Review Article

Artificial Intelligence: New Breakthrough for Diabetes Mellitus and Regulatory Perspective

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ABSTRACT

Artificial intelligence (AI) is a rapidly evolving science and its application to diabetes has the potential to transform the approach for the diagnosis and treatment of the disease. The inclusion of AI with smart devices, such as medical devices, wearables, smartphones, and sensor technology, will allow for the building of digital machines capable of supervising and monitoring people with diabetes continuously. The new digital technologies, big data-based analytics, and the application of AI to diabetes data will revolutionize the way diabetes and diabetes related complications are treated, as well as their prevention and control. The artificial intelligence is putting considerable effort into developing support systems for patient use, which automatically analyze the patient's data collected by sensors and other portable devices that offer tailored recommendations for therapy adjustments to patients. Patients are increasingly being empowered for self-management of diabetes and both patients and healthcare professionals are benefitting from clinical decision support. It is anticipated that predictive overall performance of AI will soon be maximized by a large amount of organized data and plentiful computational resources. The objectives of this article are to enlist the advancements w.r.t. artificial intelligence in the field of diabetes management using smart devices. Artificial Intelligence is a promising area of research that can significantly improve the quality of life for people affected by this disease. Leading medical device makers as well as technology giants are constantly innovating to bring novel products and solutions to the market.

Keywords: Artificial Intelligence, diabetes, medical devices, diabetes digital technology, regulatory prospective, diabetes management

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INTRODUCTION

Diabetes mellitus is a diagnostic term for a group of disorders characterized by abnormal glucose homeostasis resulting in elevated blood sugar.[1] Diabetes is an indestructible metabolic disorder that develops when the pancreas is unable to generate enough insulin or when the body is unable to utilize the insulin properly which is produced in the body. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates, insulin is released from the pancreas to normalize the glucose level by promoting the uptake of glucose into body cells. In patients with diabetes, the absence of insufficient production of or lack of response to insulin causes hyperglycemia or diabetes.[2-3]

Diabetes mellitus was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world because elevated levels of blood glucose led to spillage of glucose into the urine.[4]

It is broadly classified into type 1 (T1DM) and type 2 DM (T2DM).[5] Type 1, insulin-dependent, or juvenile-onset diabetes mellitus is characterized by onset in childhood or early adolescence, severe hyperglycemia requiring insulin therapy[6] for survival. Figure 1 indicates the pathophysiology of the Diabetes Mellitus.

Patients with T1DM should be taught to count carbohydrates and to calculate both correction and prandial insulin dosing. These patients should work with a diabetic team and be offered insulin-pump therapy[7]. Type 2, noninsulin-dependent, or adult-onset diabetes mellitus is associated with obesity, sedentary lifestyle, a family history of the disease, and increasing age. It may be controlled by dietary therapy or oral hypoglycemic agents[8]. Patients who are newly diagnosed with T2DM should be provided with a glucometer and testing instructions and referred for diabetes education and medical nutrition therapy[7]. Patients can help reduce long-term hazards and restore some control in managing their condition with the use of technology.

The discipline of artificial intelligence (AI), which is rapidly expanding, has applications that could revolutionize how this chronic ailment can be diagnosed and managed. Diabetes is a global pandemic. Algorithms supporting predictive models for the risk of getting diabetes or its complications have been developed using machine learning principles. Digital treatments have established themselves as a lifestyle therapy intervention for the control of diabetes.[9]

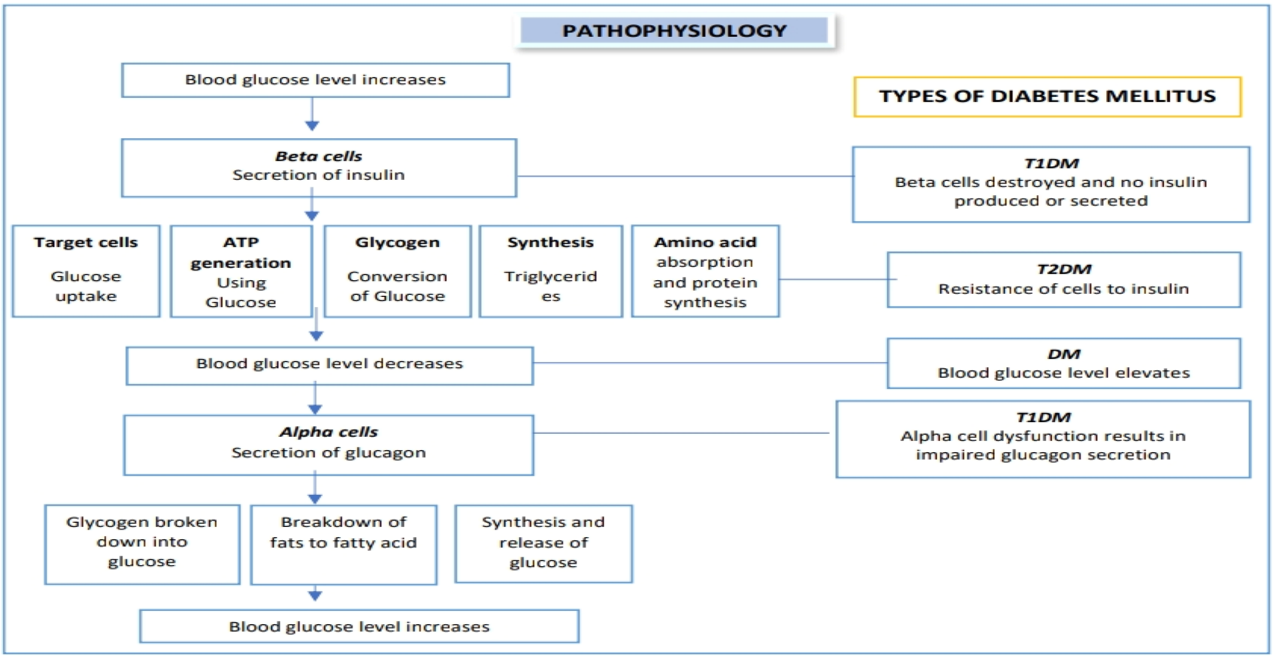

Figure 1: Pathophysiology of Diabetes Mellitus

AI can introduce a paradigm change in diabetes care from traditional management strategies to building targeted data-driven precision care.[9] AI and ML-based continuous integrated solutions enable decision-makers to prioritize the right product pipelines for innovation by quickly and effectively finding new opportunities from a variety of data sources.[10] The majority of the current AI tools (Figure 2) used in diabetes education are focused on complications monitoring, self-management, blood sugar monitoring, lifestyle advising, and insulin injection guidance.[11]

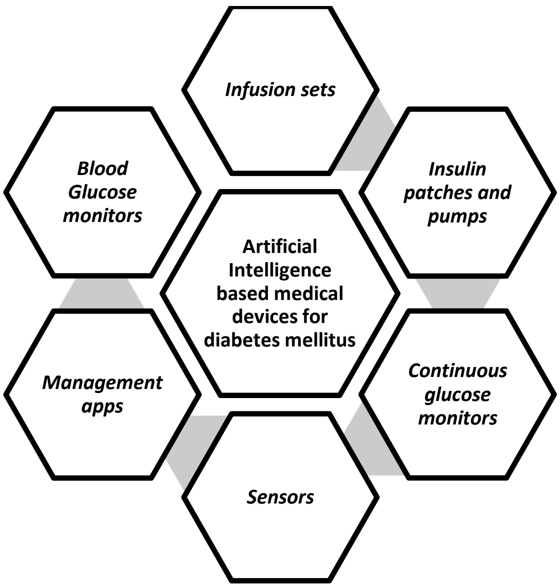

Figure 2: AI-based medical devices for Diabetes Mellitus

According to a 2017 survey, 68 % of mobile health app developers and publishers think diabetes will continue to be the one medical condition with the greatest market potential for digital health solutions in the near future, and 61% think AI will have the biggest impact on shaping the digital health sector.[12]

AI is finding widespread use in patient self-management tools. The risk of developing diabetes and its complications are being predicted by machine learning algorithms. The use of AI in the management of diabetes is generating a variety of innovative solutions.[13] Technical advances have introduced wearables, smartphones, and other gadgets that can aid continuous monitoring and tracking of the patient's symptoms and disease status. Physicians and healthcare professionals should allow patients to choose AI-assisted care for the effective management of diabetes.

From literature it was found that there are couple of companies who are engaged in developing medical devices based on the artificial intelligence technology creating an innovative system that allows the patient to focus on new possibilities in life and spend less time in managing the diabetes.

This paper provides a comprehensive study of automatic diabetic management processes of patients like weight management, diet monitoring, insulin management, glucose regulation, etc. using various diabetes care medical devices that are designed by advanced technology such as artificial intelligence. These devices have been approved by the regulatory authorities such as USFDA, EMA, MHLW for the benefit of the diabetic patient and are placed on the global market.

2. NEWEST MEDICAL DEVICES FOR DIABETES THAT OPERATES ON ARTIFICIAL INTELLIGENCE

Diabetes, a polygenic disease is known to be a lifestyle disease which can be managed by adopting a healthy lifestyle. A number of lifestyle factors are known to be important in the development of Diabetes Mellitus such as physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol.[14] Patients ought to learn to monitor their condition with regular blood tests to make sure that their blood glucose level remain controlled. The combination of artificial intelligence approaches and advanced technologies, such as medical devices, wearable devices, and sensor technologies, could enable the development and implementation of better chronic disease management services through which diabetic patients can keep track of their condition.[15-16]

With the aim of enhancing the quality of life, illness management of diabetic patients, preventing complications from diabetes and to prevent early mortality, powerful AI methods are designed for each patient.[17-18] There are number of AI methods for designing models that prevent events like hypoglycemia, predict the value of blood glucose levels, and predict the right amount of insulin to administer. Patient's self-management tools increases awareness and knowledge through digital platforms for the accountability of diabetes care.

2.1 Continuous glucose monitors

The current trend in research is to automatically monitor the blood glucose level and inject the insulin required to regulate the patient glucose level. Continuous glucose monitors (CGMs) rely on a tiny sensor[19] inserted under a patient's skin which tests interstitial glucose levels every few minutes and sends this information to a monitor or smartphone. CGM uses an invasive needle due to which the patients receive alerts when their glucose levels need to be adjusted.[20-21] CGMs such as the Dexcom G6, are becoming increasingly popular with diabetic patients and can be worn day and night to keep an eye on glucose levels. These devices are popular primarily because patients can view their glucose levels with a quick glance and have to use a finger prick blood test only twice a day to check that readings on both devices are similar. A list of currently available CGM in the market are given in Table 1.

2.2 Management apps

Apps help the patient to manage life with their condition. Various blood glucose monitoring apps have been launched by different companies. It is common for patients to make errors in their diabetes management, by either binge eating carbohydrates on a particular day, not exercising enough, or forgetting to take their medicine. Fortunately, patients today have access to mobile apps that can help them manage their diabetes and keep their blood sugar under control.[22] AI used in such apps allows a continuous and burden-free remote monitoring of the patient's symptoms and biomarkers. Technical advances have helped to optimize resource use in diabetes.[9,23]

Table 1: CGMs available in the Market

S.No.	CGM Device	Manufactured by	Validity of Sensors inserted
1.	Dexcom G6 [d1] New Dexcom G7 model (to be approved)	Dexcom	10 days
2.	Abbott Freestyle Libre 2	Abbott	14 days
3.	Eversense E3	Senseonics: ascensia Diabetes care	New version 180 days Old version 90 days
4.	Guardian 3	Medtronic	7 days

Table 2: List of various apps available for diabetes management

S. No.	Name of App	Description
1.	Bezzy T2D	Online forum to discuss about diabetes. Users can chat about daily life, diet and nutrition.
2.	Fooducate	Helps in figuring out which foods are best for keeping your blood sugar in a healthy range
3.	MySugr	It offers carb counting, glucose tracking, and bolus dose calculation estimates Estimates hemoglobin A1C based on your tracking
4.	Glucose Buddy	Allows to track steps, exercise, and meals. Offers a 12-week diabetes education plan.
5.	Diabetes:M	Offers test time reminders, a nutritional log and tracking system, integrations with fitness apps, and blood sugar trend mapping.
6.	Beat Diabetes	Provides information about the complications arises in diabetes. Provides up to date treatment options, from medical to Ayurvedic.
7.	OneTouch Verio Flex and OneTouch Verio Reflect meters	Using your blood glucose readings, the app automatically highlights the frequent range of the sugar in blood. Offers push notifications alerts to take actions.
8.	One Drop for Diabetes Health	Provides coaching from certified health professionals. The app also uses your food, activity, and medication information to help you

		achieve a holistic diabetes management plan with automated alerts, community sharing, and regular health stats reports
9.	Diabetic Recipes	Allows user to search a vast library of diabetes-friendly recipes by ingredient or style. Offers step-by-step instructions to know exactly how much glucose you're taking in throughout the day
10.	T2D Healthline: Diabetes	It is a portal letting you connect with others on a number of forums dedicated to specific topics like complications, relationships, and testing/monitoring.
11.	Calorieking	Curated food database of nutrition information
12.	Wellthy Diabetes	Provides feedback on logging meals, activity and blood sugar levels.
13.	Life in control	Offers personalised and easy-to-follow diet plans Sets daily healthcare goals Allows the doctors to track HbA1C and blood sugar levels, medicines, insulin and other health vitals of their patients.
14.	Tidepool	Compatibility with many devices (glucose meters, CGM devices, Insulin pumps) Tracking tool for insulin, CGM, Blood glucose data with notes.
15.	Apollo Sugar	Allows users to access their prescriptions, lab reports, and vitals, and gain an understanding about the results.
16.	Habits Diabetes Coach	Provides glucose tracking Provides meal recommendations Provides diabetes lessons for a course of 16 weeks

Table 3: List of marketed Glucose monitoring devices

S. No.	Name of Glucose monitor	Manufacturer
1.	Care touch blood glucose meter	Ascensia
2.	Fora 6 Connect glucose meter	ForaCare Suisse AG
3.	Truemetrix meter	Trividia Health, Inc
4.	Dario LC Blood Glucose Monitoring System	LabStyle Innovations Ltd.
5.	Contour Next EZ	Bayer India Ltd.
6.	One Drop Glucose meter	One Drop
7.	Roche Accu-Chek Guide Glucometer	Roche
8.	Auvon DS-W Blood Sugar Kit	Auvon
9.	Prodigy Voice Glucose Meter	Prodigy Diabetes Care, LLC
10.	One Touch Ultra 2 Blood Glucose Meter	LifeScan

2.3 Prick to scan Blood Glucose Monitors

Glucose monitoring is one of the most intrusive parts of living with diabetes. AI-powered mobile phone apps are about to change the way a patient can check blood glucose levels. AI has made easier to better self-manage the diabetes and help to reduce diabetes-related complications in the diabetic patients by a simple method, just moving a compatible smartphone over a sensor on the arm, to get real time blood sugar levels instead of finger-prick tests.[24]

2.4. Sensors

Diabetes mellitus patients need to consistently check their blood glucose levels throughout the day, especially after meals and physical activities. For this purpose, two types of glucose sensors[25] are currently available: blood glucose meters (BGMs) and CGMs. While classic BGMs are self-monitored, CGMs are a step towards automation and patient independence. BGMs measure the glucose concentration of fresh capillary blood samples mainly using the principles of amperometry, colorimetry or fluorescence. Amperometry-based BGMs use reagents such as glucose oxidase or dehydrogenase to electrochemically react with glucose while electrodes sense the change in current.[26] Optical BGMs utilize light to sense the change in color and absorbance of the blood sample following the same reaction. Finally, fluorescence based BGMs emit light to excite a fluorescent coated material onto which glucose can reversely bind. The change in fluorescence is proportional to the glucose concentration.[27]

2.5. Multiple daily injections

MDIs involve the self-administration of insulin doses by syringes, pens, or patches by the diabetic patients. In such practice, DM patients control their BGLs by regularly injecting themselves long-lasting insulin doses, which can be complemented by additional fast-acting insulin doses if needed. As multiple injections are needed to maintain normoglycemia throughout the day, the delivery system should minimize injection discomfort to enhance adherence to treatment.[28]

Devices acting on the transmission of pain signals to the brain can also contribute to reduce pain and anxiety – ShotBlocker® and Buzzy® are two examples.[29] These devices use a combination of vibration and cold, or simply contact points, to be applied on the injection site, prior or during the injection, to act on local nerves and stimulate nociceptors[30] and have shown to actively be able to reduce pain and fear sensations with respect to control groups.[31-32]

2.6. Insulin pens

An insulin pen is an injection device that delivers insulin into the fatty tissue below the skin with a short, thin needle. Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. [24, 33]

Several people around the world self-administer insulin dose for diabetes. The system uses a combination of wireless sensing technology and artificial intelligence (AI) to assess patients. A wall-mounted device, equipped with a sensor, emits radio waves that tracks a patient's movement. And when the patient moves, these radio waves are modified and reflected back to the sensor. This data is interpreted by AI for signs of the patient's self-administration. [34-36] This associated smartphone application (app) also tracks insulin-on-board, makes dosing recommendations, and prepares reports for health care professionals.[37]

Table 4: List of marketed insulin pens

S. No.	Brand name	Manufacturer
1.	• Insulin aspart (NovoLog) • Novolin R • Novolin R Innolet • Novolin R PenFill • Novolin N • Novolin N Innolet • Novolin N PenFill • ReliOn/Novolin R • insulin detemir (Levemir, Levemir FlexPen, Levemir FlexTouch, Levemir InnoLet, Levemir PenFill) • Insulin degludec (Tresiba FlexTouch)	Novo Nordisk
2.	• Insulin lispro (Humalog) • Humulin R • Humulin R U-500 • Humulin R U-500 KwikPen • Humulin N • Humulin N KwikPen • Humulin N Pen • ReliOn/Humulin R	Eli Lilly and Company
3.	• Insulin glulisine (Apidra) • Insulin glargine (Basaglar KwikPen, Lantus, Lantus OptiClik Cartridge, Lantus Solostar Pen, Toujeo Max Solostar, Toujeo SoloStar)	Sanofi-aventis

2.7. Infusion sets

Intravenous (IV) therapy devices are used to administer liquid substances directly into a vein. They can deliver nutrients or medications such as insulin or other hormones, antibiotics, chemotherapy drugs, and pain relievers.[38] Presently, many companies are developing various infusion devices capable of being integrated with alarm devices, monitoring devices, and data exchange systems. This integration helps prevent an overdose or reduced dose of infusion solutions to patients and minimizes dosing errors.[39]

An insulin infusion set (IIS) is an indispensable conduit in insulin pump systems that transfers insulin from the reservoir to the subcutaneous tissue depending on the technology applied. Typically, a canula is inserted subcutaneously using a guide needle that is subsequently removed, and the infusion set is fixed on the skin by an adhesive. Then, a transfer set usually connects the cannula to the insulin reservoir.[40-41]

Table 5: List of marketed infusion sets

S. No	Brand	Manufacturer
1.	MiniMed Mio Paradigm	Medtronic
2.	MiniMed Mio Advanced	Medtronic
3.	MiniMed Quick set	Medtronic
4.	MiniMed Silhouette	Medtronic
5.	MiniMed Sure T	Medtronic
6.	Cleo 90	Smith's Medical

2.8. Insulin patches and pumps

Patch pumps are wearable devices characterized by smaller dimensions with respect to conventional pumps but of comparable effectiveness. A smart insulin patch, also known as a glucose-responsive insulin patch is a type of wearable medical device for diabetes treatment. It is a transdermal patch comprising of glucose-sensitive microneedle-array loaded with insulin for blood glucose regulation. Patch pumps are the devices generally smaller than traditional pumps, attach directly to the skin, and usually have a cannula that goes directly from the device to the skin with no tubing. Some of the insulin pumps are developed with rechargeable battery and sensors which can detect flow or no flow conditions of insulin and will inform the user in real-time of occlusions, leaks, depleted drug supply, accidental misloading, and any mechanical/electrical failure. [42-43]

Table 6: List of marketed Insulin patches and pumps

S. No	Brand	Manufacturer
1.	V-Go®	Valeritas
2.	Panda™	SFC Fluidics, Inc.
3.	Grifgrips	GrifGrips, LLC
4.	Trucare I/II	Apex Medical
5.	Dibkit	IA Collaborative
6.	Wireless Insulin pump	My Life
7.	PAQ	CeQur
8.	Cellnovo Insulin pump	Cellnove
9.	JewelPump	Debiotech
10.	Solo Pump	Roche
11.	Insulet's Omnipod	Insulet Corporation
12.	T:slim X2	Tandem
13.	MiniMed 630G system.	Medtronic
14.	MiniMed 670G system.	Medtronic

"Smart" patch coupled with a glucose monitor can serve as a personal diabetes manager (PDM) and its detachable micro-pump and modular canula provides significant advantages in day-to-day use. [44]

3. PERSONAL DIABETES MANAGERS

The handheld personal diabetes manager (PDM) wirelessly manages the insulin delivery based on the settings that user programs. PDMs help diabetic patients make decisions and better control their glycaemic levels when using non-automated delivery systems. PDMs include applications, web-based management platforms and handheld smartphone-like devices (usually sensor-specific). Most PDMs use wireless technologies such as Bluetooth to communicate data between the sensors, pump, and the displaying device. PDMs can:

(i) Store information

(ii) Record BGLs overtime

(iii) Control the delivery of insulin bolus in hybrid systems

(iv) Produce graphs, charts, and reports

(v) Share data with healthcare professionals

(vi) Retrieve additional data from other applications and devices such as fitness recorders, armbands, and smartwatches.[45]

4. DIABETES MANAGEMENT TECHNOLOGY

Diabetes management technology is the term used to describe the hardware, devices, and software that people with diabetes use to help manage blood glucose levels, stave off diabetes complications, reduce the burden of living with diabetes, and improve quality of life. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump, and blood glucose monitoring as assessed by meter or continuous glucose monitor. More recently, diabetes technology has expanded to include hybrid devices that both monitor glucose and deliver insulin, some automatically, as well as software that serves as a medical device, providing diabetes self-management support. Diabetes technology, when applied appropriately, can improve the lives and health of people with diabetes; however, the complexity and rapid change of the diabetes technology landscape can also be a barrier to patient and provider implementation.[46]

New mobile health technologies can provide education and support to patients with chronic conditions, such as diabetes, while simultaneously empowering providers with real-time information about an individual's health through remote monitoring and prescription mobile health interventions.[47]

Diabetes management products are often complex, involving the integration of multiple components with many unique design and development challenges. Due to the sophistication of software-controlled technologies for diabetes management, regulatory authorities are increasingly focused on the ability of patients and healthcare professionals to operate these devices safely and with optimum effectiveness.[48]

5. REGULATORY PERSPECTIVE

Regulation of AI technologies is likely to be developed and implemented by health regulatory authorities responsible for ensuring the safety, efficacy and appropriate use of technologies for health care and therapeutic development. It raises new challenges for the regulators in order to ensure the safety and effectiveness of AI/ML-based Software as a Medical Device (SaMD) that may change over time as they are applied to new data. Regulatory approach facilitates a rapid cycle of product improvement and allows these devices to continually improve while providing effective safeguards.

The Food and Drug Administration (FDA) has long been charged with regulating medical devices, including those for use in diabetes management. In July 2011, the FDA published draft guidance on the regulation of mobile medical apps, [49-50] which described its current thinking on the regulation of software that meets the definition of a medical device and is designed for use on a mobile or technological platform.

The FDA currently regulates many of these technologies, including glucometers, continuous glucose monitors, infusion pumps, and artificial pancreas devices.[51-53] Developers of these types of technologies would be best served by enhanced guidance from the agency that further defines the types of claims that may be made without crossing into the regulated territory.[54]

Diabetes management products are often complex, involving the integration of multiple components with many unique design and development challenges. Due to the sophistication of software-controlled technologies for diabetes management, regulatory authorities are increasingly focused on the ability of patients and healthcare professionals to operate these devices safely and with optimum effectiveness.

6. CONCLUSION

The technological advancements, coupled with increasing influx of new products into the market, are expected to propel the growth of global diabetes care devices market over the forecast period. The need for accurate, personalized, and evidence-based care solutions is driving constant new trends and developments in the digital diabetes management industry.

The current research in diabetes is putting considerable effort into developing decision support systems for patient use. Artificial intelligence enables patients with diabetes to make daily decisions about diet and intensity of activities. Researchers had designed a reinforcement learning algorithm-based system that aims to personalize messages for each patient's situation in order to better encourage them to automate their treatment. These advances save time and cost as data can be collected remotely and virtual management is replacing the routine visits to a clinic.

We are finally on the point of lessening the enormous daily load encountered by millions of individuals with diabetes by utilising the ability of artificial intelligence to find patterns from insulin dosage data for the purpose of decision assistance.

It is crucial to modernize the laws or rules for the device developers to draw well-understood connections between lifestyle including exercise and diet and the management of diabetes.

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