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Diabetes Mellitus: New Novel Approaches For Treatment

Sultan Abdullah Al-Khamash[1], Mohammed Naif Alotaibi[2], Khalid Ahmed Ali Alshahrani[3], Hamad Turki Alzaidi[4], Aeshah hussain Abuhadiya[5], Abdullatif Abdullah Mesfer Alotaibi[6], Mohammed Saeed Alalawi[7], Turki Hamood Alotaibi[8], Muhammad Khalaf Al-Ruwais[9], Mohammad Hijab Alotaibi[10], Mohammad Hmood Moneer Alotaibe[10], Zaben Hazze Alotaibi[10]

Abstract

Diabetes mellitus (DM) represents a spectrum of chronic metabolic disorders characterized by persistent hyperglycemia, or elevated blood sugar levels. This condition arises from either insufficient insulin production by pancreatic β-cells (Type 1 DM) or impaired insulin action in target tissues (Type 2 DM). The global prevalence of diabetes is projected to rise significantly in the coming decades, highlighting the urgent need for improved treatment strategies. While current therapies, including anti-diabetic drugs like metformin and GLP-1 receptor agonists, offer some degree of glycemic control, they often fall short of achieving complete normalization. This review explores the pathophysiology of DM, delving into the role of insulin signaling and glucose metabolism. Additionally, it examines the limitations of current pharmacological interventions and emphasizes the ongoing research efforts directed towards developing more efficacious and holistic treatment approaches.

Keywords *Diabetes mellitus, hyperglycemia, insulin, insulin resistance, anti-diabetic drugs.*

Introduction

Diabetes mellitus (DM) is a chronic, non-communicable disease characterized by persistent hyperglycemia, or ele[1]vated blood sugar levels (1). This disruption in carbohydrate metabolism arises from three main factors: insulin resistance, inadequate insulin secretion by pancreatic beta cells, and excessive glucagon secretion (2). The global burden of DM is significant and projected to rise dramatically, becoming a major public health concern. The primary chronic complications associated with DM can be categorized into microvascular (stroke, cardiovascular disease, and peripheral artery disease) and macrovascular (nephropathy, neuropathy, and retinopathy) complications (3). Notably, microvascular complications are more prevalent than macrovascular ones. The high prevalence, significant health consequences,

[1]Pharmacy technician,Al-Sail Al-Kabeer Health Center, Saudi Arabia.
[2]Technician pharmacy,King abdulaziz hospital- Makkah, Saudi Arabia.
[3]Bachelor in Pharmaceutical Sciences,Al-Jumum General Hospital, Saudi Arabia.
[4]Technician pharmacy,Vectors Borne and Zonatic Control, Saudi Arabia.
[5]Pharmacy technician, Maternity and Children's Hospital in Al-Kharj, Saudi Arabia.
[6]PHARMACIST, HAJRAH GENERAL HOSPITAL, Saudi Arabia.
[7]Assistant pharmacist, King abdulaziz hospital Jeddah, Saudi Arabia.
[8]Pharmacy technician, Compliance Assist Administration, Compliance Third West Office, Al Duwadimi, Saudi Arabia
[9]Pharmacy technician, Third Health Cluster - Dawadmi Hospital, Saudi Arabia.
[10]Pharmacy technician, Health Affairs in Riyadh Region, Saudi Arabia.

and rising treatment costs associated with DM highlight the critical need for early diagnosis and improved management strategies (4).

DM management encompasses a multi-pronged approach, incorporating lifestyle modifications, oral medications, and insulin therapy. Lifestyle modifications form the cornerstone of management, particularly for type 2 diabetes (T2DM) (5).

The field of DM management is undergoing a transformation thanks to the emergence of promising novel approaches. One area of significant advancement lies in nanotechnology-based insulin delivery systems (6). These systems aim to enhance the precision, efficiency, and patient compliance associated with insulin therapy (7). For instance, nanoparticles with unique optical and electrical properties offer the potential to develop sensitive glucose sensors for real-time blood sugar monitoring (8). Additionally, smart insulin delivery systems are being developed using advanced technologies. These systems hold the potential for precise and automated control over insulin administration, potentially improving glycemic control and minimizing the risk of complications associated with DM (9). In this review, we aim to explore the new targets that could be the future of the diabetes treatment.

Current Treatment Protocols for Diabetes

The current pharmacological landscape for DM management features established medications like insulin, sulfonylureas, metformin, and various other oral hypoglycemic agents (10). While these therapies play a crucial role, their limitations are becoming increasingly apparent. Existing medications often fail to achieve long-term glycemic control and can be associated with adverse effects like hypoglycemia, organ dysfunction, and increased cardiovascular risk (11).

This pressing need for improved management strategies has sparked a surge in research and development efforts focused on novel therapeutic approaches (12). Promising avenues include the exploration of medicinal plants and their bioactive compounds. These naturally occurring substances exhibit diverse therapeutic effects, potentially impacting insulin synthesis, secretion, and peripheral resistance, while also mitigating inflammation and oxidative stress associated with DM (13). Furthermore, advancements in personalized medicine are fostering the development of novel formulations tailored to individual patient needs (14). While the list of potential novel agents is continuously expanding, the mechanisms of action for many remain enigmatic (15).

Regenerative Medicine: A New Approach to Treating Diabetes Mellitus

Research in stem cell therapy holds promise for the treatment of T1DM. Scientists are exploring the possibility of generating functional beta cells, the insulin-producing cells of the pancreas, from stem cell sources (16). However, a significant challenge lies in acquiring a sufficient number of appropriate stem cells for therapeutic applications, as the pancreas lacks the ability to regenerate (17). Embryonic stem cells (ESCs) possess the unique ability to differentiate into various cell types, including cells that mimic the insulin-secreting function of beta cells. In vitro and in vivo studies have demonstrated the potential of ESCs to differentiate into insulin-like cells that can improve glucose uptake and metabolism (18, 19). Similarly, research suggests that intravenous (IV) injection of embryonic-like stem cells (VSELs) in mice with pancreatic damage may promote regeneration and improve function (20, 21).

Research advancements in stem cell therapy offer promising avenues for managing both type 1 (T1DM) and type 2 diabetes mellitus (T2DM

1. Immuno-isolated Mesenchymal Stem Cells (MSCs)
Studies utilizing mesenchymal stem cells (MSCs) isolated from the umbilical cord's Wharton jelly and encapsulated in immune-isolatory microcapsules have shown promising results (22). This approach aims to restore the beta cell population in T1DM patients while protecting the implanted cells from immune rejection. Additionally, studies report a significant increase in C-peptide levels and improved postprandial blood glucose control in T2DM patients following MSC implantation (17).

2. Adiponectin-Mediated Mobilization of bone marrow-derived mesenchymal stem cells (BMSCs)
Adiponectin, a protein secreted by fat cells, holds potential in mobilizing BMSCs. Studies suggest that adiponectin facilitates the migration of BMSCs from bone marrow to the circulation, potentially promoting bone regeneration and lowering blood glucose levels in mice with obesity-induced diabetes (23).

3. Positron emission tomography (PET)-Labeled Stem Cells for Delivery Optimization
Researchers are exploring the use of positron emission tomography (PET) tracers to track and optimize stem cell delivery methods. Studies indicate that labeling stem cells with F-FDG, a PET tracer, allows for evaluation of homing and retention of these cells in the pancreas of diabetic patients (24). This information can guide the development of more targeted delivery methods, potentially improving treatment efficacy.

4. Co-infusion of Stem Cell Types
The co-infusion of mesenchymal stromal cells with insulin-secreting properties (derived from adipose tissue) and hematopoietic stem cells (extracted from bone marrow) into the thymic portal circulation and subcutaneous tissue has shown potential in regulating hyperglycemia in T1DM patients (25).

5. Insulin-Secreting Stem Cells from Adipose Tissue
Studies suggest that human eyelid insulin-secreting stem cells derived from adipose tissue may offer potential for T2DM treatment. Research indicates that these cells can contribute to lowering serum glucose levels by increasing circulating insulin levels (26, 27).

Immune Ablation and Stem Cell Therapy
This approach aims to suppress the autoimmune activity underlying T1DM. Studies involving 24 patients undergoing autologous hematopoietic stem cell transplantation (AHSCT) with high-dose cyclophosphamide and anti-thymocyte globulin have shown promising results. These studies suggest that AHSCT can induce T1DM remission and achieve good glycemic control (28, 29). However, identifying potential risk factors like pre-transplant C-peptide levels, age, and TNF-α levels is crucial for optimizing this approach and minimizing rejection risks (29).

The emergence of induced pluripotent stem cells (iPSCs) has sparked widespread interest in their potential for regenerative medicine, including T1DM treatment. Studies suggest that iPSCs offer a promising therapeutic avenue (30, 31). For instance, research has demonstrated that transplanting modified epithelial cells isolated from the pancreas of non-obese diabetic (NOD) mice into diabetic mice led to the successful differentiation of these cells into insulin-producing cells, with increased expression of pancreatic beta-cell markers and enhanced glucose- and potassium chloride-stimulated insulin release (31). Furthermore, investigations into the therapeutic potential of pancreatic stem cells are ongoing. Studies involving the intravenous injection of fetal pancreatic stem cells in T1DM patients reported a

significant increase in C-peptide levels after three months of treatment (32). These findings highlight the potential of both immune ablation and stem cell therapy for T1DM management.

Transdermal Drug Delivery System (TDDS)

While conventional diabetes management relies heavily on oral hypoglycemic drugs and insulin injections, the last decade has witnessed growing interest in transdermal drug delivery systems (TDDS) as a potential alternative (33). TDDS offers several advantages compared to traditional methods, namely offering a non-invasive and painless approach to drug delivery (34).

Beyond its potential for delivering established medications like insulin and metformin, TDDS holds promise for monitoring diabetic parameters through bio-sensing. This technology analyzes metabolites present in biological fluids like sweat to assess metabolic state (35). Building on this concept, a study described the development of a novel biosensor patch with a 3D microneedle array for non-invasive blood glucose monitoring. This patch demonstrated promising features, including long-term stability in vitro and the potential to accurately measure glucose levels even at extreme values (36). However, a notable limitation identified was the decrease in sensitivity at higher glucose concentrations due to bio-fouling around the electrodes. This highlights the need for further design improvements to address this issue and enhance the technology's efficacy.

Despite the significant potential of TDDS for diabetes management, several challenges remain to be addressed (37). However, advancements in various technological approaches are paving the way for improved patient compliance and therapeutic outcomes.

Microneedle technology is one prominent approach within TDDS. This technology utilizes tiny needles to create temporary microchannels in the skin, enhancing the permeability of antidiabetic drugs and facilitating their delivery (38). Additionally, nanoformulations hold promise for improving the delivery of various antidiabetic drugs, including insulin sensitizers and insulin itself, through the TDDS method (38).

Furthermore, innovative techniques like iontophoresis and electroporation utilize electric fields to facilitate the transdermal penetration of antidiabetic drugs and insulin (25). These approaches offer significant advantages, including their non-invasive nature, ability to provide steady and prolonged drug release, avoidance of first-pass metabolism, and potential reduction of systemic side effects (39).

As research continues to evolve, the translation of these promising technologies into clinically viable and widely accepted options remains an exciting avenue for improving diabetes care and patient well-being.

Nanotechnology

Conventional insulin injections for type 1 and type 2 diabetes (T1DM and T2DM) are often associated with pain, discomfort, and potential infection, leading to reduced patient adherence (40). To address these limitations, nanotechnology is emerging as a promising approach for improved diabetes management due to its potential for accuracy, specificity, and efficacy (41).

One of the key applications of nanotechnology in diabetes management lies in the development of miniaturized glucose sensors and closed-loop insulin delivery systems (42). These systems utilize smart nanoparticles (NPs) as drug delivery vehicles equipped with glucose sensors that monitor blood sugar levels in real-time and regulate insulin release accordingly (43). These bioengineered systems often employ microcapsules with controlled pore sizes that allow for the targeted delivery of insulin molecules (43). Compared to conventional methods, nanoformulations offer enhanced drug bioavailability and targeted delivery to specific sites within the body. However, potential concerns regarding scalability

and potential toxicity associated with nanoparticles require further investigation and mitigation strategies (43).

For instance, nanotechnology-based insulin delivery systems demonstrate the potential for precise targeting of disease-related pathways at lower doses, leading to improved pharmacokinetic profiles and reduced side effects (44). Additionally, quantum dots and mesoporous silica nanoparticles are being explored for the development of highly sensitive and selective glucose sensors (45). Furthermore, the integration of nanotechnology with smart insulin delivery systems paves the way for glucose-responsive insulin release, potentially mimicking the natural function of the pancreas (39).

Despite the significant advancements in nanotechnology-based approaches for diabetes management, several challenges remain. These include ensuring biocompatibility, establishing long-term safety, and addressing scalability concerns for successful clinical translation. Addressing these challenges is crucial for the widespread adoption of these promising technologies in diabetes care.

Conclusion

The current pharmacological landscape for diabetes management, while established, faces limitations in achieving long-term glycemic control and often comes with undesirable side effects. This paper explored promising avenues for future treatment strategies, including regenerative medicine: TDDS, and nanotechnology.

Regenerative medicine approaches, particularly stem cell therapy, hold significant potential for restoring beta-cell function in both type 1 and type 2 diabetes. Research efforts in this area encompass various methods, such as mesenchymal stem cells, immune ablation, and induced pluripotent stem cells, each demonstrating unique possibilities.

TDDS offer a non-invasive alternative to traditional injection methods, potentially improving patient compliance and offering pain-free medication delivery. Additionally, TDDS holds promise for blood glucose monitoring through bio-sensing technology. Advancements in microneedles, nano-formulations, and techniques like iontophoresis highlight the potential for improved drug delivery and patient comfort.

Nanotechnology presents exciting opportunities for diabetes management by enabling the development of miniaturized glucose sensors, smart insulin delivery systems, and targeted drug delivery with reduced side effects. Research in this field explores applications such as nano-formulations for enhanced drug bioavailability and the integration of nanotechnology with smart insulin delivery systems for mimicking the natural function of the pancreas.

Recommendations

To fully realize the potential of emerging fields in diabetes treatment, continued research and development are crucial. Refining regenerative medicine, transdermal drug delivery, and nanomaterial approaches will address current limitations and ensure safe, effective clinical translation.

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