Review Article

Role of insulin in management of type 2 diabetes mellitus

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ABSTRACT

The prevalence of type 2 diabetes mellitus and its resultant morbidity and mortality is rapidly increasing. An important factor in reducing the microvascular complications of diabetes is strict glycemic control. Most patients require additional insulin therapy in spite of regularly taking oral anti-diabetic drugs. Though classically used later in the natural course of the disease, newer treatment guidelines suggest early initiation of insulin analogues. The discovery of insulin has been hailed as one of the most dramatic events in the history of diabetes, improving the life-span of most diabetics. Replacement insulin therapy should mimic physiological insulin release patterns. Modern insulin and its analogues have been developed to serve as an ideal replacement therapy. There are various insulin preparations available in the market and each of them has their own advantages and disadvantages. The modern insulin's have been developed to overcome certain side effects of the older preparations. A range of insulin products are under development that aim to increase absorption prolong action and provide alternative delivery methods. Greater patient adherence is important since most patients are reticent about insulin therapy. This review describes the role of insulin in the management of type 2 diabetes mellitus.

Keywords: Diabetes mellitus, Insulin therapy, Recombinant insulin, Replacement insulin

INTRODUCTION

Insulin is an anabolic hormone and most effective glucose lowering agent available. It is recommended for usage in T1DM as sole therapy and in T2DM patients failing to control sugar levels with oral hypoglycemic drugs.[1,2] Insulin secretion occurs in a dose dependent manner from beta cells throughout the day. Oral carbohydrate diet secretes insulin in a dose dependent manner, which includes a large first phase insulin release suppressing hepatic glucose production and later followed by a slower second phase insulin release covering ingested carbohydrates.[3] Diabetes mellitus is a chronic disease affecting a large number of people all over the world characterized by progressive beta cell failure and failure to adhere glycemic control.[4,5] Diabetes is also a leading cause of morbidity and mortality and a burden to health care systems leading to both direct and indirect costs. Most times multi-drug therapies and life style modifications have failed to control high sugar levels, requiring doses of insulin for treatment.[6,7] Thus, effective control of prandial and post prandial sugar levels is important to prevent side effects and life threatening complications of diabetes. Also aggressive

diabetes treatment strategies have improved insulin therapies and implementation techniques.[8] Yet, studies conducted have shown delay in initiation of insulin treatment when required which ultimately lead to loss of glucose control even with oral hypoglycemic agents.[9,10]

So, there are concerns about when to start insulin treatment? Why is it delayed and why not imitated early to be effective and limit complications? Some of the setbacks found are fear of hypoglycemia, psychological stigma of being treated with insulin, concern for accompanying weight gain, fear of injection and need of an experienced professional to titrate and administer dose.

Maintenance of glucose levels with help of oral hypoglycemic agents (OHA) is frequently insufficient and if found association with beta cell failure, insulin therapy is a must and may need intensification.[11,12] In UKPDS study, it was found that more than half of new diagnosed type 2 diabetic patients needed additional insulin therapy within 6 years of OHA therapy.[13] Another non-interventional study called A1chieve study of 6 months was done on 66726 patients of type 2 diabetes having baseline diabetes of 8 years duration. Insulin users (32.8%) and non-insulin users were (67.2%) and mean HbA1c values of 9.5% (SD 1.7) and 9.4% (SD 1.8) respectively. Diabetic complications were found in 30-90 % cases.[14,15] Many studies including UKPDS follow up and ORIGIN trial have concluded saying insulin treatment to be safe if initiated early in disease but other studies like ACCORD and VADT trial found contradictory to it and quoted insulin increase cardiovascular risk and all-cause mortality.[16-19]

Research is going every day to make newer insulin formulations with a precise focus on innovative insulin delivery methods ensuring more of a physiological daily insulin profile. This will make patient life easier and reduced risk of complications. From past till today many operative manipulations are being done in insulin structure to a yield a product physiologically similar to insulin along with safety and efficacy. Many short and long acting insulin analogues are serving as alternatives to human insulin. The present article will deal with insulin history, pharmacological actions, various preparations, current insulin usage guidelines and side effects.

DISCOVERY OF INSULIN AND DEVELOPMENT

Insulin was discovered in year 1921 by Banting and Best after a lot of controversy over it, for patients suffering from diabetes mellitus (DM) Islets were described by Paul Langerhans, a german medical scientist but couldn't correlate any function for them.[20] Later in 1950, Frederick Sanger determined the molecular structure of insulin for which he was awarded with a nobel prize.[21] Isletin (a crude form of pancreatic extract) was recognized by Banting. James Collip, a chemist from

university of Toronto helped him to remove impurities from pancreatic extract and to change name of purified pancreatic extract to Insulin. Eli Lilly made potent Insulin preparations from pork pancreas. First, insulin was administered to a 14-year-old boy called Leonard Thompson suffering from type-1 DM on January 11, 1922 which played crucial role in transforming his life.[1,2] Earlier insulin preparations produced a quick action and peak effect but lacked efficacy to provide low basal level of insulin as pancreatic beta cells. As source of insulin was non-human, many recipients suffered from allergic reactions. This increased focus of researchers to create better insulin preparations.[2]

Intermediate and long acting insulin's were subsequently developed as basal insulin analogs to balance normoglycemia. Neutral Protamine Hagedorn (NPH) insulin, intermediate acting insulin was discovered in 1936 and marketed in 1950. Recent guidelines have halted use of NPH insulin, as reduced hypoglycemic risk and good consistency including basal insulin levels for 24 hours are positive upfront features of newer insulin analogs. NPH insulin is still widely used in some countries due to cost considerations.[10] Lente and ultralente were other basal insulin's, introduced in year 1950 which had extensive usage for many year but due to certain limitations like variability in absorption and duration of effect and inconsistent blood sugar level decreased their usage.[9] In 1982, production of synthetic human insulin was recommended by US FDA having faster onset and shorter duration of action when compared to animal insulin.[22] In 1990, rapid acting insulin analogues were introduced in market have a faster onset and shorter duration of action compared to human insulin. Aim was to control prandial glucose levels without hypoglycemic risk.[23] Detemir and Glargine are the long acting insulin analogues which were later introduced in market providing flatter insulin concentrations, less side effects, better fasting plasma glucose concentrations and reduced nocturnal hypoglycemia.[24] In today's era, recombinant DNA technology made possible to modify insulin structure yielding regular insulin analogs mimicking effects of endogenous insulin with similar pharmacodynamics and pharmacokinetic properties.

PHARMACOLOGICAL ACTIONS OF INSULIN

Insulin is a two-chain polypeptide having 51 amino acids and molecular weight 6000. Major role of insulin is in management of patients suffering from type 1 DM having advanced beta cell deficiency. Insulin directly acts on tissues to regulate glucose homeostasis, unlike other oral hypoglycemic agents requiring presence of sufficient endogenous insulin to act as insulin sensitizers, insulin secretagogues, incretin mimetic, amylin analogs and other factors.

Insulin has anabolic action and insulin signaling is critical for promoting uptake, use and storage of major nutrients

like glucose, lipids and amino acids. Insulin stimulates glycogenesis, lipogenesis, and protein synthesis. Some effects of insulin (e.g., activation of glucose and ion transport systems, phosphorylation or dephosphorylation of specific enzymes) occur within seconds or minutes; other effects (e.g., to promote protein synthesis and regulate cell proliferation and gene transcription) manifest over minutes to hours to days.[25]

Insulin action is mediated by tyrosine kinase receptor. Insulin receptor is composed of 2 alpha and 2 beta subunits linked by disulfide bonds. Insulin regimens are to be tailored in individuals depending on patient's type of diabetes, sugar levels, age, eyesight, and personal preferences.[26] Glucagon like peptide-1 (GLP-1) is an important incretin hormone which favors insulin release from pancreatic beta cells. Exenatide and liraglutide are the drugs available in market which mimics actions of GLP-1 stimulating insulin release and are called as Incretin mimetics. Dipeptidyl peptidase-4 (DPP-4) is another enzyme involved in GLP-1 breakdown and less insulin release. Inhibition of DPP-4 by drugs like Sitagliptin and class would enhance availability of GLP-1 enzyme and increased insulin release.[27]

MODERN INSULINS

Recombinant DNA technology made possible in year 1980 to establish production of recombinant human insulin. Standard insulin preparations had limiting pharmacokinetic and pharmacodynamics properties with frequent hypoglycemic episodes which provoked researchers to generate safer insulin formulations closely duplicating endogenous insulin secretion. Modern insulin preparations have properties characterized by flexible, predictable and physiological action profiles with reduced hypoglycemic risk.[28]

Broadly speaking, insulin analogues can be categorized in two different classes: rapid acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine); and long acting insulin analogues (insulin glargine and insulin detemir). Biphasic insulin analogues have a mixture of rapid or short acting insulin analogue with intermediate-acting insulin.[29] Table 1 shows Pharmacokinetic profiles of Insulin therapies.

Rapid acting analogues

Rapid acting analogues were developed by genetic engineering and as alternative to soluble insulin. They need to be given subcutaneously and onset of action in approximately 15 minutes, peak at 1 hour and last 3-4 hours. It can be injected before, during or immediately after meals.[29]

Insulin lispro (Humalog)

It is first genetically engineered rapid acting insulin analogue developed with aim of controlling post prandial

glycemic excursions and approved for clinical use in 1996. Reversal of proline at 28 and lysine at 29 positions in the B chain leads to creation of a molecule differing from human insulin, which pertain a faster absorption profile, high peak serum levels and shorter duration of action in comparison to regular insulin. Onset of action is in 15 minutes and duration of action for 2-3 hours. It needs to be given 15 minutes before or immediately after a meal. Lispro is also known to improve postprandial leptin and ghrelin regulation in type 1 diabetes patients and plays a role in gestational diabetes patients by keeping sugar levels in a target range and avoidance of complications like macrosomia.[30-32]

Insulin aspart

Insulin aspart (Novorapid) differs from human insulin by substitution of proline in B chain at position 28 with charged aspartic acid. It has absorption profile twice faster as compared to human insulin. When administered directly before a meal, it has shown better glycemic control with onset of action in 10-20 minutes, peak at 45 minutes and duration lasting 1-3 hours. Reduced risk of nocturnal hypoglycemia seen if used in pregnant women suffering from type 1 diabetes.[31,33,34]

Insulin glulisine

Insulin glulisine (Apidra) is the most rapid-acting insulin analogue launched in 2004. It differs from human insulin at 2 points: asparagine is substituted by lysine at position 3 and lysine substituted by glutamic acid at position 29. Such altered formulations have enhanced effect of subcutaneous insulin depots. Better therapeutic responses are seen in obese type 2 diabetes patients compared to type 1 patients.[31,35,36]

Long-acting insulin analogues

The long acting insulin analogues were developed on demand, as traditionally available intermediate and long acting insulin's like isophane, lente and ultralente did not fulfill requirements of ideal basal insulin for providing a 24 hour glycemic control.

Development was based on two principles:

- Change of insulin pH to neutral which allows precipitation in subcutaneous tissue delaying absorption.
- Binding of insulin to a serum carrier with a prolonged half-life and thus delayed activity.

Insulin glargine (Lantus)

Insulin glargine is first long-acting insulin analogue with structural amino acid modifications in both chains. In A chain, substitution of asparagine by glycine at position 21 and in B chain, there is elongation at C terminus by addition of two arginine residues. Elongation causes the

point of least solubility to shift from 5.4 to 6.7 making insulin glargine at physiological pH of subcutaneous tissue. Insulin glargine bears a stable serum concentration pharmacodynamically without peak interval and a prolonged duration of action almost up to 26 hours. It is administered subcutaneously at bed-time. Decreased risk of hypoglycemic episodes, less fluctuations and lowered risk of nocturnal hypoglycemia compared to NPH or ultralente insulin's.[37-39]

Insulin detemir (Levemir)

Insulin detemir is produced by acylation of myristic acid to the lysine residue at position 29 and deletion of threonine at position 30 in B chain. Acylation of insulin molecule with fatty acids results in albumin binding and increased self-association of insulin hexamers with a delayed resorptive capacity. Administration of insulin detemir in type 2 diabetes patients is suitable if given in a basal bolus regimen. Favored pharmacodynamics profile causes flatter plasma insulin concentrations on injection, less nocturnal hypoglycemic episodes with suppression of hepatic glucose production. Bed time administration may not be necessary. Action lasts up to 24 hours.[38,40,41]

Insulin degludec

Insulin degludec is newer inulin analogue prepared by desB30 insulin acylation at LysB29 residue with a glutamate linker and a hexadecandioyl fatty acid side chain.[42] Insulin receptor binding specificity and a metabolic to mitogenic ratio comparable to that of human insulin is seen with degludec. It has a mea half-life of 24.5 hours and metabolic effects are apparent at 42 hours post dosage.[43,44] Type 2 diabetes patients have reduced hypoglycemic risk on treatment with insulin degludec and also a cost effective alternative compared to insulin glargine.[45]

Insulin glargine U 300

GlargineU300 is a new compound approved by US FDA in 2015 which has ability to control glucose levels up to 36 hours.[46] It is given as subcutaneous depot injection in a small area which results in a more gradual, long-term and flatter insulin release. A trial comparing insulin glargine U 300 with glargine in patients with type 2 diabetes was done, who received basal-bolus insulin or basal insulin plus OHA's. HbA1c reductions were equivalent in both groups but less incidences of hypoglycemia were found in glargine U 300 group after 6 months of treatment.[47-49]

Intermediate acting insulin analogues

Standard insulin analogue is isophane insulin - also known as Neutral protamine Hagedorn (NPH). It has onset of action in 2-4 hours, peak at 6-7 hours and lasting up to 16 hours. Isophane insulin's are used as twice daily insulin regimens. It can be mixed with soluble insulin but

already mixed preparations are available in market such as biphasic isophane insulin, biphasic insulin aspart or biphasic insulin lispro.[50]

Another route of administration is continuous subcutaneous insulin infusion (CSII)- insulin pump therapy-with an adjustable infusion given via an indwelling catheter, supplied from syringe reservoir worn under patient's clothing. CSII is particularly helpful for patients with recurrent hypoglycemic episodes, delayed meals or pre-breakfast hyperglycemia.[51]

Table 1: Pharmacokinetic profiles of various insulin analogues. reference from article (permitted).[114]

Insulin type	Onset	Peak	Duration
Long Acting			
Detemir	3 to 4 hours	6 to 8 hours	6 to 23 hours
Glargine	90 minutes	None	24 hours
Intermediate-acting			
NPH	1 to 2 hours	4 to 10	14 or more
Short-acting			
Aspart	15 minutes	1 to 3 hours	3 to 5 hours
Glulisine	15 to 30 minutes	30 to 60 minutes	4 hours
Lispro	15 minutes	30 to 90 minutes	3 to 5 hours
Regular	30 to 60 minutes	2 to 4 hours	5 to 8 hours
Mixed			
NPH/Lispro or Aspart	15 to 30 minutes	Dual	14 to 24 hours
NPH/regular	30 to 60 minutes	Dual	14 to 24 hours

ADVANTAGES, DISADVANTAGES AND SIDE EFFECTS

Insulin advantages and disadvantages depend upon type of therapy, route of administration and dosage. Insulin therapy offers advantage when effective and proper doses are selected. Major benefit is seen in patients who have elevated sugar levels in morning. The prime advantage of insulin is that the dose can be adjusted in very fine gradations allowing more precise control of sugar. Insulin analogues vary in cost depending upon what kind is prescribed and the expected dose, but is less expensive that the newer diabetes medications.[52]

Desired objectives of blood glucose levels up to 120 mg/dl and HbA1c less than up to 7% or less can be effectively achieved by insulin therapies. Insulin usage has reduced the incidence of microvascular complications, such as nephropathy, neuropathy, and retinopathy by strict glycemic controls in both types of diabetes mellitus patients.[53-55]

Multiple injection therapy is cost effective, simple and reliable to use. Both long acting and short acting preparations can be given by insulin syringe or pen. Some people find it embarrassing to use syringe or a pen at public places as sites of administration being lower abdomen and upper arm due to clothing. Injections are painful at times. In contrast to insulin pumps, insulin injections if required 5-6 times can be inconvenient. Insulin pumps are size of a cell phone and acts as a reservoir connected to a catheter for continuous subcutaneous infusion. Pumps help to maintain blood glucose levels in desired range. Sometimes pumps can be uncomfortable and cause skin irritations.[56]

Recently approved inhaled insulin is getting popularity in treatment of diabetes in which is injected directly to lungs (pulmonary insulin). This technology has reduced daily injection regimens and beneficial for those who harbor needle phobias. Insulin absorption is better over large surface area of lung and can be used in both types of diabetes patients.

Needs training for proper use of inhaled insulin device and concerns are still been raised about safety of inhaled insulin preparations regarding compromised lung capacity or damage to lung tissue on long term use.[57]

Hypoglycemia is the most common and serious side effect of insulin, occurring in approximately 10% cases of type 2 diabetes. The incidence however varies greatly depending on the population studies; type of diabetes, etc.[58] The risk for developing hypoglycemia is higher in patients receiving intensive or continuous infusion insulin therapy. An unusual ocular disturbance during the beginning of therapy is bilateral presbyopia (blurry vision). This is thought to be due to changes in the osmotic equilibrium between the lens and the ocular fluids, and is usually self- limiting.[59]

Dermatologic reactions to insulin can result in lipohypertrophy, since insulin is lipogenic and probably immunologically- mediated. Subcutaneous insulin injections may be complicated by infection if proper hygiene is not maintained.[60] Hypersensitivity reactions, both local and systemic are rarely seen (less than 1% of patients) due to availability of purer forms of insulin.[61]

The cardiovascular consequences of hyperinsulinemia are being evaluated. Its role in hypertension and heart rate stimulation are being studied.[62] Generalized weight gain is seen in most diabetic patients on insulin therapy. It may present as edema associated with abrupt restoration of glucose control in previously uncontrolled cases. Intensive therapy leads to increased body fat as a consequence of elimination of glycosuria and a reduction in 24-hour energy expenditure.[63]

Rare cases of gastrointestinal distress have been associated with insulin therapy which tends to resolve with dose reduction.[64]

ROLE OF INSULIN IN CURRENT TREATMENT

Insulin has classically been considered as the only option for the treatment of type 1 diabetes mellitus. However, as a treatment regimen for type 2 diabetes mellitus, it is considered as last resort and is delayed until all options by the patient and the healthcare provider have been exhausted.[65] As treatment guidelines and insulin products are being refined, it is recommended to include insulin, particularly basal insulin, as a component of the treatment regimen earlier in the disease process.[66] Timely insulin administration has the potential of achieving the most effective reductions in hyperglycemia. However, the initiation of insulin therapy requires a greater use of resources, time and a combined effort from patient and the healthcare provider.[67] Since most patients are reluctant to initiate multiple daily injections of insulin, insulin initiation often involves basal-only therapy in addition to existing oral drug therapy. When used in this fashion, the role of basal insulin changes to preventive nature from the existing damage control role.[68]

Many patients are reticent about initiating insulin, so therapies allowing insulin treatment needs to be tailored to individual needs, which might likely resulting in greater acceptance and patient compliance.[69] Existing treatments are effective enough to control diabetes in most patients, but continuous efforts are made to keep developing new products and improve old ones. Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. Many patients with type 2 diabetes eventually require and benefit from insulin therapy. Providers may wish to consider regimen flexibility when de vising a plan for the initiation and adjustment of insulin therapy in people with type 2 diabetes (Figure 7.2). The progressive nature of type 2 diabetes and its therapies should be regularly and objectively explained to patients. For patients with type 2 diabetes who are not achieving glycemic goals, providers should promptly initiate insulin therapy. Providers should avoid using insulin as a threat or describing it as a failure or punishment. Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in patients with type 2 diabetes initiating insulin.[70]

CONTROVERSIES ASSOCIATED WITH INSULIN THERAPY

Proliferation of normal and malignant cells is seen with growth like factor action of insulin. Multiple receptors interact with insulin and stimulate cell growth. This states that insulin has a dual action including glucose lowering and cell proliferation.[71-74] Many epidemiologic studies have also shown that patients who receive chronic insulin therapies are more susceptible for malignancies.[75] Greater proliferative effect in vitro is seen with insulin glargine as a result of increased affinity to IGF-1

receptor.[76] Epidemiological studies and surveys conducted have denied such effect of glargine on overall cancer rate.[77-82] Debate regarding cardiovascular effects of insulin has been going on for many years. Pro-atherogenic and anti-atherogenic effects of insulin has been observed in experimental studies.

Vasodilator and vaso-protective actions of insulin are seen in healthy individuals but contradictorily but opposite effects prevail in insulin resistant subjects. A higher incidence of cardiovascular mortality was observed in patients who received prolonged insulin therapy.[83] This aspect of insulin was supported by ACCORD trial, where increased cardiovascular mortality was noted with intensified insulin therapy.[84]

RECENT ADVANCES AND FUTURE PROSPECTS

Insulin degludec

Insulin degludec is novel basal insulin comprising recombinant DesB30 human insulin acylated at the LysB29 residue with a hexadecandioyl-gamma-L-Glu side chain that has a unique mode of protraction.[85-87] Degludec shows an insulin-receptor binding specificity and a metabolic-to-mitogenic ratio that is comparable with that of human insulin.[88] Its mean half-life is 24.5 hours and its metabolic effect is still apparent 42 hours after injection.[89]

A meta-analysis of phase 3 studies which included 5299 people with diabetes, a significantly lower rate of nocturnal episodes of hypoglycemia was observed with insulin degludec as compared to insulin glargine (relative risk of 0.83 and 0.68 respectively).[90] Whether this difference translates into clinical benefits in real-life settings, however, needs extensive assessment.[91] The molecular structure of insulin degludec permits the production of a co-formulation containing 70% insulin degludec and 30% insulin aspart (Ryzodeg; Novo Nordisk Inc).[65]

Pegylated Insulin Lispro (LY2605541)

PEGylated insulin, which consists of insulin lispro with a covalently bound polyethylene glycol moiety at lysineB28, slows the absorption of insulin from the injection site and reduces renal insulin clearance, resulting in a long half-life of 75 hours with a flat time-action profile.[92,93]

It is postulated that the fenestrated sinusoidal endothelium of the liver may allow preferential transport of PEG-lispro into the liver relative to peripheral tissues, and a clamp study suggested that PEG-lispro had a preferential hepatic versus peripheral effect on glucose metabolism. A phase 3 study comparing insulin glargine to PEGylated insulin lispro reported similar efficacy in HbA1C reduction.[94]

High dose formulations

A new high dose formulation approved by the FDA and the European Medicine Agency in the beginning of 2015 is Glargine U300. It is more concentrated formulation than insulin glargine U100 without any molecular changes. Phase 3 studies comparing insulin glargine U300 and insulin glargine U100 showed similar reductions in the HbA1C levels, but the rate of severe hypoglycemia was 23% lower in the U300 arm.[95] Glargine U300 forms a compact subcutaneous depot with a small surface area upon injection, resulting in a more gradual, long-term, and flatter release than with standard glargine U100, enabling glucose control up to 36 hours.[90]

Reduced cases of nocturnal hypoglycemia is like a clinical benefit provided by ultra-long pharmacokinetic profile of these novel analogues. However, possible benefits of these novel insulin analogues need to be effectively supported by long-term safety and efficacy data.

Ultra-rapid acting insulin analogues

Rapid-acting insulin's are designed in such a way that they are absorbed quickly and limit post-prandial hyperglycemia when taken before meals. They attempt to mimic the physiologic prandial insulin response. Faster acting insulin-aspart is a new ultra-rapid acting formulation of insulin aspart being developed by Novo Nordisk that has entered phase III trials.[65] A further approach to increasing the speed of insulin absorption is to combine it with human recombinant hyaluronidase.[96]

NEW TREATMENT COMBINATIONS

Studies show that co-administration of incretin-based therapy with basal insulin can be used as an alternative for introducing prandial insulin injections in patients inadequately controlled on monotherapy.[66] Retrospective analyses of type 2 diabetes patients with inadequate control who were prescribed insulin glargine and exenatide combination therapy on a long-term basis, reduced HbA1C levels without significant weight gain or increase in episodes of hypoglycemia.[97,98] Similar outcomes were observed in those receiving lixisenatide as add-on therapy to basal insulin.[99-101]

A product IDegLira (Novo Nordisk Inc) contains a fixed ratio of 1 unit of degludec and 0.036 mg of liraglutide per unit drug. The combination product showed superior HbA1C reductions as compared with insulin degludec or liraglutide alone, each as an addition to metformin with or without pioglitazone.[102-104] Another basal insulin/ glucagon-like peptide- 1 receptor agonist fixed-dose combination product, namely, insulin glargine/lixisenatide, is under clinical development by Sanofi.[105-108]

Table 2: Molecules under development.[98]

New insulin formulations	Chemical or physical structure	Features
BioD-090 (VIAject)	Recombinant insulin plus edetic acid (EDTA)	Loosely packed insulin multimers with rapid dissociation into monomers and dimers
rHuPH20 (Hylenex)	Recombinant insulin plus hyaluronidase	Accelerated pharmacokinetics
Ultra-fast-acting insulin aspart (FIAsp)	Recombinant insulin plus nicotinamide plus arginine	Increased blood flow
BioChaperone ultra-rapid acting insulin	BioChaperone plus lispro insulin	Enhanced insulin diffusion to aid absorption into blood circulation
Smart insulin	Dextran nanoparticles loaded with insulin and glucose-specific enzymes	Glucose-dependent insulin release

CONCULSION

Insulin therapy should be simplified for primary care physicians, nurse practitioners, physician assistants, and other health care professionals, as they will have a pivotal role in helping patients manage T2DM. Though the role of insulin in the management of type 2 diabetes mellitus is pivotal, the dilemma regarding the timing of insulin initiation remains debatable.

One of the few cornerstones of diabetes treatment is the comment made by Elliot P Joslin, the founder of modern diabetology 85 years ago. He stated that "Insulin is a remedy primarily for the wise and not for the foolish, be they patients or doctors. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more brains."[109] It's been 90 years since the discovery of insulin but insulin treatment is still developing in terms of new formulations, novel routes of administration, and treatment strategies.

Effective control of diabetes mellitus and hyperglycemia is a challenge without insulin therapy. Straightforward algorithms regarding insulin initiation, titration, and follow-up management can help physicians effectively treat patients with type 2 diabetes mellitus. Simplified insulin initiation and titration regimens allow primary care physicians and other health care professionals to care for patients with type 2 diabetes mellitus.

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