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Review Article

Future Prospects of Insulin Mutants, Biosimilars, Bioconjugates, and Newer Insulin-delivery Devices in Diabetes Mellitus

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Abstract

Insulin is the cornerstone of type 1 diabetes therapy and a crucial component for controlling type 2 diabetes. Despite significant advancements in insulin therapy research, including the creation of innovative insulin formulations and delivery systems, there are still numerous difficulties and unknowns surrounding insulin therapy. The main issues with more recent pharmacological and technological methods are biocompatibility, degradation/clearance of delivery materials, immunogenicity, stability, the precision of dosing, reproducibility of an effect similar to that of endogenous insulin, predictability of performance, and safety over time. In order to achieve a protracted, flatter profile, with fewer instances of hypoglycemia and an improvement in postprandial glucose level, more recent insulin mutants have been developed. The "meal" (glucose-responsive) insulins, which are supplied in accordance with an endogenous glucose-sensing feedback mechanism, best represent the future generation of insulin treatment. Insulin delivery methods with novel jet injectors, smart pens, patch pumps, and other needle-free tools for subcutaneous doses are another area of ongoing advancements. Digital health has significantly advanced treatments in recent years. As such, insulin treatments should become more scalable and potentially more cost-effective.

Introduction

Diabetes is one of the world's fastest-growing non-communicable chronic disorders. In 1980 a total of 108 million people worldwide had diabetes, and this number grew to 422 million in 2014.[1] Based on a report by the International Diabetes Federation (IDF) an estimated 700 million adults will have diabetes by 2045.[2] China has the highest number of diabetic patients worldwide (116 million), followed by India (77 million) and then the United States (31 million).[3]

A global study found that roughly 63 million people with type 2 diabetes need insulin treatment, while about 9 million people with type 1 diabetes mellistus (T1DM) depend on it for survival. Natural insulin, a polypeptide hormone produced by the pancreatic islets of Langerhans beta cells, largely controls how fat and glucose are metabolized, making it a vital and significant drug.[3] Frederick Banting and Charles Best initially identified the therapeutic applications of insulin in the year 1921, which was a significant turning point for contemporary medicine. Insulin thereafter took over as the cornerstone of T1DM treatment and a crucial supplement for the care of other kinds of diabetes and diabetic emergencies.[4,5]

Exogenous insulin formulations have made considerable advances, however, there are still several obstacles. The possible downsides that need to be addressed include immunogenicity, biocompatibility, degradation/clearance of the delivery substance, stability, dosage accuracy, repeatability, performance predictability, and safety over time. New formulations and delivery methods also need to be affordable and easily available in addition to having a good safety profile.

Novel insulin formulations that speed up the rate of rapid-acting insulin absorption and lengthen and flatten the action of basal insulins were developed to address these treatment-related difficulties (Table 1).[6–21,23a31a] The rate of insulin conversion can be altered, and its absorption from the injection site can be reduced using one of three main strategies: 1) changing the amino acid sequence of

Keywords: Insulin mutants; Biosimilar; Bioconjugates; Insulin-delivery devices; Diabetes mellitus.

Abbreviations: AI, artificial intelligence; BCLIS, bio chaperone lispro insulin; CGM, continuous glucose monitoring; ConA, concanavalin A; DNA, deoxyribonucleic acid; EDE, experimental device exemption; FDA, Food and Drug Administration; GBPs, glucose binding proteins; GOx, glucose oxidase; GRI, glucose responsive insulin; HbA1c, haemoglobin A1c; IDF, international diabetes federation; NPH, neutral protamine hagedorn; PBAs, phenylboronic acids; PK/PD, pharmacokinetics/pharmacodynamics; r-DNA, recombinant depxyribonucleic acid; T1DM, type 1 diabetes mellitous; T2DM, type 2 diabetes mellitous; TMR, transparency market research; URLi, ultra rapid lispro insulin.

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Table 1. Types of insulin preparation, uses, adverse effects and contraindications

Types of Insulin	Trade Name of Biosimilar	Uses	Adverse drug reactions	Contraindications	References
Insulin lispro	LY900014 (URLi)	ultra-rapid insulin	Hypoglycemia; Injection site reactions; Weight gain	Hypoglycemia. In patients who are hypersensitive to insulin lispro or to any of the excipients.	6–11
Insulin lispro	BioChaperone	ultra-rapid insulin	Hypoglycemia; skin rash, itching, redness,	Hypoglycemia. In patients who are hypersensitive to insulin lispro or to any of the excipients	12–14
Insulin aspart	AT247	Short-acting insulin	low potassium; swelling in your hands and feet; skin rash, itching, redness, or swelling;	Hypoglycemia. In patients who are hypersensitive to insulin aspart or to any of the excipients	15–17
Insulin glargine	ADMELOG	long-acting type of insulin	Severe hypoglycemia; Lipodystrophy; Weight gain; Peripheral Edema; Infusion site erythema and infusion site reaction	Hypoglycemia. In patients who are hypersensitive to insulin glargine or to any of the excipients.	18,19
Insulin aspart	Kixelle	Short-acting insulin	Hypoglycemia; Urticaria, rash, eruptions; Refraction disorders, diabetic retinopathy; Lipodystrophy; Injection site reactions, oedema; Peripheral neuropathy (painful neuropathy)	Hypoglycemia. In patients who are hypersensitive to insulin aspart or to any of the excipients.	20
Insulin glargine	Basaglar	long-acting type of insulin	Hypoglycemia; Urticaria, rash, eruptions; Lipodystrophy	Hypoglycemia. In patients who are hypersensitive to insulin glargine or to any of the excipients	21,22
Insulin glargine	SEMGLEE	long-acting type of insulin	Hypoglycemia; Lipodystrophy; Injection site reactions, oedema	Hypoglycemia. In patients who are hypersensitive to insulin glargine or to any of the excipients	22,23
Insulin glargine	REZVOGLAR™	long-acting type of insulin	Hypoglycemia; Lipodystrophy; Injection site reactions, oedema	Hypoglycemia. In patients who are hypersensitive to insulin glargine or to any of the excipients	24
Insulin glargine	Glaritus	long-acting type of insulin	Hypoglycemia; Injection site reactions, oedema	Hypoglycemia. In patients who are hypersensitive to insulin glargine or to any of the excipients	25–27
Glucose responsive insulin	MK-2640		Hypoglycemia; Lipodystrophy; Injection site reactions, oedema	Hypoglycemia.	28–31

insulin, 2) adding fatty acid components that change the link between insulin hexamers and affect their binding with albumin in the bloodstream, or 3) using additives that affect the insulin absorption rate. At the same time, researchers are looking at other possible treatments, including different insulin delivery methods that avoid conventional subcutaneous absorption and closed-loop technologies that dynamically regulate insulin supply depending on *in vivo* glucose levels.[5] This article analyzes future prospects and emphasizes current developments in insulin treatment.

Progress in insulin mutants: the link between structure and function

In a healthy person, insulin levels reach their peak 1 hour after eating a meal and then begin to fall within the next 2 hours. For diabetic patients, on the other hand, achieving a normal blood sugar profile and preventing nocturnal hypoglycemia requires a precise insulin peak timing and duration of action.[32] The single zinc ion that holds the insulin hexamer molecules together dissociates, releasing dimers and monomers into the circulation. By swapping one or two amino acid residues in the insulin molecule, recombinant DNA technology can create formulations of rapid-acting insulin. The ProB28 and LysB29 residues on the C-terminal end of the B-chain of the lispros homologue can be switched to LysB28 and ProB29 (Fig. 1).[33] Position 28 on the B-chain of aspart insulin has an aspartic acid substitution for proline.[34] Insulin with a speedier onset of action is produced via the alteration of aspartamine, which results in an increase in charge repulsion. Because protamine, a little nuclear protein rich in arginine, is present in neutral protamine hagedorn (NPH), the absorption rates are reduced. Protamine also prolongs the duration of insulin action and delays its beginning. By including zinc in its formulation, Lente does the same.

Meal insulin

Insulin can be given as a meal or a bolus to reduce the postprandial hyperglycemic peak that occurs after eating. The optimal meal insulin should enter the circulation quickly in order to replicate the natural physiological insulin prandial production. Since the devel-

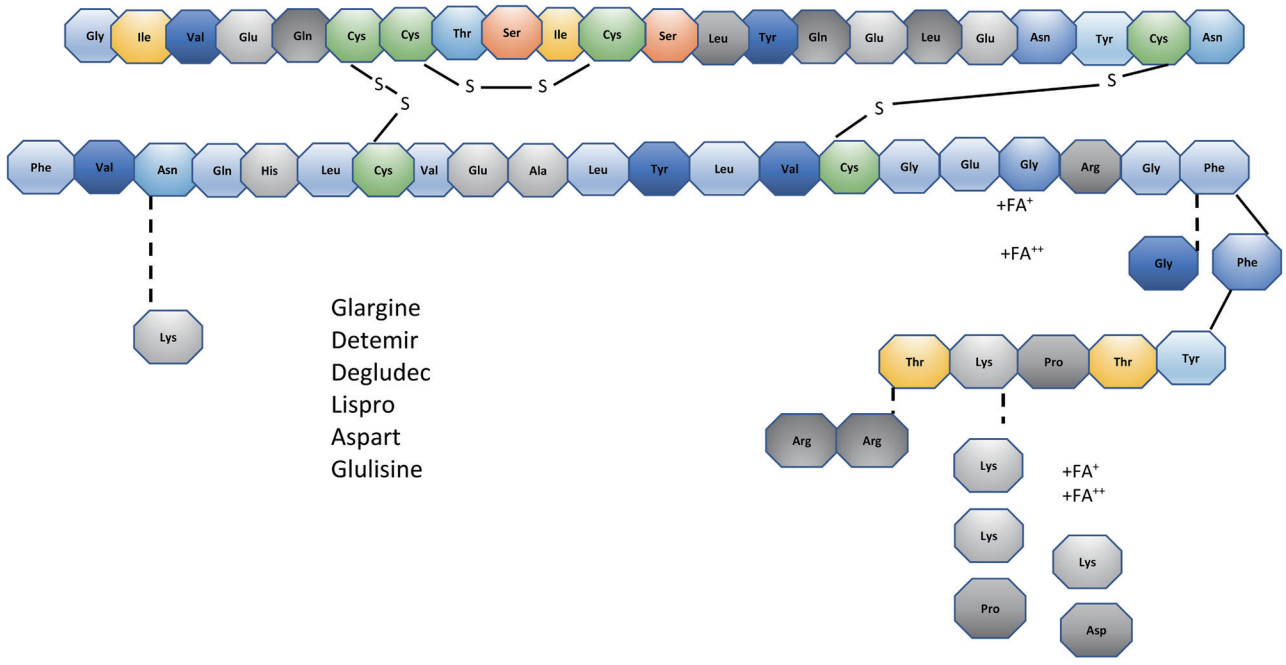

Fig. 1. Schematic representation of human insulin polypeptide and insulin analog showing the amino acid sequences of the two chains (A-chain and B-chain) linked by two disulfide bridges and changes in amino acid sequences in selected insulin analogues. *FA, fatty acid; **FA, fatty acid linked to lysine through a glutamic acid linker.

opment of a rapid-acting analogue, regular insulin has been seen as a less desirable alternative to meal insulin because of its delayed onset and prolonged duration compared to endogenous insulin in response to meals.

By altering one or two amino acids in the primary structure of the insulin molecule, it is possible to weaken the self-association of insulin monomers and create formulations with a quicker onset and shorter duration of action. This was done to overcome the slow onset and prolonged duration of regular insulin.[35]

These rapid-acting analogues showed a slight favourable effect in clinical tests on reducing HbA1c in T1DM patients, although a decreased incidence of hypoglycemia was noted compared to ordinary human insulin.[36] Patients with type 2 diabetes mellitus (T2DM) show less evidence of this therapeutic benefit.[37] Additionally, using rapid insulin right before meals rather than normal insulin (30–45 minutes beforehand) may increase adherence.

LY900014 lispro

The new ultrarapid formulation of insulin lispro, known as LY900014 (URLi), is intended to enhance glycemic control in individuals with T1DM and T2DM. It was created to lower HBA1c levels and hasten insulin absorption in circulation.

The effectiveness and safety of 1222 in comparison to lispro were reported in a double-blind, treat-to-target 26-week study of T2DM patients. The experiment showed a non-inferiority of 1222 with regard to HBA1c changes.[6] The frequency of severe hypoglycemia did not decrease much. URLi showed lower hypoglycemia rates 4 hours after a meal and better glucose excursions at 1 and 2 hours after on a meal test. With this insulin, there were no noted variations in tolerability.[7–11]

BioChaperone lispro insulin

Adocia created two ultra-rapid versions of the insulin analogue lispro, BioChaperone® Lispro U100 and BioChaperone® Lispro U200, to address the need for ultra-rapid insulin. For quicker absorption, BioChaperone® Lispro incorporates a unique excipient called BioChaperone BC222, a modified oligosaccharide molecule. The area under the curve for the 1 and 2 hour postprandial glucose excursions was 31% smaller with BCLIS than lispro in a different trial including T1DM patients who self-administered BCLIS at the beginning of a mixed meal test.[12] Adocia is a long-acting/short-acting combination formulation that combines BCLIS and insulin glargine with BioChaperone147, a polyanionic amphiphilic polymer. In T2DM patients who ingested a substantial mixed meal, this combination product demonstrated modest improvements in postprandial parameters compared with NPH/lispro mixed insulin and separate injections of glargine and lispro.[13,14] With this insulin, there have been no documented changes in local tolerability.

"Superfast" insulin aspart

AT247 (Arecor Limited Little Chester-ford, UK) is a new insulin aspartamine formulation that uses excipients with metal ion binding ability. It is intended to deliver an improved time-action profile following subcutaneous injection. Insulin's excipient component binds to calcium ions. By temporarily disrupting calcium-dependent cell adhesion at the injection site through reversible interactions with the calcium-cadherin complex on the cell surface, this increases tissue permeability and speeds up the absorption rate.[15–17] AT247 has been shown to dramatically improve postprandial glucose control in T1DM patients in a newly published European Phase I clinical investigation, and it was reported to prevent episodes of both hypoglycemia and hyperglycemia.

Admelog

Admelog is the first short-acting insulin that has been authorised

for use as a "follow-on" medication, which is given right before meals to regulate blood sugar levels after meal consumption. They can also be used in conjunction with insulin pumps to accommodate both the pre-meal and post-meal insulin requirements.

Admelog was authorised under the 505(b)(2) route, a streamlined approval process under the Federal Food, Drug, and Cosmetic Act. In accordance with this method, the Food and Drug Administration's (FDA's) assessment of the safety and efficacy of a newer drug application or published research supporting the safety and/or effectiveness of the proposed product may be used to approve the application. Because of these shortened drug development processes, patients may get medications for less cost.

Hypoglycemia, itching, and rash were the most frequently reported adverse medication responses during the clinical trial. Injection site responses, allergic reactions, and thickening or thinning of the adipose tissue at the injection site were among the other negative side effects (lipodystrophy).[18,19]

Kixelle (MYL 1601D)

The human insulin analogue Kixelle, developed by Biocon as a biosimilar of Novo Nordisk's NovoRapid/Novolog (insulin aspart), is made using recombinant DNA technology and Pichia pastoris (yeast). Except for the substitution of an aspartic acid residue for a single proline amino acid at position 28 in the C-terminal region of the insulin B-chain, the main structure is comparable to that of endogenous insulin.

Compared to regular human insulin, MYL-1601D starts working faster and wears out faster. Insulin aspart, a fast-acting counterpart of insulin, is the ingredient that makes MYL-1601D active. Lower blood glucose levels result from insulin aspart's facilitation of glucose absorption in muscle and fat cells and concurrent reduction of glucose production from the liver.

MYL-1601D was given approval because it exhibits similar clinical efficacy to NovoLog® (NovoLog), which the US has licenced, and NovoRapid® (NovoRapid), which the EU has authorized, in terms of physicochemical properties, biological activity, phramacokinetic and pharmacodynamic (PK/PD), safety, and efficacy, including immunogenicity. Other effectiveness endpoints, including the treatment-emergent antibody response (TEAR), were similar in both groups.[20,38]

Basaglar

An analogue of human insulin called Basaglar is created using recombinant DNA technology and a particular strain of E. coli. It is intended to be more predictable and to have fewer hypoglycemic spells, particularly at night. Its structural makeup is based on that of human insulin and insulin glargine, where two more amino acids, arginine at the C and B chains, are added and glycine replaces aspartic acid at position 21 at the C end of the A chain. Glycine with a neutral charge at the C terminus of the A chain stabilizes insulin glargine and inhibits the generation of deamination products. Basaglar was also authorized under the Federal Food, Drug, and Cosmetic Act through a shortened approval process known as the 505(b)(2) pathway. Its use is recommended for adults with T2DM and pediatric patients with T1DM to maintain better glycemic control. The solubility of insulin glargine is decreased after subcutaneous injection, generating a tiny precipitate that is progressively broken down into monomers and released into the circulation because the pH value (7.4) of tissue fluid is near the isoelectric point of insulin glargine. Its baseline insulin released throughout the day is comparable to that of healthy individuals and can have a consistent and long-lasting effect.[39,40]

Insulin biosimilar products

A biological product is considered to be biosimilar if it is extremely comparable to another biological product that has already received FDA approval (also known as the reference product) and is not significantly different in any other clinical aspects.[21] This implies that a biosimilar produce will provide the same level of safety and efficacy as the reference product. Similar to how generic pharmaceuticals have cut prices, biosimilar and interchangeable biosimilar goods have the potential to lower health care expenses. The first list costs of biosimilars sold in the United States were generally 15% to 35% less expensive than the comparable list prices of the reference drugs.[22]

SEMGLEE (insulin glargine-yfgn)

Exogenous insulin is injected subcutaneously after a delayed absorption to maintain 24 hour stable blood insulin levels. Initially, this effect was produced by the insulin molecule's isoelectric point changing, which reduces solubility at the injection site and encourages delayed absorption. Its reference product Lantus (insulin glargine), a long-acting insulin analogue, is interchangeable with SEMGLEE (insulin glargine-yfgn), the first biosimilar. SEMGLEE can be expected to produce the same clinical outcome as Lantus in any given patient, according to its clinical trials, and switching between SEMGLEE and Lantus carries no additional risk over simply using Lantus without switching. In the US, SEMGLEE is 64% less expensive than Lantus based on its wholesale purchase cost, which is around 22% less than Lantus. Hypoglycemia, life-threatening allergic responses, hypokalemia, and heart failure are just a few of the dangerous adverse effects associated with SEMGLEE. Oedema (fluid retention), lipodystrophy (pitting at the injection site), weight gain, and allergic responses, such as injection site reactions, rash, redness, discomfort, and severe itching, are the most frequent adverse effects associated with insulin glargine products other than hypoglycemia.[22,23]

REZVOGLAR™

A biosimilar of Lantus is REZVOGLAR™ (insulin glargine). Its mechanism of action is extremely similar to that of insulin glargine because it is a biosimilar of insulin glargine-aglr. Although Rezvoglar can be taken in place of Lantus, patients require a prescription written expressly for Rezvoglar, as the two medications are not interchangeable. Rezvoglar, like Lantus, cannot be used to manage diabetic ketoacidosis. The recognized major adverse effects of Rezvoglar include hypoglycemia, severe allergic responses, hypokalemia, and heart failure.[24]

Glaritus®

Wockhardt created Glaritus®, a biosimilar of insulin glargine. Glaritus® is administered as an injection of 100 IU/mL insulin glargine generated from r-DNA. Glaritus® and Lantus® have contrasting effects in both T1DM and T2DM patients, as well as healthy volunteers. Glaritus® and Lantus are bioequivalent, according to research involving healthy volunteers.[25] In a 12-week trial of adult patients with T1DM, Glaritus®, a biosimilar insulin glargine, was found to have glycemic control that was on par with Lantus®.[26,27]

Insulin bioconjugates

The majority of glucose-responsive insulin (GRI) devices employ polymeric biomaterials with embedded insulin. This polymeric substance contains glucose-responsive components, including glucose-binding proteins (GBPs), glucose oxidase (GOx), and phenylboronic acids (PBAs), which control the release of insulin

by degrading the polymer, altering the structure of the matrix, or competing with glucose for binding.[41] The most popular GBP utilized in polymeric materials for insulin administration is concanavalin A (ConA). ConA is employed as a crosslinker for the production of glucose-containing biopolymers because it possesses four high-affinity glucose binding sites.[42] Free glucose competes with bound glucose for binding sites as blood sugar levels rise, breaking the polymer bond and causing the release of insulin. As a catalyst, enzyme GOx transforms glucose into gluconic acid and produces hydrogen peroxide. When GOx is incorporated into the polymer matrix, acid-sensitive groups induce a glucose-triggered reaction (volume change or matrix disintegration), which causes the matrices to release insulin. PBAs, a subclass of tiny molecules, combine with 1,2- or 1,3-cis diols to create a complex that is negatively charged. Because PBAs may bind to glucose and other sugar sources, they are frequently used in cross-linked polymeric matrices. They swell and combine with glucose to produce a negatively charged complex, which triggers the release of insulin.[43] All of these methods for delivering insulin required either administration tools (such as microneedles) or matrices to encapsulate the insulin that will be released when blood glucose levels are raised. However, a few bioconjugation techniques are accessible that do not impair insulin's bioactivity due to its tiny size.[44,45] The most recent four methods to achieve glucose responsiveness using modified insulin molecules without the need for exogenous matrices are PBA-Modified Aliphatic Insulin Conjugate, Red Blood Cell-Bound Insulin Conjugate, PBA-Modified Aliphatic Insulin Conjugate, and Glucose-Responsive Insulin Through Mannose Receptor Interactions.

MK-2640 as a future novel GRI bioconjugate

The most advanced GRI bioconjugate is the Merck candidate, MK-2640. The findings of a phase 1 study released in 2018[28] implied that careful consideration should be given before clinical administration of GRI bioconjugates that are created through adding partners such as mannose receptors, albumin, and red blood cells. Designing new GRI bioconjugates presents a number of challenges, but the main one is the method for detecting glucose. The only minor molecule other than sugar currently employed in GRI designs is PBA. Although PBA's glucose interaction fits serum glucose levels well, its poor selectivity (10-fold greater affinity to fructose than glucose) raises questions. However, one potential future approach to overcome this issue is to employ bidentate PBA as a selective glucose sensor.[29,30] Utilizing *de novo* glucose sensors to produce GRIs - lectin molecules that bind selectively to glucose - is another tactic to address this low glucose selectivity.[31] A patent application on glucose-sensitive hydrazone reactions was recently published by Jensen *et al* (Glucose-sensitive peptide hormones, WO2018115462A1). They noticed that the hydrazone dissociation characteristic was glucose dependent. For GRI designs, these hydrazone linkers might be linked onto insulin molecules.

Newer devices in the diabetes therapy area

According to a recent industry report by Transparency Market Research (TMR), there are different companies worldwide manufacturing global digital therapy devices, and there is fierce competition between them. This market of digital therapy devices is growing daily, as more and more people use technology to treat their medical conditions. The availability of knowledgeable consumers who are aware that technologically cutting-edge items are available to cure a medical condition, as well as greater disposable income that enables them to choose these products, promote the market for digital therapeutic devices. As more medical device companies enter this market with their technological prowess, the competitive environment is likely to intensify. By the end of 2025, the digital therapy device market is expected to generate $2,082.3 million in revenue.

A collaboration between Danish pharmaceutical giant Novo Nordisk and a Taiwanese chronic disease company Health2Sync will enable patients receiving insulin therapy to wirelessly transmit dose logs to a mobile health app. Field comms can now synchronize patient dose logs, including the time and dose of each injection. Because of this connectivity, patients can view their insulin data on the patient management platform, while doctors can view their insulin readings and analysis along with other health data on the Health2Sync app. The Alliance is also launching a patient support initiative that will develop age-appropriate, customized educational materials for T1DM patients. These materials include information about their condition, how to use insulin, what to look out for with the changing seasons, how to manage adverse health conditions, and stories from other T1DM patients.[46]

By the mid-2000s, technology had progressed to continuous glucose monitor-driven predictive insulin suspension that reduced severe hypoglycemic episodes by 83%. The year 2016 saw the launch of the hybrid closed-loop algorithm (MiniMedTM 670G) for automated basal insulin administration. The 670G study improved time in range (70–180 mg/dL) and decreased time under range (70 and 50 mg/dL) in a clinical trial. The MiniMedTM 780G*, an advanced hybrid closed-loop system, provided even better glycemic control and minimized post-meal hyperglycemia brought on by missing, delayed, or underestimated meal boluses by providing a lower glucose goal and autocorrection boluses administered every five minutes.

The FDA has approved DreaMed Advisor Pro, an artificial intelligence (AI)-based diabetes treatment decision support tool that is intended to help medical professionals manage persons with T1DM who use insulin pumps and continuous glucose monitoring (CGM). DreaMed Advisor Pro, a cloud-based digital tool, analyzes data from an insulin pump, a CGM, and blood glucose self-monitoring to offer suggestions for administering insulin. The system, according to DreaMed, employs event-driven learning to better understand each individual before recommending adjustments to the patient's basal rate, carbohydrate ratio, and insulin pump correction factor. The FDA's decision supports what we consider to be an important step in forging a deeper bond between healthcare professionals and their T1DM patients. The *de novo* request for the DreaMed Advisor Pro is the most recent illustration of how AI is reshaping the diabetes sector. The FDA has granted a start-up company Beta Bionics an Experimental Device Exemption (EDE), enabling Beta Bionics to enroll patients in home trials of the iLet Bionic Pancreas System in its insulin-only configuration. The business uses AI and glucose monitoring to design the system.[46]

The US FDA produced Insulia, a thoroughly proven digital therapeutic solution that has CE approval for numerous international markets. Diabetes patients may self-manage their condition with Insulia, and healthcare companies can remotely monitor changes. Insulia is the first regulatory-approved digital therapeutic to offer automatic titration for all types of basal insulins.[47]

Future perspectives

Due to the expanding variety of insulin therapy options, diabetes

care is transitioning from a one-size-fits-all approach to customized treatment regimens suited to the patient's needs. Proper dose titration is essential to achieve glycemic goals. In practice, doctors and people with diabetes often disregard recommendations for optimal titration because they find them very stressful. If fasting blood glucose is the determining factor, a digital therapeutic platform for diabetes management could develop an immediate feedback system that encourages patients to follow their treatment recommendations. An observational study illustrates the potential use of a digital diabetes management platform for the self-management needed by insulin-treated users, including their daily use and maintaining behavioural changes.[48]

Digital health-aided treatments have the potential to be a cost-effective, scalable, and effective for treating T2DM patients in underserved groups. Telemedicine education programs for diabetes in primary care are reasonably priced in the short term, while additional long-term research is required. The majority of behavioural or community health treatments for T2DM need a sizable commitment from participants as well as staff in terms of time, money, and effort. As a result, these methods only succeeded in reaching 1% of their intended viewers. Finding ways to integrate real-time participant feedback, device-free remote participant monitoring, and coaching via the phone and SMS can not only address some of these difficulties but also raise participant engagement and self-efficacy. Additionally, personalization can help treat diabetes by removing some obstacles. Motivational interviewing and health coaching are used to assist patients in creating SMART goals–specific, measurable, achievable, relevant, and time-based—that are catered to the patients' particular requirements and circumstances. It should be noted, though, that studies on diabetes health coaching have yielded different levels of positive clinical effects.[49]

Demand for telemedicine and home care is growing rapidly around the world, and several healthcare systems are now offering reimbursements to individuals who qualify for such services. Voluntis is developing digital medicines that enable people with chronic illnesses to take control of their daily care to improve outcomes. Voluntis solutions combines mobile and online apps to give the patient and care team personalized advice, such as changing medication dosage, controlling side effects, or monitoring symptoms. These instant suggestions are based on digitized clinical algorithms. Using its Theraxium technology platform, Voluntis has developed and managed a range of digital therapies, particularly in the areas of oncology and diabetes.

AI will be essential to accomplish the ultimate dual objectives of near-normal glycemia and decreased burden. It is important to control diabetes mentally, and this cannot be stressed enough. Patients who are constantly faced with choices may get overwhelmed, abandoning even the greatest technologies. Multiple dosing decisions must be made by meals, exercise, and other activities under the current methods. By encouraging pharmaco-adherence and offering individualized care, incorporating AI through a frequently updated "digital twin" could mitigated daily obstacles to self-care. Machine learning can interact with the digital twin using physiologic and/or activity sensors built into smartphones or wearables to give individualized therapy that improves glycaemia while reducing load. For instance, geolocation on a smartphone can give the proper insulin dose before the meal and forecast the contents of an upcoming meal based on historical behavior. The amount of food consumed, as well as the start and end of the meal, can be determined using hand gesture sensing.

Fitness trackers can measure the duration, intensity, and glycemic response of exercise so that insulin supply can be modified as necessary. By maximizing glycaemic control through individualized medication, iteratively updating algorithms put us on the verge of creating a real artificial pancreas.

Conclusions

This review highlights the various types of insulin and recent development in insulin therapy. Additionally, this review focuses on various difficulties and challenges faced by diabetes patients and tries to identify possible solutions for them. Due importance has been given to recent developments in the space of AI and machine learning in diabetes therapy and digital therapeutics. With fast technological development and research in diabetes space, reversal of diabetes, precision and integrative medicine could significantly benefit patient in the near future.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

AB proposed the review aim. AB, HP, and AG collected and organized literature and data. AB and HP drafted the manuscript. HP and AG advised on the structure and the content of the manuscript. AB and HP revised the manuscript. All authors have read the manuscript and approved the final manuscript.

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