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Advances in Devices for Insulin Delivery and Glucose Monitoring

Mariyam Sakha Abdul Hakeem[1] and Archana Singh Sikarwar[1*]

[1]Faculty of Medicine and Health Sciences, Applied Biomedical Science and Biotechnology Division, School of Health Sciences, International Medical University, Kuala Lumpur, Malaysia.

Authors' contributions

This work was carried out in collaboration between both authors. Author AS designed the study. Author MS managed the literature searches and wrote the first draft of the manuscript. Author AS analyzed the study performed. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Diabetes mellitus is a metabolic disease which poses a major challenge to healthcare and is characterized by elevated blood glucose levels resulting from either an underproduction or underutilization of the insulin hormone. The actual cause of Type 1 diabetes is unknown, but it most likely results from an autoimmune mediated destruction of the insulin producing pancreatic beta cells that reduces or terminates insulin production. On the other hand, type 2 diabetes is often caused by obesity and induces a gradual desensitization of the body's cells to insulin. Recent advances in diagnostic methods have heralded in a new era of diabetes management with improved glucose control, reduced fear of complications and better compliance with intensive therapies. Additional efforts are being made to refine these methods to allow their implementation into clinical practice and gain universal acceptance. Advances in diagnostic methods for insulin delivery and glucose monitoring are an important step forward in greatly improving the lives of diabetic patients.

Keywords: Advanced diagnostic kits; insulin; diabetes; self-monitoring of blood glucose.

**Corresponding author: E-mail: archana_sikarwar@imu.edu.my;*

ABBREVIATIONS

SMBG : Self-monitoring of Blood Glucose
HbA1c : Haemoglobin A1C
MDI : Multiple Daily Injections
CGM : Continuous Glucose Monitoring
NGM : Noninvasive Glucose Monitoring
APS : Artificial Pancreas
SAP : Sensor-Augmented Pump
LGS : Low Glucose Suspend

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that is attaining epidemic proportions across the globe. International Federation of Diabetes estimated that there were 381.8 million people with diabetes worldwide in 2013 and this figure is expected to rise to 591.9 million by 2035 [1].

Diabetes mellitus is characterized by elevated blood glucose levels resulting from either an underproduction or underutilization of the insulin hormone. Type 1 diabetes is caused by an autoimmune mediated destruction of the insulin producing pancreatic beta cells; whereas type 2 diabetes is often caused by obesity and induces a gradual desensitization of the body's cells to insulin [2].

Intensive glycemic control using self-monitoring of blood glucose (SMBG) and multiple daily injections are the cornerstone of diabetes therapy. However, significant subsets of patients fail to reach their target Haemoglobin A1c (HbA1c); a measure of glycemic control with these therapies thereby increasing the risk of diabetes complications [3,4]. Globally, USD 376 billion is spent on diabetes treatment with uncontrolled diabetes and diabetes-related complications accounting for a substantial portion of the cost. Thus, there is an urgent unmet need for advanced methods that can achieve better glucose control and subsequently, reduce healthcare costs [5-7].

Despite the use of current therapies, chronically elevated HbA1c levels, multiple hypoglycemic events and substantial glycemic variability remain in both type 1 and 2 patients [8]. It has been proven that reduction of glycemic variability can prevent or delay the onset of diabetes-related complications. Evidence-based studies have suggested that hyperglycemia can leave an early imprint on the cells of the vasculature and in target organs, favoring the future development of complications. It has also been found that 'memory' can appear even when good glycemic control is achieved, and this is known as 'metabolic memory' (7a). The drastic rise in the prevalence of diabetes (Fig. 2) and the significant costs incurred by diabetes-related complications (Fig. 3) underscore the importance of utilizing advanced methods in diabetes management to mitigate these adverse consequences [5,7].

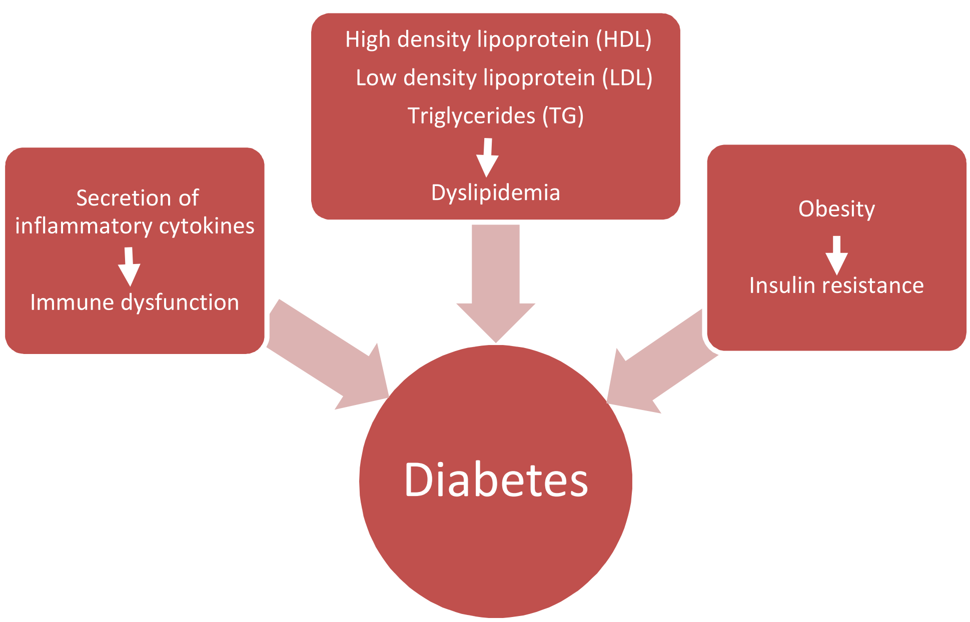

Fig. 1. Shows the relationship of diabetes to immunity, lipids and obesity

The following review will describe the barriers faced in achieving normoglycaemia with the conventional methods used in diabetes management and it will provide an overview of the advanced methods which include; continuous glucose monitoring (CGM), inhaled insulin, insulin pumps and the closed loop system (artificial pancreas).

2. CONVENTIONAL METHODS FOR DIABETES MANAGEMENT

2.1 Self-Monitoring of Blood Glucose (SMBG)

Blood glucose monitoring is a fundamental requirement of diabetes management as it allows adjustments to be made to diabetes therapy according to glucose readings. Currently, SMBG is primarily performed using capillary blood glucose meters. The newest meters have improved accuracy and only require a minute volume of blood to produce instantaneous results. They also contain data management systems to store and download previous glucose readings and an insulin dosage calculator [9,10].

Despite these developments, the devices can only provide snapshot readings and offer limited information on blood glucose trends [8] Several studies have established the importance of frequent SMBG measurements to sustain HbA1c of <7% to effectively reduce diabetic complications [11,12]. Unfortunately, two-thirds of patients test less frequently than recommended because of the pain and inconvenience associated with testing [13,14].

2.2 Multiple Daily Injections (MDI) and Insulin Pens

Insulin is traditionally administered through syringes; however, poor dose accuracy, pain and training associated with syringes led to the advent of insulin pens which were able to bypass some of these factors and improve treatment adherence. Although these pens are simple to use [8,15] they still cannot eliminate the pain and inconvenience associated with delivering multiple large doses [16,17].

3. COMPARATIVE ANALYSIS OF THE NEW ADVANCEMENTS IN DIABETES MANAGEMENT

Due to the technical issues, training and the significant expenses associated with the following advanced methods; they are only indicated for type 1 diabetics with poor glycemic control, recurrent hypoglycemia and also for type 2 diabetics who are unable to achieve normoglycemia with intensive use of recommended therapies [18].

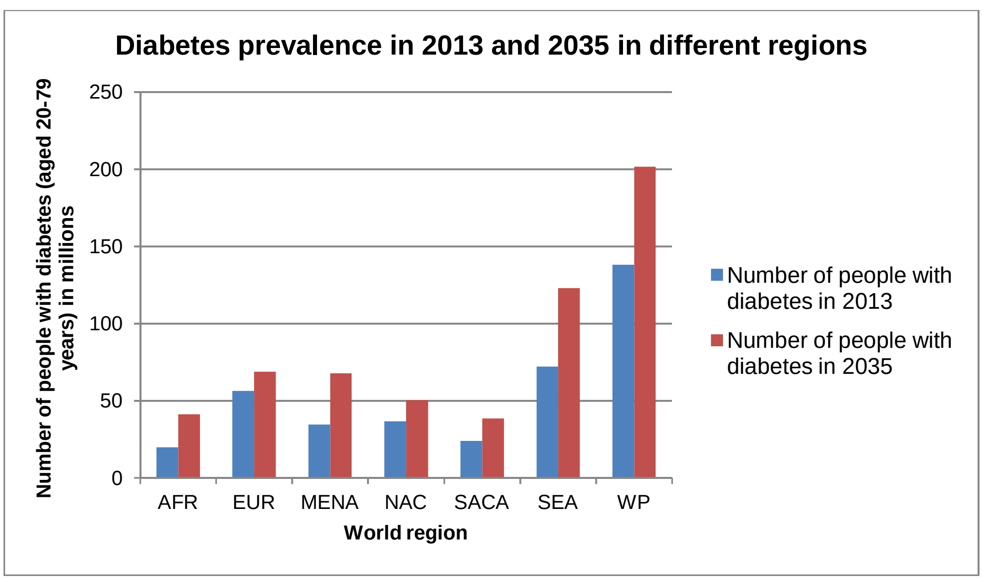

Fig. 2. Prevalence of diabetes in 2013 and projected increase for 2035 in 7 regions of the world: Africa (AFR), Europe (EUR), Middle East & North Africa (MENA), North America & Carribean (NAC), South And Central America (SACA), South East Asia (SEA) and Western Pacific (WP)

3.1 Continuous Glucose Monitoring (CGM)

The major advancement in glucose monitoring has been the development of continuous glucose monitoring (CGM) devices. Unlike SMBG, they provide continuous measurements of glucose levels to reveal glucose trends that are not evident with SMBG, both retrospectively and in real-time. There are two approaches to this technique; minimally invasive and non-invasive monitoring [18].

3.1.1 Non-invasive glucose monitoring (NGM)

Non-invasive glucose monitoring (NGM) is of particular interest as it offers the potential of eliminating the physiological stress, pain, and inconvenience associated with SMBG. A wide variety of approaches have been investigated over the years (as summarized in Table 2) however, there aren't any clinically accurate and reliable devices on the market. Despite many failed attempts, research in this area is ongoing due to the tremendous appeal and market potential of NGM devices. Key challenges facing the development of NGM devices include; weak signal to noise ratio, prolonged response time, lack of precision, comfort, safety and cost effectiveness. Intensive efforts are required to overcome these technical issues in order to develop robust NGM devices [19-21].

3.1.2 Minimally invasive glucose monitoring

CGM devices based on the minimally invasive approach have been successfully commercialized. They utilize electrochemical subcutaneous sensors to detect glucose levels in the interstitial fluid every 1-5 minutes and transmit these readings wirelessly to a receiver for display. This allows a better indication of glucose variation throughout the day by means of rate of glucose change, and trends that are superimposed onto preset targets. Thus, it can be used as diagnostic tools by physicians and patients to review glucose patterns to detect hypoglycemic and hyperglycemic durations and guide insulin therapy accordingly [9,22]. Alarms can also be set at specified levels to alert the patient of actual or pending glucose excursions [18].

Currently, CGM devices can only be used as an adjunct to SMBG and therapeutic decisions need to be made after confirming the glucose measurement with SMBG.

3.1.2.1 CGM versus SMBG

Since adding CGM devices as an adjunct to SMBG adds to the overall cost of diabetes care, it is crucial to determine the effectiveness of CGM in achieving better glucose control. In multiple clinical trials conducted among adults, children and adolescents with type 1 diabetes, CGM usage compared to SMBG has shown significant reductions in HbA1c and frequency of hypoglycemic episodes along with an increased time spent in target glucose range [3,23-25]. Sustained HbA1c improvement following short term usage of CGM has also been demonstrated in type 2 diabetic patients [26,27].

These benefits in HbA1c reduction, however, are only observed with sufficient patient training and usage of CGM at least 60-70% of the time [23]. A study conducted to investigate the underutilization of CGM devices among patients despite its established positive outcomes stated; problematic equipment and inaccuracy (64%), intrusive nature of the device (36%) and insufficient insurance coverage (29%) as reasons for intermittent CGM usage [28,29].

There are several factors that contribute to the inaccuracies and difficulties with these devices. This includes intermittent calibration of the device with SMBG, a 2 hour startup period and short lifetime of the sensors [30] However, the most crucial concern is the inaccuracy of CGM caused by a time lag of ~8-10 minutes; which stems from delays in glucose transportation from plasma to interstitial fluid and other sensor dependent delays. This lag is especially pronounced during rapid glucose changes, thus, any calibration performed during a period of glucose excursion will invariably lead to erroneous readings [31,32] Alarms for detecting glucose excursions have also not been particularly beneficial as most studies report frequent episodes of prolonged nocturnal hypoglycemia with patients sleeping through 71% of alarms [33].

3.2 Insulin Pumps and Patch Pumps

Although insulin pumps were introduced three decades ago, there are still marked geographical differences in the utilization of insulin pumps which could be due to; resistance from physicians because of unfamiliarity, lack of supportive infrastructure, cost of insulin pen as well as insurance issues [14].

Table 1. lists the advantages and disadvantages for CGM, insulin pumps and inhaled insulin

Device	Advantages	Disadvantages
Continuous glucose monitor (CGM)	• Minimally invasive • Displays glucose trend graphs • Built-in alarms to alert the user of glucose excursions • Significantly reduces HbA1c and time spent in target glucose range	• Requires training before usage • Sensor needs a 2-hour start-up period before results can be displayed • Lag time of ~8 to 10 minutes may cause inaccurate results
Insulin pumps	• Small, discreet, safe and easy to use • Contains built-in alarms, data management systems and integrated blood glucose meters • Offers precise dosage control • Significantly reduces HbA1c	• More expensive compared to multiple daily injections • Requires training before usage
Inhaled insulin	• Painless • Fast onset and short duration of action • Emulates physiological release of prandial insulin • Effective in controlling post prandial hyperglycemia	• Some safety concerns due to reports of increased coughing and decline in lung function • Expensive

Table 2. Non-invasive glucose monitoring devices that have been developed or are currently under clinical trials

Device	Principle used	Status
Glucotrack	Uses ultrasound, electromagnetic, and heat capacity to measure BG through an ear clip sensor	Available in select countries not FDA approved
Symphony	Prelude skin prep system to increase permeability and transdermal sensor	R&D phase
Glucowise	Radio waves	R&D phase
Glucowatch biographer	Reverse iontophoresis	Discontinued
Pendra	Bioimpedance spectroscopy	Discontinued
HG1-c	Raman spectroscopy	Discontinued
OrSense NBM-200G	Occlusion near infrared spectroscopy	NA

3.2.1 Evolution of insulin pumps

Insulin pumps have undergone remarkable changes throughout the years; although the basic design remains the same with a portable electromechanical pump infusing insulin through a subcutaneous catheter at preselected rates [34]. The newest generation of pumps is called patch pumps as they work without loops of tubing and are composed of an insulin reservoir, a delivery system and a cannula. These pumps are smaller, more discreet, and easier to use; all of which improves patient compliance [35].

The most recent models are referred to as 'smart pumps' as they allow programming of multiple basal rates, contain built-in alarms and data management systems to track and download daily blood glucose values, dose history and calorie intake. It also comes with integrated blood glucose meters and a bolus calculator to estimate required insulin dosage based on current glucose level, insulin sensitivity, target glucose level and insulin on board [36].

3.2.2 Challenges and benefits of insulin pumps

Compared to MDI, insulin pumps offer precise control over dosage rates, whereby basal and bolus rates can be adjusted to account for pre and post exercise, thereby minimizing the occurrences of hypoglycemia [30]. The effectiveness of insulin pumps over MDI in type 1 diabetic patients was evaluated in a meta-analysis of 22 studies; which showed a significant improvement in HbA1c without an increased risk of hypoglycemia with pump usage [37]. Safety and efficacy of pump therapy in type 2 diabetic patients have also been assessed in a multicenter trial that resulted in a significant HbA1c improvement with pump usage [16,38].

Although the cost of pump therapy is approximately 80% higher than MDI, long-term savings incurred by lower rates of diabetes complications establishes its cost effectiveness [14].

There are two safety concerns regarding pump usage; one is the possibility of pump malfunction leading to diabetic ketoacidosis and second is the slow absorption of insulin resulting in an increased risk of hypoglycemia [8,10]. Patients would need to be trained on this aspect to prevent overcorrection of glucose excursions in addition to the training on infusion site care and insulin dose adjustment [30].

3.3 Inhaled Insulin

The administration of insulin via the subcutaneous route is slow, variable and the maximum blood glucose lowering effect occurs after 90-120 minutes thus resulting in poor post prandial glucose control [32]. In an attempt to overcome this dilemma, inhaled insulin has been investigated as an alternative route of delivery. Currently, the only commercialized inhaled insulin is an ultra-rapid acting insulin with fast onset and short duration of action working on the basis of Technosphere technology. The inhaled insulin reaches maximum concentration after 15 minutes, approximately 2 hours earlier than recombinant insulin thereby emulating the physiological release of prandial insulin [39,40]. Clinical studies have established the effectiveness of inhaled insulin in controlling postprandial hyperglycemia and preventing postprandial hypoglycemia compared to subcutaneous regimens in both type 1 and type 2 diabetic patients [41].

Studies evaluating the safety of inhaled insulin have observed an increased incidence of cough and decline in lung function; although some studies report these changes as being non-progressive. Concerns about lung cancer have also been raised due to reports of mortality from lung cancer observed in a previously available inhaled insulin formulation [42]. Despite the extra cost of inhaled insulin, it should be noted that this painless and convenient route of insulin delivery is more likely to be accepted by patients; thus translating to improved glucose control and lower risk of long-term complications [39].

3.4 Closed Loop Insulin Delivery

Closed-loop insulin delivery, also called as the artificial pancreas (APS) has been an elusive goal of diabetes researchers for several decades. APS has the potential to revolutionize diabetes management by drastically improving glycemic control, reducing complications of diabetes and mitigating the burden of diabetes self-management [32]. Ideally, it is an automated system that utilizes a control algorithm to modulate insulin delivery according to real-time interstitial glucose readings by coupling a CGM device with an insulin pump. Tremendous progress has been made in the development and refinement of these two components, thus making real-life clinical use of such a device a possibility [43–45]. An illustrative representation of the closed loop system is shown below in Fig. 4.

The first step towards APS has been the integration of a CGM and an insulin pump to produce a sensor-augmented pump (SAP) in which insulin delivery is manually adjusted according to real-time data from CGM [46]. This technology has been commercialized and tested in the large-scale STAR 1 study in which SAP demonstrated a significant and persistent decrease in HbA1c compared to MDI therapy in type 1 diabetics [46].

The simplest approach to an APS is the suspension of insulin delivery to prevent episodes of nocturnal hypoglycemia [22,32]. This approach has been successfully commercialized with devices that contain a Low Glucose Suspend (LGS) function to automatically suspend insulin delivery for 2 hours in response a fall in interstitial glucose level. ASPIRE study demonstrated a 38% reduction in hypoglycemia exposure without an increase in HbA1c with the LGS function [47] and other studies have reported similar positive outcomes [33,48].

Several studies are underway to determine the effectiveness of APS in overnight glucose control [49], overnight glucose control in response to challenges (meals and exercise) [50,51] and day and night closed loop systems under real-life conditions [52].

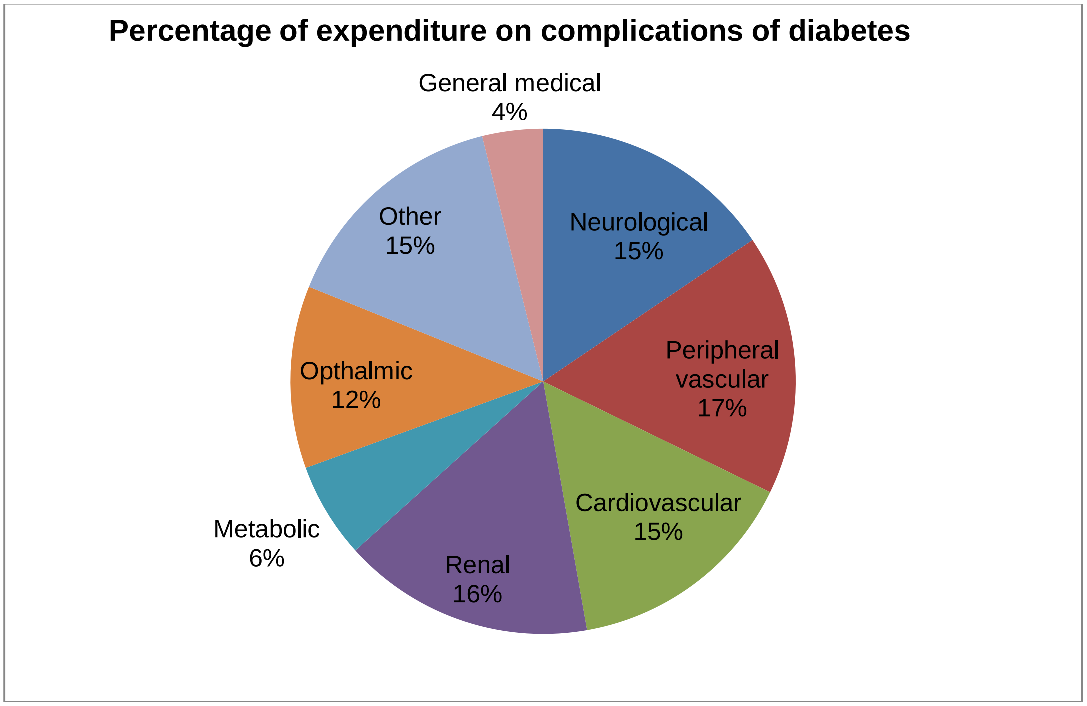

Fig. 3. Percentage of expenditure on treatment of diabetes-related complications

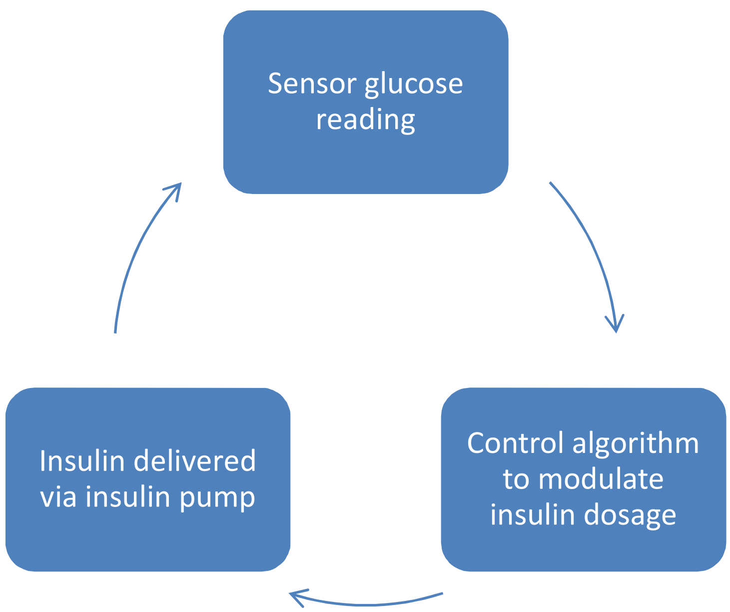

Fig. 4. An illustrative representation of the closed loop system

3.5 Stem Cell-Based Therapy

In addition to the rapid advances in the development of insulin delivery and glucose monitoring devices, an exciting new avenue of diabetes therapy that has been gaining momentum, is stem cell-based therapy [53]. Stem cells represent a potentially unlimited source of undifferentiated cells that could in theory be induced to differentiate into insulinsecreting beta cells, thereby reversing the diabetic state [54]. Considerable progress has been made in this field of research with the use of human embryonic stem cells and induced pluripotent cells (iPS); however, there are major challenges facing this approach that need to be overcome before this technology can be brought into clinical application [53,55]. Advancements in our understanding of stem cell biology have also led to concentrated efforts on the use of stem cells for alternative approaches in diabetes treatment [56]. One such approach is the use of mesenchymal stromal cells to modulate the autoimmune response seen in type 1 diabetes or to promote islet cell regeneration. Stem cells could also be used to treat the problems of obesity and insulin resistance by directing adipocyte stem cells to produce more energy consuming brown fat [53]. Other approaches include the use of stem in cells in the treatment of diabetic complications through regeneration of kidney or retinal cells. Despite these intensive efforts to enable the reconstitution of pancreatic endocrine function in diabetic patients, more research is required before stem cell-based therapy can become a viable treatment option [56].

4. CONCLUSION

Widespread clinical utility of these advancements are constrained by issues of inaccuracies, safety and effectiveness; all of which are being gradually addressed [57].

Proposed methods of rectifying CGM inaccuracy include the use of superior sensors or multiple sensors based on different technologies to reduce the time delay; and subsequently patient response times to glucose excursions [45,58]. Fluorescent glucose sensors are already being investigated as an alternative and have exhibited a higher degree of accuracy compared to electrochemical sensors [59]. Faster acting insulin analogs and modes of accelerating insulin absorption are critical in overcoming the slow absorption of subcutaneously administered insulin [22,32]. Intraperitoneal route is being researched as an alternative route of delivery as its pharmacokinetic profile more closely mimics the physiological delivery and its use has yielded promising results [60,61]. Current control algorithms employed in APS need to be refined to improve handling of post prandial glucose control, exercise and other physiological stressor-induced changes to insulin sensitivity [22,45].

Co-administration of glucagon and insulin is being studied to mitigate the risk of hypoglycemia and poor post prandial control that is still present with the advanced methods. This dual-hormone system can effectively counteract over insulization from delayed insulin absorption and has already demonstrated a greater reduction in the frequency of hypoglycemia compared to the use of insulin alone [62,63]. Another approach under investigation is the use of pre-meal pramlintide injections that cause delayed gastric absorption resulting in a much better match between carbohydrate and insulin absorption [64].

Establishment of structured training programs for healthcare professionals and patients, together with a network for managing troubleshooting issues are imperative to overcoming the technical issues related to these new methods. The cost barrier, that poses the main hindrance in the utilization of these tools can be circumvented with collaborative efforts between the medical device industry and insurance companies [32].

Recent advances in diagnostic methods have heralded in a new era in diabetes management with improved glucose control, reduced fear of complications and better compliance with intensive therapies. Additional efforts are being made to refine these methods to allow their implementation into clinical practice and gain universal acceptance.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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