

# Multimodal Therapeutics for Grade 1 Diabetic Foot Ulcers: Challenges and Breakthroughs

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## Abstract

Diabetic foot ulcers (DFUs) are a significant complication of diabetes, with Grade 1 ulcers representing a critical early-stage opportunity for intervention. This review article synthesizes current knowledge on the pathophysiology of Grade 1 DFUs and evaluates the challenges and breakthroughs in multimodal therapeutic approaches. We explore the limitations of conventional wound care and highlight the potential of innovative topical delivery systems, including nanotechnology-based carriers, hydrogel formulations, and bioengineered scaffolds. Furthermore, we discuss the integration of Quality by Design (QBD) principles to optimize therapeutic development. The insights presented in this review underscore the importance of a comprehensive, multidisciplinary approach to DFU management, paving the way for more effective, personalized, and patient-centered treatment strategies to prevent ulcer progression and reduce the risk of amputation.

**Keywords:** Diabetic Foot Ulcer (DFU), Grade 1, Multimodal Therapy, Nanotechnology, Hydrogels, Bioengineered Scaffolds, Quality by Design (QBD)

## 1. Introduction

Diabetic foot ulcers (DFUs) affect a substantial portion of the diabetic population, with estimates suggesting that 15–25% of individuals with diabetes will develop a foot ulcer in their lifetime [1]. These ulcers are a leading cause of non-traumatic lower extremity amputations and are associated with a five-year mortality rate that is higher than many cancers [2]. The economic burden of DFUs is also immense, with annual costs for treatment exceeding \$9 billion in the United States alone [3]. Given the high prevalence and severe consequences, effective management of DFUs remains a top priority in diabetes care. Grade 1 DFUs, characterized as superficial ulcers confined to the skin without deep tissue, bone, or joint involvement, represent a crucial point for early intervention. This stage provides a critical window of opportunity to implement therapies that can prevent the ulcer from progressing to a more severe state, which often involves infection, tissue necrosis, and a heightened risk of amputation. The initial focus of treatment at this

stage is to create an optimal healing environment and address the underlying causes of the ulcer before complications arise.

## 2. Pathophysiology and Classification of Grade 1 DFUs

The development of Grade 1 DFUs is driven by a complex interplay of factors, primarily peripheral neuropathy, peripheral arterial disease (PAD), and biomechanical stress [4]. Diabetic peripheral neuropathy, a direct consequence of chronic hyperglycemia, leads to sensory, motor, and autonomic dysfunction. Sensory neuropathy results in a loss of protective sensation, leaving patients unaware of minor traumas from friction or pressure. Motor neuropathy causes muscle atrophy and structural foot deformities, creating high-pressure points, while autonomic neuropathy impairs sweat gland function, leading to dry, cracked skin that is more susceptible to breakdown.

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Beyond neuropathy, underlying vascular and metabolic changes play a critical role. **Peripheral arterial disease (PAD)** is common in diabetic patients and leads to reduced blood supply to the lower extremities, resulting in tissue hypoxia and delayed wound healing. Furthermore, chronic hyperglycemia impairs the body's natural wound healing response by affecting multiple cellular processes. It activates the **polyol pathway**, leading to oxidative stress and nerve damage, and promotes the formation of **Advanced Glycation End Products (AGEs)**, which stiffen the extracellular matrix and impair cellular function [5]. The accumulation of AGEs also triggers a pro-inflammatory response that hinders the healing cascade.

Accurate classification of DFUs is essential for guiding treatment and predicting outcomes. Several systems exist, each with a different focus. The **Wagner-Meggitt system**, for example, is a simple, depth-based classification where a Grade 1 ulcer is superficial [6]. While useful for surgical decision-making, it does not account for critical factors like infection or ischemia. The **University of Texas (UT) Diabetic Wound Classification system** improves upon this by introducing a dual-axis system, where Grade I, Stage A represents a superficial ulcer that is both non-infected and non-ischemic [7]. This system provides a more comprehensive picture for clinical assessment.

More advanced systems like the **PEDIS (Perfusion, Extent, Depth, Infection, Sensation)** and **SINBAD (Site, Ischemia, Neuropathy, Bacterial infection, Area, Depth)** classifications are often used in clinical research due to their multi-factorial scoring [8,9]. A Grade 1 ulcer under the PEDIS system is a superficial wound with intact perfusion and no signs of infection. Similarly, a low SINBAD score typically indicates a superficial, non-infected, and non-ischemic ulcer. Understanding these different classification systems is vital for standardized assessment, comparison of treatment outcomes, and for tracking a patient's progress over time.

### 3. Innovative Topical Delivery Approaches

The advent of novel drug delivery systems has opened new avenues for treating Grade 1 DFUs. These systems are designed to overcome the limitations of conventional therapies by enhancing drug stability, ensuring controlled release, and improving drug penetration to the wound bed. These technologies provide a platform for delivering a combination of therapeutic agents, such as antimicrobial drugs, growth factors, and anti-inflammatory compounds, directly to the site of injury.

#### 3.1. Nanotechnology-Based Carriers

Nanoparticles, such as **liposomes**, **niosomes**, and **nanoemulsions**, offer a powerful means of delivering therapeutic agents. The small size of these carriers allows them to penetrate the complex wound bed more effectively, and their high surface-area-to-volume ratio allows for the encapsulation of a wide range of drugs, from small molecules to large protein-based growth factors [10]. This encapsulation protects the drugs from premature degradation by wound enzymes and provides a controlled-release mechanism, ensuring a sustained therapeutic effect over a longer period. A key application

of nanotechnology in DFU treatment is in combating infection. For instance, **silver nanoparticles (AgNPs)** have demonstrated potent, broad-spectrum antimicrobial properties, and can be incorporated into wound dressings or hydrogels to prevent and treat local infections without the systemic side effects of oral antibiotics [11-13].

#### 3.2. Hydrogel-Based Formulations

Hydrogels are polymeric networks with a high water content, making them ideal for creating and maintaining a moist wound environment, which is known to be optimal for healing [14].

A major breakthrough in hydrogel technology is the development of "smart" or bio-responsive hydrogels. These systems can be engineered to release encapsulated drugs in response to changes in the wound environment, such as variations in pH, temperature, or the presence of specific enzymes [15,16].

##### 3.2.1. Smart Hydrogels

A major advancement highlighted in the Canvas is the development of "smart" or **bio-responsive hydrogels**. These innovative systems can be engineered to release drugs based on changes in the wound's environment. For example, a smart hydrogel could be designed to release an antibiotic only when it detects a specific enzyme produced by bacteria. This allows for targeted therapy, which minimizes harm to healthy tissue. Similarly, they can release growth factors at a precise moment in the healing process.

##### 3.2.2. What are Smart Hydrogels?

**Smart hydrogels**, also known as "bio-responsive hydrogels," are advanced polymeric materials that can undergo a significant physical or chemical change in response to a specific environmental stimulus. This targeted and on-demand delivery system is a major advancement over conventional topical therapies, which often provide a constant, non-responsive release of medication [20].

##### 3.2.3. How Do They Work?

The "intelligence" of these hydrogels is derived from their chemical composition. The polymer chains are designed with specific functional groups that are sensitive to various stimuli found in a healing or infected wound bed.

##### 3.2.4. Applications in Diabetic Foot Ulcer Treatment

Smart hydrogels are particularly promising for **Grade 1 diabetic foot ulcers** because they can address multiple issues simultaneously and adapt to the changing nature of the wound [1].

- **Targeted Antimicrobial Delivery:** A smart hydrogel can be designed to release an antimicrobial agent only when a bacterial infection is detected (e.g., via a drop in pH or the presence of bacterial enzymes), preventing infection from taking hold without unnecessary drug exposure.
- **Controlled Release of Growth Factors:** The chronic, non-healing nature of diabetic wounds is often due to a deficiency of critical growth factors. A smart hydrogel can be engineered to release growth factors in response to the specific chemical signals of a stalled wound healing phase, kickstarting the

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process and promoting tissue regeneration.

- **Dual-Action Functionality:** Hydrogels can be loaded with multiple therapeutic agents. A single hydrogel could, for example, contain a pH-sensitive component for antimicrobial release and a temperature-sensitive component for anti-inflammatory drug release, providing a truly multimodal therapeutic solution that responds to different phases of the healing process [2].

### 3.2.5. Advantages Over Conventional Dressings

The primary advantage of smart hydrogels lies in their ability to provide **on-demand, personalized therapy**. By providing a stable, moist, and responsive environment, smart hydrogels represent a significant step toward more intelligent and effective wound care for diabetic patients [21].

### 3.3. Bioengineered Scaffolds

Bioengineered scaffolds provide a physical matrix that mimics the natural extracellular matrix (ECM) of healthy skin, offering a structural template for cell migration, proliferation, and differentiation. These advanced dressings are a major breakthrough, moving beyond passive protection to active wound healing promotion. They can be derived from natural polymers such as collagen and hyaluronic acid, or synthetic materials like polylactic acid (PLA) and polyglycolic acid (PGA), each offering unique advantages in terms of biocompatibility, biodegradability, and mechanical properties [17].

The true potential of these scaffolds lies in their ability to be functionalized with a range of therapeutic agents. They can be loaded with growth factors, such as platelet-derived growth factor (PDGF) or vascular endothelial growth factor (VEGF), to actively stimulate angiogenesis and granulation tissue formation [18]. They can also be integrated with antimicrobial agents to prevent infection or with anti-inflammatory molecules to modulate the immune response. By providing both a physical and biological environment conducive to healing, these bioengineered materials offer a more effective alternative to traditional dressings for complex or slow-healing wounds.

Furthermore, the development of **microneedle patches** can be considered a type of bioengineered scaffold, where a matrix of tiny needles painlessly pierces the stratum corneum to deliver drugs directly into the skin, bypassing the need for an injection and offering a new paradigm for localized drug delivery.

#### 3.3.1. Applications in Diabetic Foot Ulcer Treatment

Bioengineered scaffolds are particularly effective for Grade 1

diabetic foot ulcers because they go beyond a simple protective barrier to actively promote regeneration. They are a powerful tool for preventing a minor, superficial wound from progressing into a chronic, non-healing ulcer.

- **Promoting Tissue Regeneration:** The scaffold's matrix provides a perfect environment for cell growth, helping to form healthy granulation tissue and facilitate re-epithelialization. This is critical in diabetic wounds where the natural healing process is impaired.
- **Targeted Delivery of Therapeutics:** The scaffolds can be functionalized with a range of therapeutic agents to provide a truly multimodal approach. They can be loaded with growth factors, such as platelet-derived **growth factor** (PDGF) or vascular endothelial growth factor (VEGF), to actively stimulate angiogenesis (new blood vessel formation) [1]. They can also be integrated with **antimicrobial agents** or **anti-inflammatory molecules** to simultaneously combat infection and modulate the chronic inflammation that can hinder healing.
- **Replacing Damaged Tissue:** In some cases, bioengineered scaffolds are used as skin substitutes. They can be designed as a two-layer structure to replace both the dermal and epidermal layers of damaged skin, providing a durable cover while promoting the regeneration of the underlying tissue [2].

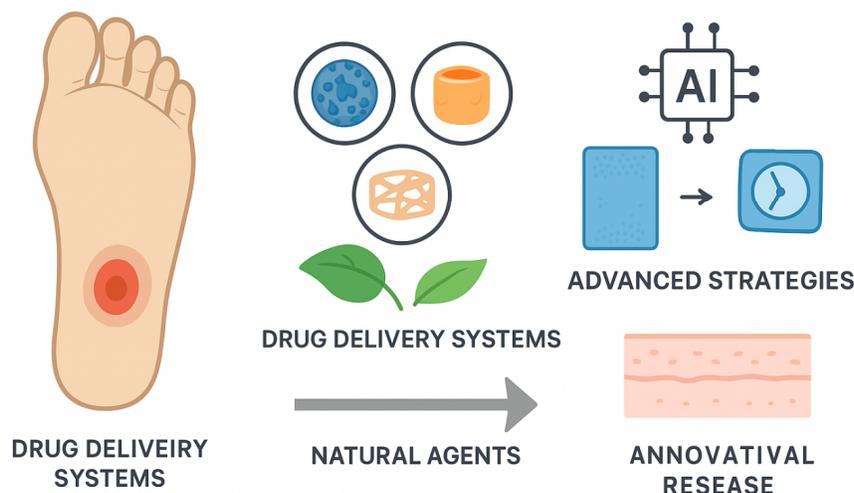
### 3.3.2. Advantages Over Conventional Dressings

The key advantage of bioengineered scaffolds is their active role in wound healing. While conventional dressings are primarily passive, providing a moist environment and protection from external contaminants, scaffolds actively participate in the regenerative process. By providing physical support, guiding cell growth, and delivering therapeutic agents, these scaffolds can significantly reduce healing time, lower the risk of infection, and prevent the severe complications that can arise from a Grade 1 ulcer [21].

## 4. Quality by Design (QbD) in DFU Treatment Development

The **Quality by Design (QbD)** approach is a systematic, risk-based methodology for pharmaceutical development that ensures the safety, efficacy, and consistency of the final product [19]. It represents a paradigm shift from traditional quality control, which focuses on testing the final product, to a proactive approach that builds quality into the product from the very beginning. By applying QbD to DFU treatments, researchers can create more robust and reliable therapeutic solutions. The first step in the QbD process is to **Define a Target Product Profile (TPP)**. This involves clearly outlining the desired characteristics of the therapeutic product from the patient's perspective.

## ADVANCES IN THE TREATMENT OF GRADE 1 DIABETIC FOOT ULCER:



**Figure 1:** Advances in The Diabetic Foot Ulcer Grade I treatment

Advances in the treatment of Grade 1 diabetic foot ulcer include drug delivery systems (niosomes, hydrogels, nanofibers), integration of natural agents (curcumin, aloe vera, honey, chitosan), advanced strategies such as artificial intelligence for wound monitoring and personalized therapy, and innovative drug release approaches enabling controlled and sustained delivery (Boulton et al., 2023; Game et al., 2022; Khanna et al., 2021; Li et al., 2020; Wang et al., 2021).

Next, researchers must **Identify Critical Quality Attributes (CQAs)**. These are the physical and chemical properties of the drug product that are critical to its performance. For a DFU hydrogel, CQAs might include the pH, viscosity, drug loading capacity, and the rate of drug release.

Finally, a **Design Space** is established. This is a multidimensional space of input parameters and process variables that have been demonstrated to provide assurance of quality. The Design Space defines the acceptable range of manufacturing conditions (e.g., temperature, mixing speed, polymer concentration) that will consistently produce a product meeting the CQAs. This systematic approach minimizes trial-and-error, reduces risks, and leads to more robust and reliable therapeutic solutions for DFUs.

### 4.1. Current Treatment Protocols for Grade 1 DFUs:

- **Pressure Off-Loading:** This is considered the mainstay of initial treatment. Methods include using total contact casts, removable cast walkers, or specialized footwear. Knowledge of proper footwear and offloading is crucial for prevention and healing. Patient adherence to pressure reduction regimens can be a challenge.
- **Wound Care and Dressings:** The goal is to provide a moist environment, absorb exudate, and act as a barrier.
- **Debridement:** Sharp debridement of non-viable or necrotic

tissue is critical to allow full visualization of the ulcer's extent and promote healing. Surgical debridement is often the preferred method, promoting granulation tissue formation and re-epithelialization, and aiding in infection control.

- **Dressings:** Conventional dressings like semipermeable films, foams, hydrocolloids, and calcium alginate swabs are used to maintain a moist wound environment.
- **Infection Management:** Prompt and aggressive treatment of any underlying infection is paramount, typically involving antibiotics.
- **Glycemic Control:** Strict management of blood glucose levels is a critical factor in both preventing and managing DFUs, though it is often insufficient for complete ulcer resolution on its own.

### 4.2. Emerging and Advanced Therapies for Grade 1 DFUs:

- **Bioengineered Skin Substitutes:** A new autologous skin construct has been applied to Wagner grade 1 DFUs in clinical trials. Bioengineered skin substitutes like Apligraf are also used for full-thickness neuropathic DFUs that haven't responded to conventional therapy.
- **Keratin-Based Grafts:** A multicenter clinical trial evaluated a human keratin matrix graft for chronic Wagner grade 1 DFUs, showing high rates of complete healing with both weekly and bi-weekly applications.
- **Botanical-Based Gels:** A botanical-based hydrogel has shown promising results in clinical trials for DFUs, demonstrating comparable healing outcomes to standard hydrogels and superior pain reduction.
- **Transforming Powder Dressings:** A clinical trial is comparing standard of care wound dressings with a transforming powder dressing for Wagner grade 1 or 2 DFUs.

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### 4.3. Potential Role of Smart Wound Dressings for Grade 1 DFUs:

While specific smart dressing trials for Grade 1 DFUs are not extensively detailed, the general capabilities of smart wound dressings could offer significant benefits:

- **Real-time Monitoring:** Smart dressings can continuously monitor critical parameters like temperature, pH, and moisture levels. For Grade 1 ulcers, this could help detect early signs of inflammation or infection (e.g., a temperature increase of 2.2 °C or an alkaline pH shift), allowing for timely intervention before the ulcer progresses to a higher grade or becomes severely infected.
- **Targeted Therapy:** Some smart dressings can deliver therapeutic agents, such as antimicrobials or anti-inflammatory drugs, directly to the wound site in a controlled manner. This localized delivery could be beneficial for Grade 1 ulcers to prevent infection or manage localized inflammation, minimizing systemic side effects.
- **Remote Monitoring:** The telehealth capabilities of smart dressings allow healthcare professionals to monitor wound healing remotely. This is particularly useful for patients with limited mobility or those in remote areas, ensuring continuous care without frequent in-person visits.
- **Patient Comfort and Adherence:** Smart dressings are designed to be thin, flexible, and comfortable, potentially reducing the need for frequent dressing changes and minimizing discomfort, which can improve patient adherence to treatment regimens.

#### 4.3.1. Enhanced Diagnosis and Monitoring

AI and ML can help healthcare professionals, and even patients, with early detection and continuous monitoring.

- **Image Analysis:** ML models can be trained on large datasets of wound images to automatically classify the severity and type of an ulcer, including identifying Grade 1 ulcers. This helps in early diagnosis and ensures the correct treatment is started promptly. Some AI-powered smartphone apps allow patients or caregivers to take a photo of the wound for an initial assessment, which can be particularly useful in remote monitoring.
- **Thermal Imaging:** AI algorithms can analyze thermal images of the foot to detect subtle temperature changes that may indicate the early onset of inflammation or an ulcer before it is visible to the naked eye. This kind of predictive screening can enable preventative interventions even before a Grade 1 ulcer forms.
- **Predictive Analytics:** ML models can analyze various patient data points—such as blood glucose levels, blood pressure, patient history, and activity levels—to predict a person's risk of developing a foot ulcer. This allows for proactive care and targeted preventive measures for high-risk individuals.

#### 4.3.2. Optimizing Treatment Plans

Once a Grade 1 ulcer is diagnosed, AI and ML can help personalize the treatment.

- **Off-loading Prescription:** One of the most critical aspects of Grade 1 ulcer treatment is off-loading, or reducing pressure on

the wound. AI can analyze biomechanical data from pressure-sensor insoles to provide personalized recommendations for the most effective off-loading devices and footwear. This can help ensure that the treatment is tailored to the individual's specific gait and foot anatomy.

- **Wound Healing Prediction:** By analyzing various factors like wound size, depth, and patient health markers, ML models can predict the likelihood of an ulcer healing within a specific timeframe. This helps clinicians and patients set realistic expectations and adjust the treatment plan if the wound is not progressing as expected.
- **Genomic and Molecular Insights:** Advanced ML techniques are being used to analyze a patient's gene expression and other molecular data to identify specific genes that influence the healing process. This research aims to develop highly personalized, "molecularly informed" wound care strategies in the future.

### 5. Summary

For a Grade 1 diabetic foot ulcer, AI and ML are not a replacement for traditional treatments like proper wound care and off-loading. Instead, they serve as powerful tools to enhance and personalize these existing treatments. The technologies help with **early detection and risk prediction, streamlining diagnosis, and optimizing off-loading and wound care** by providing data-driven insights. While research is ongoing, these technologies have the potential to significantly improve patient outcomes and reduce the risk of more serious complications.

#### 5.1. Advanced Image Analysis for Diagnosis and Classification

The goal of using AI for image analysis is to move from subjective visual assessments to objective, data-driven wound care.

- **Deep Learning for Classification:** Using deep learning models, particularly Convolutional Neural Networks (CNNs), researchers are developing systems that can analyze a digital photograph of a foot ulcer and automatically classify its grade (e.g., Wagner Grade 1, 2, etc.). These models are trained on thousands of labeled images, allowing them to identify subtle visual cues that a human eye might miss. For a Grade 1 ulcer, this means the system can confidently confirm its superficial nature and lack of infection signs, helping to ensure the correct initial treatment protocol is followed.
- **Wound Measurement and Segmentation:** AI can also precisely measure the size (length, width, and depth) and surface area of an ulcer from an image. This provides an objective, consistent method for tracking healing progress over time. The AI can "segment" the wound from the surrounding healthy skin, providing a clear visual and numerical record that is more reliable than manual measurements.
- **Predicting Healing Outcomes:** By analyzing the color, texture, and size of the wound over multiple visits, AI can predict the probability of the ulcer healing within a specific timeframe. If the model predicts a poor healing trajectory, it can alert the clinician to re-evaluate the treatment plan,

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potentially suggesting a more aggressive approach.

### 5.2. Personalized Off-Loading Strategies

Off-loading is the single most important treatment for a Grade 1 ulcer, and AI is revolutionizing how it's done.

- **Smart Insoles and Wearable Sensors:** This is a major area of innovation. Insoles embedded with pressure and temperature sensors are worn by patients daily. These sensors collect real-time data on plantar pressure distribution, foot temperature, and gait patterns.
- **Machine Learning for Pressure Analysis:** The data from these smart insoles is fed into an ML model, which analyzes patterns to identify specific "hot spots" of high pressure. For a Grade 1 ulcer, the model can tell if the off-loading device (e.g., specialized shoe or cast) is working effectively or if pressure is still being applied to the ulcer site.
- **Automated Feedback and Alerts:** If the ML model detects excessive pressure or a significant temperature increase (which can be an early sign of inflammation or infection), it can send an alert to the patient's smartphone or a healthcare provider. This proactive, real-time feedback can empower patients to adjust their activity or seek medical advice before the Grade 1 ulcer worsens.
- **AI-Driven Customization:** In the future, AI models could take data from a patient's foot scan and gait analysis to design and even 3D-print a perfectly customized off-loading insole. This ensures the pressure redistribution is precise and highly effective for that individual's unique foot structure.

### 5.3. Remote Monitoring and Telemedicine

AI and ML are enabling a new era of remote care, which is particularly beneficial for diabetic foot ulcer management.

- **Mobile Health (mHealth) Apps:** AI-powered mobile apps allow patients to monitor their own foot health. They can take photos of their foot, which an AI model can analyze to check for signs of worsening. The apps can also send reminders for daily foot inspections, proper foot hygiene, and medication adherence.
- **Clinical Decision Support Systems (CDSS):** An AI-powered CDSS can integrate data from a patient's electronic health records (EHRs), lab results, and wearable sensors. When a clinician inputs a Grade 1 ulcer diagnosis, the system can provide evidence-based recommendations for off-loading, wound dressings, and follow-up schedules. This ensures consistency of care and helps clinicians make more informed decisions.
- **Predictive Risk Stratification:** ML models can analyze a combination of clinical, demographic, and lifestyle data to identify patients at a high risk of developing a Grade 1 ulcer or progressing to a more severe grade. This allows for targeted, preventative interventions, such as prescribing smart insoles

or enrolling the patient in an intensive foot care education program, even before a wound develops. In essence, AI and ML are shifting the paradigm from reactive to proactive care. They are not replacing the human clinician but rather augmenting their ability to make better, faster, and more personalized decisions, ultimately improving outcomes for patients with Grade 1 diabetic foot ulcers.

### 6. Conclusion

Multimodal therapeutic strategies represent a significant step forward in the treatment of Grade 1 DFUs. By combining conventional care with innovative topical drug delivery systems and systematic development approaches like QbD, we can address the key challenges of DFU management, which are often compounded by the complex pathophysiology of diabetes. The breakthroughs in nanotechnology, hydrogels, and bioengineered scaffolds offer powerful tools to accelerate healing and prevent progression. Moving forward, a focus on personalized medicine and the adoption of cutting-edge technologies will be essential to reduce the morbidity and economic burden of this pervasive diabetic complication, ultimately improving the quality of life for millions of patients.

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