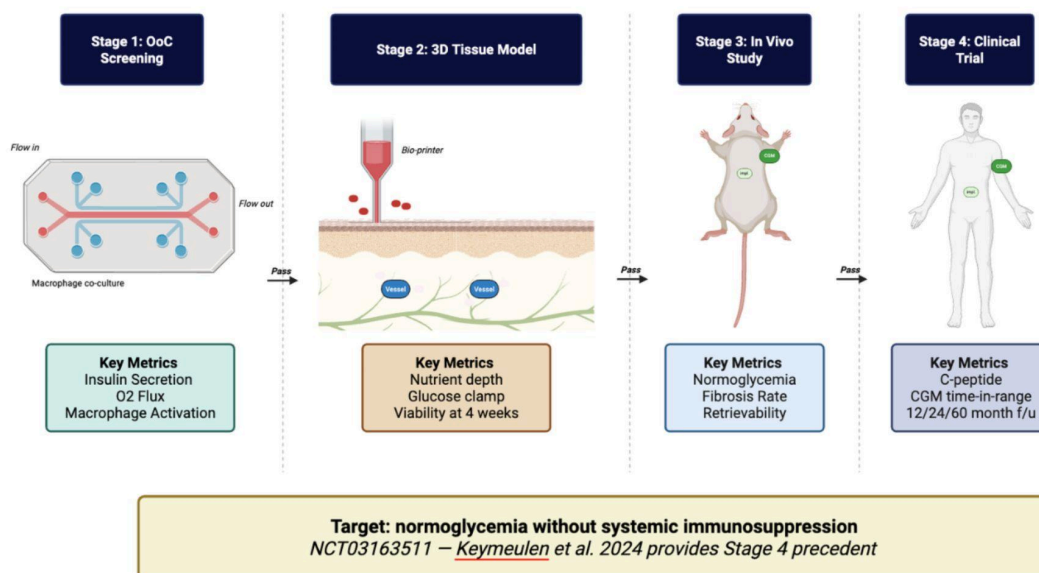


Figure 5: Proposed four-stage integrated preclinical and clinical pipeline for tissue-engineered diabetes therapies. Schematic overview of a sequential pipeline framework designed to evaluate encapsulated β -cell constructs across standardized platforms before first-in-human implantation. Stage 1 (islet-on-a-chip screening) employs microfluidic devices with controlled glucose oscillations, tunable oxygen gradients, and macrophage co-culture to simultaneously assess diffusion kinetics, glucose-stimulated insulin secretion index, and early immune activation. Stage 2 (3D bioprinted tissue model) evaluates vascularized constructs for nutrient supply at tissue depth and structural viability at four weeks post-printing. Stage 3 (in vivo animal study) receives only pre-validated constructs; key endpoints include normoglycemia duration and fibrotic capsule formation rate. Stage 4 (structured clinical trial) follows a Phase 1/2 regulatory pathway under FDA Center for Biologics Evaluation and Research (CBER) guidance, with continuous glucose monitoring time-in-range improvement and C-peptide levels as primary endpoints. The overall target outcome is sustained normoglycemia without systemic immunosuppression. Stage 4 design is informed by the precedent set by Keymeulen et al. [49]. Created with BioRender.com.

DISCUSSION

9.1: Cross-Technology Synthesis

The five tissue engineering strategies reviewed here: biomaterial scaffolds, hydrogels, encapsulation devices, 3D bioprinting, and organ-on-a-chip platforms which collectively represent a broad toolkit for addressing the cellular and tissue-level defects underlying diabetes. Each approach has a distinct position in the translational landscape, from relatively mature scaffold and hydrogel systems already used in

clinical wound care, to earlier-stage platforms such as bioprinted pancreatic constructs and organ-on-a-chip models that remain largely confined to research settings. Table 1 summarizes the key characteristics of each strategy across primary application, advantage, limitation, and current clinical translation status. Among the five strategies, encapsulation devices are arguably closest to clinical translation for β -cell replacement. The recent Nature Biotechnology report by Keymeulen et al. demonstrating measurable C-peptide production in patients receiving encapsulated stem cell-derived β cells represents the most direct clinical evidence to date that functional insulin secretion can be restored with systemic immunosuppression [49]. However, the persistent challenge of fibrotic overgrowth and oxygenation failure in both micro- and macrodevices means that clinical durability remains unproven beyond the short-to-medium term [17,49,55]. Hydrogels and scaffolds, while less advanced for β -cell replacement specifically, are already in clinical use for diabetic wound care, with alginate dressings and collagen-based skin substitutes representing translated examples [24,25,41]. Their integration with cell therapies remains largely preclinical. 3D bioprinting and organ-on-a-chip occupy complementary positions in the pipeline. Bioprinting enables fabrication of complex, multi-cell-type constructs that encapsulation and hydrogel platforms cannot produce, but vascularization and scale-up remain barriers to clinical use [60,61,65]. Organ-on-a-chip, by contrast, is not a therapy in itself but a research and screening tool. Its value lies precisely in its ability to generate physiologically relevant data under controlled conditions before constructs advance to animal or human testing [77,79]. The underutilization of OoC as a screening platform for encapsulated constructs: the gap identified in future research is arguably the most actionable near-term opportunity in the field, as it does not require new technology, only a new experimental design [71,77,78]. A broader pattern across all five strategies is that immune rejection and inadequate vascularization are the two recurring barriers that no single technology has fully resolved [17,49,55,60]. Immune rejection manifests differently across platforms, as foreign-body capsule formation around encapsulation devices, as inflammatory infiltration around scaffolds, and as direct cytotoxic attack on unprotected transplanted cells, but the underlying mechanism is shared [20,41,55]. Similarly, vascularization is insufficient in scaffold-based grafts, unresolved in thick bioprinted constructs, and a primary design challenge for large macroencapsulation devices [49,60,61]. This convergence of challenges across different technological approaches suggests that a platform-agnostic solution, such as gene-edited β -cells with reduced immunogenicity, or universal pro-vascularization biomaterial coatings, would be more impactful than continuing to optimize each technology independently [54,66]. The integrated pipeline proposed in Section 8 is offered here as a methodological hypothesis rather than a demonstrated solution: a framework for evaluating existing technologies together more rigorously, whose own predictive value remains to be tested. Its appeal lies in requiring no new scientific discoveries [77,78,79], but this should not be mistaken for evidence that the sequence performs as intended. The specific metrics proposed, glucose-stimulated insulin secretion thresholds, oxygen consumption rates, and macrophage activation markers at the chip-screening stage, are all measurable with currently available tools, making this a tractable near-term research direction [68,71,74].

9.2: Comparative Technological Readiness

The five strategies reviewed here occupy markedly different positions along the path to clinical use, and the reasons for this divergence are instructive. Encapsulation devices are the most clinically advanced for

β -cell replacement, having reached first-in-human testing in which encapsulated stem cell-derived β cells produced measurable C-peptide and partial glycemic benefit [49]. Their relative maturity reflects a comparatively contained translational problem: the core therapeutic principle, permselective immunoisolation of insulin-secreting cells: was established decades ago in microencapsulation work [41], and subsequent effort has concentrated on refining materials, oxygenation, and device geometry rather than inventing a new modality [17,49,55]. Biomaterial scaffolds and hydrogels are similarly mature, but in a different application domain: alginate dressings and collagen-based skin substitutes are already in routine clinical use for diabetic wound care [24,25,41], whereas their integration with cell therapies for β -cell replacement remains largely preclinical. Three-dimensional bioprinting and organ-on-a-chip platforms sit earliest in the pipeline, bioprinting because vascularization and scale-up of thick constructs remain unsolved [60,61,65], and organ-on-a-chip because it is a screening and modeling tool rather than an implantable therapy [77].

These differences are not explained by biological difficulty alone; regulatory pathway, manufacturing complexity, and clinical feasibility each contribute. From a regulatory standpoint, encapsulation devices benefit from an established, if demanding, route: they are treated as combination products under existing FDA guidance, a pathway that clinical programs such as that of Keymeulen et al. have already navigated [49]. Scaffold and hydrogel wound-care products likewise follow familiar device and biologic-device approval routes, with FDA-cleared collagen skin substitutes providing precedent [24]. Bioprinted constructs and chip-based systems, by contrast, lack settled regulatory frameworks, bioprinted living implants raise unresolved questions of characterization and release testing, while organ-on-a-chip platforms have no direct therapeutic approval pathway because they are not themselves administered to patients [77,79]. Manufacturing complexity follows a similar gradient. Alginate microcapsules and hydrogel dressings can be produced with comparatively simple, well-characterized chemistry [41], whereas encapsulated stem cell-derived β -cell products must integrate a scalable, differentiated cell source with a reproducible device under good manufacturing practice conditions, a substantially harder problem [17,49,55]. Bioprinting adds further burden, requiring reproducible bioinks, print fidelity, and post-print maturation that are difficult to standardize across batches [60,61].

Taken together, the strategies closest to the clinic are those combining an established therapeutic principle, a recognized regulatory route, and tractable manufacturing, criteria that encapsulation and wound-care applications satisfy more fully than bioprinting or chip-based platforms. This framing also clarifies the complementary roles the technologies can play: rather than competing, the more mature platforms offer near-term clinical value while the earlier-stage tools are best positioned as enabling and screening technologies. Table 1 summarizes these positions, and the pipeline proposed in Section 8 is intended precisely to let the earlier-stage platforms accelerate the more clinically advanced ones rather than progress in isolation.

9.3: Non-Biological Barriers to Translation

Beyond the biological barriers of vascularization, fibrosis, and immune rejection, a second class of challenges: manufacturing, cost, safety, durability, and regulation, will substantially shape whether these

therapies reach patients, and these have received comparatively little attention in the tissue engineering literature. Producing cell-containing constructs at clinical scale under good manufacturing practice (GMP) conditions is a recognized bottleneck: encapsulation and cell-replacement products must deliver uniformly sized, sterile, and functionally consistent units, which imposes complex process-control, storage, and distribution requirements not encountered with conventional pharmaceuticals [17,41,55]. Bioprinted constructs compound this difficulty, since reproducible bioink formulation and print fidelity are hard to standardize across batches [60,61]. Cost and scalability are tightly coupled to these manufacturing demands. Achieving insulin independence is thought to require large numbers of functional β cells per patient [49,50,55], and scaling a differentiated stem-cell source together with its device to population level, while maintaining potency and sterility, is likely to be expensive, with direct implications for the access disparities discussed in §9.5. Long-term safety adds a further dimension: durable follow-up is needed to assess not only the persistence of glycemic control but also fibrotic encapsulation, device retrievability, and the theoretical risks associated with stem-cell-derived grafts, which is why the framework proposed here specifies monitoring at 12, 24, and 60 months. Finally, the regulatory pathway for these combination products is demanding and not fully settled; engagement with the FDA Center for Biologics Evaluation and Research and alignment with combination-product guidance would be prerequisites to clinical translation [17,49,55]. Manufacturing variability, sterilization, and the regulatory approval of biologic-device combinations have already been identified as hurdles for hydrogel and scaffold systems [43,45], and these considerations will only intensify for more complex cellular constructs.

9.4: Applicable Patient Populations

The tissue engineering strategies reviewed in this paper are most directly applicable to patients with Type 1 diabetes mellitus and a specific subset of patients with longstanding Type 2 diabetes who have progressed to near-complete β -cell failure [2,3,49]. Eligibility criteria across current encapsulation and islet transplantation clinical trials consistently require confirmed Type 1 diabetes of at least five years duration, undetectable or severely diminished C-peptide levels, and documented failure of intensive insulin management, defined in most protocols as recurrent severe hypoglycemia, hypoglycemic unawareness, or persistent HbA1c above 10% despite optimized care [17,49]. These criteria define the population with the most urgent unmet need and the clearest mechanistic rationale for β -cell replacement, one in which endogenous insulin production has been eliminated and pharmacologic management alone cannot provide physiologically regulated glycemic control [2,11,54]. For diabetic wound care applications, specifically scaffold and hydrogel-based therapies for diabetic foot ulcers, the applicable population is considerably broader, encompassing any patient with diabetes-related peripheral neuropathy, ischemia, or chronic wound failure regardless of diabetes type, age, or insulin dependence status [35,36,37,40]. Mesenchymal stem cell-based scaffold therapies for diabetic foot ulcers have been evaluated across mixed populations of type 1 diabetes and type 2 diabetes patients and show benefit in both groups, as the underlying mechanism of impaired wound healing is shared across diabetes types [37,38,39]. Organ-on-a-chip platforms, as research tools rather than therapies, are applicable across the full spectrum of diabetes research, both type 1 diabetes and type 2 diabetes islet biology can be modeled, and the platforms have been used to study the distinct failure modes of each condition including

autoimmune β -cell destruction in type 1 diabetes and glucotoxicity-driven β -cell exhaustion in T2D [71,72,73,74].

9.5: Non-Applicable Patient Populations

Not all patients with diabetes will be suitable candidates for the tissue engineering approaches described in this review, and the eligibility gap is both clinical and structural.

9.6: Clinically Excluded Populations

Across islet transplantation and encapsulation trials, consistent exclusion criteria include Body Mass Index (BMI) above 29-33 kg/m² depending on the protocol, insulin requirements exceeding 1.0 IU/kg/day, significant renal dysfunction with glomerular filtration rate (GFR) below 60-70 mL/min, active liver disease, portal hypertension, active malignancy within five years, uncontrolled cardiovascular disease, untreated proliferative diabetic retinopathy, coagulopathy, and active substance abuse [17,49,55]. These exclusions are clinically justified, the procedures carry significant surgical and immunological risk, and comorbidities in these categories would compromise both safety and the likelihood of graft success. However, they also define a large group of diabetic patients for whom β -cell replacement therapy is not currently an option. Patients with longstanding T2D, who often have the highest comorbidity burden which includes obesity, renal insufficiency, cardiovascular disease, and retinopathy, are therefore largely excluded from the very therapies that might most benefit them if their β -cell function is exhausted [3,10,55]. This represents an important limitation of the current clinical translation pathway that tissue engineering research has not yet adequately addressed.

9.7: Structurally Excluded Populations: The Equity Gap

Beyond clinical eligibility, a substantial portion of the population most burdened by diabetes faces structural barriers that would prevent access to tissue-engineered therapies even if they were clinically eligible. As documented in Section 1.2, Native American, Alaska Native, Black, and Hispanic adults carry significantly higher diabetes prevalence than White adults in the United States [4]. Studies have demonstrated that racial disparities in access to and prescribing of diabetes technologies are well-documented, with Black patients with Type 1 diabetes showing significantly lower rates of technology discussions and prescribing compared to non-Black patients at the same academic medical centers [80]. Even when insurance coverage exists for new treatments, uninsured individuals and those with high out-of-pocket costs continue to face financial barriers that make advanced therapies inaccessible, and growing use of clinical algorithms in care delivery risks perpetuating existing disparities if those algorithms are not designed with equity considerations [81]. Clinical guidelines increasingly identify socioeconomic factors including food insecurity, housing instability, and financial barriers as determinants of diabetes outcomes that providers must address in treatment planning, and these structural factors compound the institutional inequities described above, indicating that addressing them requires more than improvements in clinical care alone [82]. Yet none of the tissue engineering approaches reviewed here have been evaluated for feasibility or effectiveness in populations facing these structural barriers. This is not merely a downstream access problem. Research populations enrolled in tissue engineering trials to date have been predominantly drawn from academic medical center patient bases in

North America and Europe, which do not reflect the demographic composition of the populations most burdened by diabetes. Studies of diabetes care quality have found that racial and ethnic disparities persist even in top-performing healthcare facilities, indicating that institutional quality alone does not eliminate inequity, and that equity must be designed into care pathways explicitly rather than assumed to follow from clinical excellence [82]. If the five technologies reviewed here proceed toward clinical translation without deliberate attention to enrollment diversity, informed consent processes accessible to patients with varying health literacy, and reimbursement pathways that include underinsured populations, they risk becoming treatments that address the biology of diabetes in a narrow eligible population while leaving the most-burdened populations behind [4,80,81].

9.8: Implications for Research Design

These demographic and equity considerations carry direct implications for how tissue engineering research should be designed going forward. Clinical trials for β -cell replacement therapies should prospectively track the racial, ethnic, and socioeconomic composition of enrolled populations and report these as primary demographic outcomes alongside safety and efficacy data [80,81]. Eligibility criteria should be revisited with input from endocrinologists serving underserved populations to assess whether some exclusions, particularly BMI thresholds, are medically necessary or reflect historical assumptions that may disadvantage populations with higher average BMI [3,55,82]. Bioprinted and OoC platforms, as research tools, offer an opportunity to model islet biology across genetically and demographically diverse cell sources before clinical translation, which could improve the generalizability of preclinical findings to the full population of patients who will ultimately need these therapies [60,71,72,78]. A comparative summary of all five strategies is presented in Table 1.

Strategy	Primary diabetic application	Key advantage	Key limitation	Clinical translation status
Biomaterial scaffolds	Islet engraftment, diabetic foot ulcer repair	Structural support, guided cell growth	Immune rejection, degradation control	Preclinical; some diabetic foot ulcer scaffolds in clinical use
Hydrogels	Islet encapsulation, wound healing	Tunable release, injectable, biocompatible	Diffusion limits, mechanical fragility	Preclinical to early clinical; alginate in trials
Encapsulation devices	β -cell replacement,	Immune protection, retrievable	Fibrosis, oxygenation,	Clinical trials ongoing; partial glycemic benefit

	type 1 diabetes		scale-up	shown
3D bioprinting	Bioprinted pancreatic constructs	Spatial precision, multicell architecture	Vascularization, scale-up	Preclinical; no human trials yet
Organ-on-a -chip	Islet physiology modeling, therapy screening	Controlled microenvironment, real-time sensing	Not yet used with encapsulated constructs	Research tool; not a therapy itself

Table 1. *Comparative overview of tissue engineering strategies for diabetes treatment.*

Comparative overview of tissue engineering strategies for diabetes treatment. Summary of the five tissue engineering approaches reviewed, characterized by primary diabetic application, key advantage, key limitation, and current clinical translation status.

9.9: Limitations of This Review

This review has several limitations inherent to its design. As a narrative rather than systematic review, study selection did not follow a formal, pre-registered protocol with dual independent screening; screening and inclusion decisions were made by a single author, which introduces the potential for selection and publication bias, since positive and higher-profile findings are more likely to be published and retrieved. The literature search, while structured across two databases, was not exhaustive and may have missed relevant work indexed elsewhere or published in languages other than English. The field is also evolving rapidly, and conclusions drawn here reflect the evidence available at the time of writing (search conducted June 2026); newer findings may modify the relative standing of the strategies compared. Finally, much of the evidence synthesized: particularly for bioprinting and organ-on-a-chip platforms, remains preclinical, so inferences about eventual clinical performance are necessarily provisional. These limitations should be weighed alongside the synthesis and the framework proposed above.

CONCLUSION

Tissue engineering offers a regenerative strategy for diabetes that directly targets the underlying loss or dysfunction of β -cells, in contrast to current therapies that primarily address glycemic symptoms. Biomaterial scaffolds, hydrogels, and encapsulation devices provide structural and immunoprotective support for transplanted or stem-cell-derived β -cells, while 3D bioprinting enables precise spatial arrangement of multiple cell types into islet-like constructs. Organ-on-a-chip platforms, though not therapies themselves, provide physiologically controlled environments for screening encapsulated constructs and studying β -cell physiology before animal or clinical translation. Across all five strategies,

immune rejection and inadequate vascularization remain the two recurring barriers to clinical success that no individual technology has fully resolved. The most actionable near-term direction is the integration of these technologies into a coherent preclinical screening pipeline rather than continued optimization in isolation. The four-stage framework proposed here, islet-on-a-chip screening, 3D bioprinted tissue modeling, in vivo validation, and structured clinical translation, is designed to address fragmentation at the experimental design level using tools that already exist. Equitable translation of these therapies will additionally require deliberate attention to the structural barriers that currently exclude the populations most burdened by diabetes from both clinical trials and access to advanced care.

REFERENCES

1. Centers for Disease Control and Prevention. Diabetes basics. U.S. Department of Health and Human Services.. (2025). Accessed: 01 January 2025: <https://www.cdc.gov/diabetes/about/index.html>.
2. Katsarou A, Gudbjornsdottir S, Rawshani A, et al.: Type 1 diabetes mellitus. *Nature Reviews Disease Primers*. 2017, 3:17016. 10.1038/nrdp.2017.16
3. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Simonson DC: Type 2 diabetes mellitus. *Nature Reviews Disease Primers*. 2015, 1:15019. 10.1038/nrdp.2015.19
4. Centers for Disease Control and Prevention. National diabetes statistics report. U.S. Department of Health and Human Services. (2024|2025). Accessed: 01 January 2025: <https://www.cdc.gov/diabetes/php/data-research/index.html> .
5. Goyal S, Rani J, Bhat MA, Vanita V: Genetics of diabetes. *World Journal of Diabetes*. 2023, 14:656-679. 10.4239/wjd.v14.i6.656
6. MedlinePlus: Blood glucose. U.S. National Library of Medicine.. (2025). Accessed: 01 January 2025: <https://medlineplus.gov/bloodglucose.html>.
7. van Gerwen J, Shun-Shion AS, Fazakerley DJ: Insulin signalling and GLUT4 trafficking in insulin resistance . *Biochemical Society Transactions*. 2023, 51:1057-1069. 10.1042/BST20221066
8. Mukherjee N, Lin L, Contreras CJ, Templin AT: β -cell death in diabetes: past discoveries, present understanding, and potential future advances. *Metabolites*. 2021, 11:796. 10.3390/metabo11110796
9. Pugliese A: Autoreactive T cells in type 1 diabetes: *Journal of Clinical Investigation*. 2017, 127:2881-2891. 10.1172/JCI94549

10. Cerf ME: Beta cell dysfunction and insulin resistance. *Front Endocrinol.* 2013, 4:37. 10.3389/fendo.2013.00037
11. Nwokolo M, Hovorka R: The artificial pancreas and type 1 diabetes. *J Clin Endocrinol Metab.* 2023, 108:1614-1623. 10.1210/clinem/dgad068
12. Home P, Riddle M, Cefalu WT, et al.: Insulin therapy in people with type 2 diabetes: opportunities and challenges?. *Diabetes Care.* 2014, 37:1499-1508. 10.2337/dc13-2743
13. Shupe T, Atala A: Tissue engineering methods for the production of implantable bioartificial organs . StatPearls. StatPearls Publishing, Treasure Island, FL; 2023.
14. Aigner T, Soder S, Gebhard PM, McAlinden A, Haag J: Mechanisms of disease: role of chondrocytes in the pathogenesis of osteoarthritis — structure, chaos and senescence. *Nature Clinical Practice Rheumatology.* 2007, 3:391-399. 10.1038/ncprheum0534
15. Park S, Rahaman KA, Kim Y, et al.: Fostering tissue engineering and regenerative medicine to treat musculoskeletal disorders in bone and muscle. *Bioactive Materials.* 2024, 40:345-365. 10.1016/j.bioactmat.2024.06.022
16. Smink AM, de Vos P: Polymer scaffolds for pancreatic islet transplantation — progress and challenges . *American Journal of Transplantation.* 2018, 18:2113-2119. 10.1111/ajt.14942
17. Zhang Q, Gonelle-Gispert C, Li Y, Geng Z, Gerber-Lemaire S, Wang Y, Buhler L: Islet encapsulation: new developments for the treatment of type 1 diabetes. *Frontiers in Immunology.* 2022, 13:869984. 10.3389/fimmu.2022.869984
18. Kim H, Cho DW: 3D bioprinting for artificial pancreas organ. *Biofabrication.* 2019, 11:015002. 10.1088/1758-5090/aae534
19. Leung CM, de Haan P, Ronaldson-Bouchard K, et al.: A guide to the organ-on-a-chip. *Nature Reviews Methods Primers.* 2022, 2:33. 10.1038/s43586-022-00118-6
20. Langer R, Vacanti JP: Tissue engineering. *Science.* 1993, 260:920-926. 10.1126/science.8493529
21. Ferreira AM, Gentile P, Chiono V, Ciardelli G: Collagen for bone tissue regeneration. *Acta Biomaterialia.* 2012, 8:3191-3200. 10.1016/j.actbio.2012.06.014
22. Parenteau-Bareil R, Gauvin R, Berthod F: Collagen-based biomaterials for tissue engineering applications . *Materials.* 2010, 3:1863-1887. 10.3390/ma3031863
23. Shoulders MD, Raines RT: Collagen structure and stability. *Annu Rev Biochem.* 2009, 78:929-958. 10.1146/annurev.biochem.77.032207.120833
24. Integra LifeSciences: Integra dermal regeneration template: product information. . (2025). Accessed: 01 January 2025:

<https://products.integralife.com/integra-dermal-regeneration-template/product/wound-reconstruction-care-inpatient-acu....>

25. Yannas IV: Hesitant steps from the artificial skin to organ regeneration . *Regenerative Biomaterials*. 2018, 5:189-195. 10.1093/rb/rby012
26. Lee CH, Singla A, Lee Y: Biomedical applications of collagen. *International Journal of Pharmaceutics*. 2001, 221:1-22. 10.1016/S0378-5173(01)00691-3
27. Rodriguez-Vazquez M, Vega-Ruiz B, Ramos-Zuniga R, Saldana-Koppel DA, Quinones-Olvera LF: Chitosan and its potential use as a scaffold for tissue engineering in regenerative medicine. *BioMed Research International*. 2015, 2015:821279. 10.1155/2015/821279
28. Lee KY, Mooney DJ: Alginate: properties and biomedical applications. *Progress in Polymer Science*. 2012, 37:106-126. 10.1016/j.progpolymsci.2011.06.003
29. Draget KI: Alginates. *Handbook of Hydrocolloids*. Phillips GO, Williams PA (ed: Woodhead Publishing, Cambridge, UK; 2009. 807:828. 10.1533/9781845695873.807
30. Mano JF, Sousa RA, Boesel LF, Neves NM, Reis RL: Bioinert, biodegradable and injectable polymeric matrix composites for hard tissue replacement. *Composites Science and Technology*. 2004, 64:789-817. 10.1016/j.compscitech.2003.09.001
31. Gentile P, Chiono V, Carmagnola I, Hatton PV: An overview of poly(lactic-co-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering. *International Journal of Molecular Sciences*. 2014, 15:3640-3659. 10.3390/ijms15033640
32. Ulery BD, Nair LS, Laurencin CT: Biomedical applications of biodegradable polymers . *Journal of Polymer Science Part B: Polymer Physics*. 2011, 49:832-864. 10.1002/polb.22259
33. Qi B, Ding Y, Zhang Y, Kou L, Zhao YZ, Yao Q: Biomaterial-assisted strategies to improve islet graft revascularization and transplant outcomes. *Biomaterials Science*. 2024, 12:821-836. 10.1039/d3bm01295f
34. Nemati M, Ebrahimi Z, Karbalaee N, Dastghaib S, Khakshournia S, Sargazi M: In vitro and in vivo improvement of islet quality and transplantation successes following islet treatment with biomaterials in diabetic rats. *Journal of Diabetes Research*. 2023, 2023:1399917. 10.1155/2023/1399917
35. Alexiadou K, Doupis J: Management of diabetic foot ulcers. *Diabetes Therapy*. 2012, 3:4. 10.1007/s13300-012-0004-9

36. Mahmoudvand G, Karimi Rouzbahani A, Razavi ZS, Mahjoor M, Afkhami H: Mesenchymal stem cell therapy for non-healing diabetic foot ulcer infection: new insight. *Frontiers in Bioengineering and Biotechnology*. 2023, 11:1158484. 10.3389/fbioe.2023.1158484
37. Cao Y, Gang X, Sun C, Wang G: Mesenchymal stem cells improve healing of diabetic foot ulcer. *Journal of Diabetes Research*. 2017, 2017:9328347. 10.1155/2017/9328347
38. Zhang J, Qu X, Li J, et al.: Tissue sheet engineered using human umbilical cord-derived mesenchymal stem cells improves diabetic wound healing. *International Journal of Molecular Sciences*. 2022, 23:12697. 10.3390/ijms232012697
39. Nalisa DL, Moneruzzaman M, Changwe GJ, et al.: Stem cell therapy for diabetic foot ulcers: theory and practice. *Journal of Diabetes Research*. 2022:6028743. 10.1155/2022/6028743
40. Du S, Zeugolis DI, O'Brien T: Scaffold-based delivery of mesenchymal stromal cells to diabetic wounds . *Stem Cell Res Ther*. 2022, 13:1-15. 10.1186/s13287-022-03115-4
41. Ashimova A, Yegorov S, Negmetzhanov B, Hortelano G: Cell encapsulation within alginate microcapsules: immunological challenges and outlook. *Frontiers in Bioengineering and Biotechnology*. 2019, 7:380. 10.3389/fbioe.2019.00380
42. Ghasemi A, Akbari E, Imani R: An overview of engineered hydrogel-based biomaterials for improved beta-cell survival and insulin secretion. *Frontiers in Bioengineering and Biotechnology*. 2021, 9:662084. 10.3389/fbioe.2021.662084
43. Huan Z, Li J, Luo Z, Yu Y, Li L: Hydrogel-encapsulated pancreatic islet cells as a promising strategy for diabetic cell therapy. *Research*. 2024, 7:0403. 10.34133/research.0403
44. Li L, Wang Y: Advancements in injectable hydrogels for controlled insulin delivery: a comprehensive review of the design, properties and therapeutic applications for diabetes and its complications. *Polymers*. 2025, 17:780. 10.3390/polym17060780
45. Mansoor S, Kondiah PPD, Choonara YE: Advanced hydrogels for the controlled delivery of insulin . *Pharmaceutics*. 2021, 13:2113. 10.3390/pharmaceutics13122113
46. Xiang T, Guo Q, Jia L, Yin T, Huang W, Zhang X, Zhou S: Multifunctional hydrogels for the healing of diabetic wounds. *Advanced Healthcare Materials*. 2024, 13:2301885. 10.1002/adhm.202301885
47. Bercea M, Lupu A: Recent insights into glucose-responsive concanavalin A-based smart hydrogels for controlled insulin delivery. *Gels*. 2024, 10:260. 10.3390/gels10040260

48. Pal S, Rakshit T, Saha S, Jinagal D: Glucose-responsive materials for smart insulin delivery: from protein-based to protein-free design. *ACS Mater Au.* 2025, 5:239-252.
10.1021/acsmaterialsau.4c00138
49. Keymeulen B, De Groot K, Jacobs-Tulleneers-Thevissen D, Thompson DM, Bellin MD, Kroon EJ, Pipeleers D: Encapsulated stem cell-derived beta cells exert glucose control in patients with type 1 diabetes: *Nature Biotechnology.* 2024, 42:1507-1514. 10.1038/s41587-023-02055-5
50. Raoufinia R, Motalebnejad P, Ghanbari A, Keyhanvar N, Talebi M: Advances and challenges of the cell-based therapies among diabetes treatments. *J Transl Med.* 2024, 22:433.
10.1186/s12967-024-05226-3
51. Waris S, Hameetha Begam H, Praveen Kumar M, et al.: Stem cell-derived beta-cell therapies: encapsulation advances and immunological hurdles in diabetes treatment. *Cells.* 2026, 15:191.
10.3390/cells15020191
52. Neumann M, Arnould T, Su BL: Encapsulation of stem-cell derived β -cells: a promising approach for the treatment for type 1 diabetes mellitus. *Journal of Colloid and Interface Science.* 2023, 636:90-102. 10.1016/j.jcis.2022.12.123
53. Veres A, Faust AL, Bushnell HL, et al.: Charting cellular identity during human in vitro beta-cell differentiation. *Nature.* 2019, 569:368-373. 10.1038/s41586-019-1168-5
54. Vegas AJ, Veisheh O, Gurtler M, et al.: Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. *Nature Medicine.* 2016, 22:306-311. 10.1038/nm.4030
55. Ermakova P, Vasilchikova E, Baten'kin M, et al.: Probing of new polymer-based microcapsules for islet cell immunoisolation. *Polymers.* 2024, 16:2479. 10.3390/polym16172479
56. Jeong W, Perrier Q, Rengaraj A, et al.: Scalable 3D bioprinting of human islets in a pancreatic decellularized extracellular matrix-enriched bioink for beta-cell replacement therapy. *bioRxiv.* 2025, 10.1101/2025.06.06.658360
57. Salg GA, Poisel E, Neulinger-Munoz M, et al.: Toward 3D-bioprinting of an endocrine pancreas: a building-block concept for bioartificial insulin-secreting tissue. *Journal of Tissue Engineering.* 2022, 13:20417314221091033. 10.1177/20417314221091033
58. Duin S, Schutz K, Ahlfeld T, Lehmann S, Lode A, Ludwig B, Gelinsky M: 3D bioprinting of functional islets of Langerhans in an alginate/methylcellulose hydrogel blend. *Advanced Healthcare Materials.* 2019, 8:1801631. 10.1002/adhm.201801631

59. Donath MY: Type 1 diabetes: what is the role of autoimmunity in beta cell death? . J Clin Invest. 2022, 132:164460. 10.1172/JCI164460
60. Zhu B, Wang D, Pan H, Gong T, Ren Q, Wang Z, Guo Y: Three-in-one customized bioink for islet organoid: GelMA/ECM/PRP orchestrate pro-angiogenic and immunoregulatory function. Colloids Surf B Biointerfaces. 2023, 221:113017. 10.1016/j.colsurfb.2022.113017
61. Su Y, Ding S, Liu T, et al.: Bioprinting vascularized human islet tissue models via aggregate-based co-culture and self-assembly. International Journal of Bioprinting. 2025, 11:025360368. 10.36922/IJB025360368
62. Soetedjo AAP, Lee JM, Lau HH, et al.: Tissue engineering and 3D printing of bioartificial pancreas for regenerative medicine in diabetes. Trends in Endocrinology and Metabolism. 2021, 32:609-622. 10.1016/j.tem.2021.05.007
63. Daly AC, Prendergast ME, Hughes AJ, Burdick JA: Bioprinting for the biologist. Cell. 2021, 184:18-32. 10.1016/j.cell.2020.12.002
64. Tsakmaki A, Fonseca Pedro P, Bewick GA: Diabetes through a 3D lens: organoid models . Diabetologia. 2020, 63:1093-1102. 10.1007/s00125-020-05126-3
65. Ghosh A, Sanyal A, Mallick A: Recent advances in the development of bioartificial pancreas using 3D bioprinting for the treatment of type 1 diabetes: a review. Exploratory Medicine. 2023, 4:886-922. 10.37349/emed.2023.00184
66. Edri S, Newman Frisch A, Safina D, et al.: 3D bioprinting of multicellular stem cell-derived constructs to model pancreatic cell differentiation. Advanced Functional Materials. 2024, 34:2315488. 10.1002/adfm.202315488
67. Ingber DE: Human organs-on-chips for disease modelling, drug development and precision medicine. Nature Reviews Genetics. 2022, 23:739-757. 10.1038/s41576-022-00466-9
68. Rogal J, Zbinden A, Schenke-Layland K, Loskill P: Stem-cell based organ-on-a-chip models for diabetes research. Advanced Drug Delivery Reviews. 2019, 140:101-128. 10.1016/j.addr.2018.10.010
69. Zhang B, Radisic M: Organ-on-a-chip devices advance to market. Lab Chip: 2017, 17:2395-2420. 10.1039/C6LC01554A
70. Sosa-Hernandez JE, Villalba-Rodriguez AM, Romero-Castillo KD, et al.: Organs-on-a-chip module: a review from the development and applications perspective. Micromachines. 2018, 9:536. 10.3390/mi9100536

71. Regeenes R, Rocheleau JV: Twenty years of islet-on-a-chip: microfluidic tools for dissecting islet metabolism and function. *Lab on a Chip*. 2024, 24:1327-1350. 10.1039/D3LC00696D
72. Rodriguez-Comas J, Ramon-Azcon J: Islet-on-a-chip for the study of pancreatic beta-cell function. *In Vitro Models*. 2021, 1:1-15. 10.1007/s44164-021-00005-6
73. Tao T, Wang Y, Chen W, et al.: Engineering human islet organoids from iPSCs using an organ-on-chip platform. *Lab on a Chip*. 2019, 19:948-958. 10.1039/C8LC01298A
74. Bauer S, Hultdt CW, Kanebratt KP, Durieux I, Gunne D, Andersson S, Andersson TB: Functional coupling of human pancreatic islets and liver spheroids on-a-chip. *Nature*. 2017, 7:14620. 10.1038/s41598-017-14815-w
75. Goswami I, de Klerk E, Carnese P, Hebrok M, Healy KE: Multiplexed microfluidic platform for stem-cell derived pancreatic islet β cells. *Lab Chip*. 2022, 22:4430-4442. 10.1039/d2lc00468b
76. Sun J, Wu Z, Li J, Shang L, Zhao Y, Li L: Organs-on-a-chip recapitulating the gut-islets axis for endocrine hormone secretion regulator evaluation. *Research*. 2025, 8:0923. 10.34133/research.0923
77. Low LA, Mummery C, Berridge BR, Austin CP, Tagle DA: Organs-on-chips: into the next decade. *Nature Reviews Drug Discovery*. 2021, 20:345-361. 10.1038/s41573-020-0079-3
78. Ingber DE: Is it time for reviewer 3 to request human organ chip experiments instead of animal validation studies?. *Advanced Science*. 2018, 7:2002030. 10.1002/advs.202002030
79. Skardal A, Shupe T, Atala A: Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. *Drug Discovery Today*. 2016, 21:1399-1411. 10.1016/j.drudis.2016.07.003
80. Kanbour S, Jones M, Abusamaan MS, et al.: Racial disparities in access and use of diabetes technology among adult patients with type 1 diabetes in a U.S. academic medical center. *Diabetes Care*. 2023, 46:56-64. 10.2337/dc22-1055
81. Ndugga N, Pillai D, Artiga S: Racial and ethnic disparities in access to medical advancements and technologies. *KFF*. 202412025,
82. Wong MS, Tseng CH, Moy E, Jones KT, Kothari AJ, Washington DL: Relationship between health system quality and racial and ethnic equity in diabetes care. *Health Affairs Scholar*. 2024, 2:073. 10.1093/haschl/qxae073

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