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A REVIEW ON RECENT ADVANCES IN THE TREATMENT OF DIABETES MELLITUS.

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Abstract:

The previous and the newer advances performed in the management of the diabetes mellitus is reviewed shortly and the newer insulins and other hypoglycemic agents are overlooked under this review article.

Key Words: **Recent advances, Diabetes, Diabetes Mellitus, Treatment of DM.**

Introduction:

Diabetes mellitus is a chronic endocrine condition defined by hyperglycemia caused by insulin insufficiency, either absolute or relative. Diabetes can be caused by a variety of factors, but the vast majority of cases are classed as Type 1 or Type 2 diabetes. Type 1 diabetes is caused by the autoimmune destruction of insulin-secreting pancreatic -cells, which results in insulin insufficiency and subsequent hyperglycemia. Type 1 diabetes affects approximately 10-15% of diabetics. Type 2 diabetes is defined by aberrant insulin production caused by peripheral resistance, and it affects 85-90 percent of diabetics.[1] While type 1 diabetes commonly appears in childhood or adolescence, and type 2 diabetes appears later in life, clinical manifestation and progression differ greatly, and some individuals may not be clearly identified as having type 1 or type 2 diabetes at first. Both types of diabetes are characterised by increased hepatic glucose output and decreased glucose uptake in the muscles and adipose tissue. Type 1 diabetes can strike at any age and has a slower progression, whereas type 2 diabetes appears earlier in life, even in childhood and adolescence, sometimes allowing for accurate diagnosis only over time in the uncontrolled state. Type 1 diabetes patients are at risk for severe lipolysis, which can progress to diabetic ketoacidosis. [2] Because type 2 diabetes patients' remaining insulin activity reduces lipolysis and ketone generation, they are less likely to suffer ketoacidosis but more likely to enter a hyperosmolar, non-ketotic condition. Diabetes is increasing in incidence and prevalence worldwide, owing to an increase in type 1 diabetes in children and type 2 diabetes due to lifestyle changes, particularly in developing nations. Diabetes is prevalent in sports at all levels of competition, and it is becoming more prevalent due to the growing number of master athletes and the occurrence of type 2 diabetes at younger ages.[3]

History of Diabetes:

Physicians have known about diabetes mellitus as a disease, with a constellation of symptoms but no cause, for about 3,500 years in ancient Egypt. [4] The Ebers papyrus, which dates from 1550 BC and was discovered in a cemetery in Thebes, Egypt in 1862, was named by Egyptologist Geary Ebers. [5] Diabetes was described as a polyuric wasting disease by Araetus of Cappodocia, who was most known for his distinction between physical and mental disease.[6] To characterise the ailment, Araetus adopted the Greek word

Diabetes, which literally means "to stream through or syphon." Avicenna, an Arab physician, precisely characterised the clinical symptoms and problems of diabetes (peripheral neuropathy, gangrene and erectile dysfunction).[7] Avicenna promoted the idea of a sweet urine taste and may have introduced it to European observers, as his book (Kanon) affected medical practise for decades. Apollonius of Memphis developed the term "Diabetes," which means "to syphon through."

Thomas Willis in 1675 added “mellitus” to the word “diabetes”.

1865- Paul Langerhans, a German medical student, discovered islet cells in the pancreas.

1910- Sharpey-Shafer of Edinburgh suggested a single chemical was missing from the pancreas. He proposed calling this chemical “Insulin”.

1923- 1st Nobel prize for insulin

14th November is celebrated as “words diabetes day” on birthday of Frederick Banting.

Physiology and metabolism:

Hyperglycemia and physiological and behavioural responses are inextricably linked. When hyperglycemia occurs, the brain identifies it and sends a message to the pancreas and other organs via nerve impulses to reduce the effect. [8]

Type 1 diabetes mellitus:

CD4+ and CD8+ T lymphocytes, as well as macrophages entering the islets, destroy insulin-producing cells in the pancreas, resulting in Type 1 Diabetes. [9]

Several features characterize type 1 diabetes mellitus as an autoimmune disease. [10]

Presence of immuno-competent and accessory cells in infiltrated pancreatic islets; [11] The autoimmune death of pancreatic -cells causes a lack of insulin secretion, leading to the metabolic abnormalities associated with T1DM. T1DM patients have aberrant pancreatic-cell function as well as increased glucagon secretion in addition to the lack of insulin secretion. Hyperglycemia normally reduces glucagon secretion; however, in patients with T1DM, hyperglycemia does not inhibit glucagon secretion. [12] The improperly high glucagon levels that arise worsen the metabolic abnormalities caused by insulin insufficiency. Although insulin insufficiency is the fundamental problem with T1DM, there is also a problem with insulin administration. Insulin deficiency causes uncontrolled lipolysis and high plasma levels of free fatty acids, which decreases glucose utilisation in peripheral tissues like skeletal muscle. [12] Insulin shortage also reduces the expression of a number of genes required for target tissues to respond appropriately to insulin, including glucokinase in the liver and the GLUT 4 class of glucose transporters in adipose tissue. [12] explained that decreased glucose, lipid, and protein metabolism are the primary metabolic derangements caused by insulin insufficiency in T1DM.

Type 2 diabetes mellitus:

These pathways fail in type 2 diabetes, resulting in two major clinical defects: decreased insulin production due to pancreatic B-cell dysfunction and impaired insulin action due to insulin resistance. [13]

When insulin resistance is prevalent, the mass of B-cells undergoes a metamorphosis that increases insulin supply while adjusting for the excessive and abnormal demand. Although the plasma insulin concentration (both fasting and meal stimulated) is usually increased in absolute terms, it is insufficient to maintain normal glucose homeostasis "relative" to the severity of insulin resistance. Given the intricate link between insulin secretion and hormone action sensitivity in the complex maintenance of glucose homeostasis, it's nearly impossible to separate their contributions to the etiopathogenesis of DM2. [14] Insulin resistance and hyperinsulinemia cause poor glucose tolerance over time. The mode of inheritance for type 2 diabetes mellitus is unknown, with the exception of maturity onset diabetes of the young (MODY). Mutations in the glucokinase gene on chromosome 7p may cause MODY, which is inherited as an autosomal dominant condition. MODY is hyperglycemia detected before the age of twenty-five years that can be treated without insulin for more than five years in cases where islet cell antibodies (ICA) are negative. [15]

Diagnosis And Classification Of Diabetes Mellitus

Diagnosis:

Blood glucose testing and blood glucose monitoring: Because structural components of blood cells are missing, the glucose concentration in plasma or serum is 10-15% greater than in whole blood. Venous blood sample: Enzymatic, colorimetric, and automated methods are routinely used in laboratories to determine plasma glucose levels. Blood samples from capillaries: The glucose oxidase technique is used in several portable, battery-operated metres. The latest gadgets use infrared absorption spectra to provide a noninvasive method.

Ketonuria / Ketonemia testing- The majority of strips use a nitroprusside reaction that only assesses acetone and acetoacetate. Despite the fact that these tests do not identify -hydroxybutyric acid, the semi-quantitative estimation of the other ketone bodies is usually sufficient for clinical ketonuria assessment.

Glycosylated Hemoglobin-

In diabetics, the primary type of glycohemoglobin (HbA1C) is unusually high. Glycohemoglobin reflects the condition of glycemia over the previous 8-12 weeks, making it a useful tool for evaluating chronic diabetes management.

Diagnostic Criteria:

The diagnosis of diabetes mellitus is based on measuring venous plasma glucose in the fasting state and 2 hours after a 75gram glucose load (recommended by the WHO).

• All values are venous plasma glucose

• To convert mg/dl to mmol/L, divide by 18.

• In case of an abnormal test result, the Diabetes he tests should be repeated on a different day.

Oral glucose tolerance test (OGTT) is recommended by WHO and not by ADA for epidemiological purposes.

Category	WHO	ADA
Impaired fasting glucose (IFG)	BGF=100 to < 126 mg/dl	BGF=100 to < 126 mg/dl
Impaired glucose tolerance (IGT)	2 hr post glucose > 140 mg/dl and < 200 mg/dl	-
Diabetes mellitus (DM)	BGF ≥126 mg /dl or 2 hr Post glucose ≥ 200 mg/dl (OGTT)	BGF ≥126 mg /dl or Casual = 200 mg/dl + Osmotic Symptoms
Normal	FPG=100 mg/dl and PP ≤ 140 mg/dl	FPG=100 mg/dl and PP ≤ 140 mg/dl

Diagnostic criteria for Diagnosis of diabetes mellitus.

Classification:

1. Type 1 DM : ß cells destruction

   a. Immune mediated

   b. Idiopathic

2. Type 2 DM

3. Other specific types of diabetic:

   a. genetic defects of ß cell function: MODY

b. genetic defects in insulin action

c. diseases of the exocrine pancreas

d. endocrinopathies

e. drug or chemical induced

f. infectious

4. Gestational diabetes mellitus (GDM).

Type 1 diabetes mellitus:

Type 1 diabetes mellitus (juvenile diabetes) is characterised by an autoimmune response that destroys mellitus cells, resulting in absolute insulin insufficiency. [14]

Anti–glutamic acid decarboxylase, islet cell, or insulin antibodies, which identify the autoimmune mechanisms that lead to beta cell death, are commonly present in Type 1. To maintain normoglycemia, all type 1 diabetes patients will eventually require insulin therapy.

Type 2 diabetes mellitus:

The relative relevance of insulin secretion or peripheral insulin action in the development of DM2 has been and will continue to be a source of debate. DM2 accounts for 80 percent to 90 percent of all DM cases. The majority of people with Type 2 diabetes have intra-abdominal (visceral) obesity, which is directly linked to insulin resistance. In addition, these people frequently have hypertension and dyslipidemia (high triglyceride and low HDL cholesterol levels; postprandial hyperlipidemia). This is the most common kind of diabetes and is strongly linked to a family history of diabetes, advanced age, obesity, and a lack of physical activity. Women, particularly those with a history of gestational diabetes, as well as Blacks, Hispanics, and Native Americans, are more likely to develop it.

Gestational Diabetes Mellitus (GDM):

Gestational diabetes mellitus is a functional classification (rather than a pathophysiologic illness) for women who develop diabetes during pregnancy. Gestational Diabetes Mellitus is a term used to describe women who develop Type 1 diabetes during pregnancy or women who discover undetected asymptomatic Type 2 diabetes throughout pregnancy (GDM). GDM usually appears in the third trimester of pregnancy in the majority of women.

Other specific type (Monogenic diabetes):

Diabetes mellitus types with multiple known etiologies are put together in the "Other Specific Types" classification. Persons with genetic defects of beta-cell function (formerly known as MODY or maturity-onset diabetes in youth) or defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies (e.g. acromegaly); and persons with pancreatic dysfunction caused by drugs, chemicals, or infections, who make up less than 10% of the population.

Combined Type 1 and Type 2 Diabetes:

Despite the fact that type 1 and type 2 diabetes are regarded to be distinct disease processes with hyperglycemia as a common denominator, there is no reason why both diseases, or at least certain components of each condition, cannot exist in the same people. Because type 1 diabetes does not protect against the development of obesity and associated insulin resistance, an increasing percentage of people with type 1 diabetes may acquire type 2 diabetes symptoms in the face of pandemic obesity. When islet cell antibodies were discovered as a marker of the autoimmune mechanism underlying type 1 diabetes, patients with phenotypic type 2 diabetes had a substantially greater prevalence of autoantibodies (5–10%) than nondiabetic controls (1 percent). The most constant feature of these patients is that beta cell activity diminishes more quickly than in autoantibody-negative type 2 diabetes patients, requiring insulin administration earlier in autoantibody-positive phenotypic type 2 diabetes patients. [16]

Prediabetes:

Prediabetes is a word used to describe people who have a high chance of developing type 1 or type 2 diabetes in the future, with the awareness that not everyone with prediabetes will acquire diabetes. People with high but subdiabetic fasting glucose levels (called "impaired fasting glucose" or IFG), postprandial glucose intolerance ("impaired glucose tolerance" or IGT), and prediabetes for type 2 diabetes are considered prediabetic. Although there is no universally agreed diagnosis of type 1 diabetes prediabetes, a combination of

genetic, immunological, and metabolic markers can be utilised to correctly predict the risk of developing type 1 diabetes in the future. [17]. The use of such data to assess the risk of type 1 diabetes in the future has been verified and has been utilised successfully in type 1 diabetes prevention trials. [18,19,20]

Literature:

Current therapy of diabetes mellitus:
Non pharmacological

a. Weight loss.

b. regular physical activity

c. medical nutrition therapy

d. lifestyle changes

Insulins:

Insulin is the only treatment option for T1 diabetes. Insulin is a peptide hormone that is produced by beta cells in the pancreatic islets and is the body's principal anabolic hormone. It affects carbohydrate, lipid, and protein metabolism by boosting glucose absorption from the blood into the liver, fat, and skeletal muscle cells.

Human insulin:

By rDNA technology

Soluble in aqueous solution.

Conventional insulins-

Rapid acting: Lispro, aspart, glulisine.

Short acting: Regular

Intermediate acting: NPH, Lente.

Oral Hypoglycemic agents:

For best glycemic management, healthcare providers should advise patients to combine lifestyle changes with oral pharmacologic medications, especially as type 2 diabetes mellitus advances with ongoing loss of pancreatic beta-cell function and insulin production. [21-25]

Insulin secretogogues:

Insulin secretagogues are one type of medicine for type 2 diabetes. Insulin secretagogues help your pancreas make and release (or secrete) insulin.

a. Sulphonylureas: (Primarily stimulate insulin release by binding to sulfonylurea receptor.)

- 1st gen: Tolazamide, Chlorpropamide.

- 2nd gen: Glibenclamide (Glyburide), Glipizide, .

b. Meglitinides analogs.

-Mitiglinide, Repaglinide.

c. D-Phenylalanine derivative.

- Nateglinide.

Insulin sensitizers:

[Sensitize tissue (liver & adipose) to the action of insulin.]

Insulin sensitizers, often known as TZDs, are blood sugar normalizers or euglycemics (drugs that help return the blood sugar to the normal range without the risk of low blood sugars.) TZDs take several weeks to start functioning, so don't stop taking them if your blood sugar doesn't respond immediately away. a. Bigunides:

- Metformin, Phenformin

b. TZDs (PPAR):

- Pioglitazone, rosiglitazone.

Newer Drugs:

Incretin mimetics:

Incretin- These are the insulinotropic hormones, secreted from specialized neuroendocrine cells in small intestinal mucosa. It stimulates insulin secretion.

Incretin mimetics:

Exenatide (Amylin Pharmaceuticals/Eli Lilly) was the first medicine in this new class to hit the market in the United States in 2005 and Europe in 2007. Liraglutide was first launched to the market in Europe in July 2009, and then in the United States and Japan in January 2010. (Novo Nordisk). Only these two incretin mimics are discussed in this review.

Pharmacology:

Exenatide was isolated from the saliva of the lizard Heloderma suspectum in a search for biologically active peptides [26] Exenatide shares 53% homology with native GLP-1 and binds to and activates GLP-1 receptors on pancreatic beta-cells following which insulin secretion and synthesis is initiated. [27] Exenatide is readily absorbed after SC injection, reaching peak concentrations in around 2 hours. Exenatide has a half-life of around 2 hours, and substantial elevations of exenatide in plasma can be observed for 5 to 6 hours after SC injection of the maximally tolerated dose. After 12 hours, exposure is negligible, which is why twice-daily dosing is required to achieve optimal glycemic control. [29] Exenatide's pharmacokinetics, safety, and efficacy have been studied in several subsets of type 2 diabetic patients. Exenatide treatment appears to be well tolerated in a short study of adolescent individuals with type 2 diabetes. [30] in a study of Japanese patients with type 2 diabetes the pharmacokinetics seemed to be similar to that of Caucasian patients [31] (no racial differences have been reported). Lastly, age does not seem to influence the pharmacokinetic properties of exenatide. [32]

Efficacy:

E.g.- GLP-1 (glucagon like peptide-1)

and GIP (gastric inhibitory peptide). (Successful drug target)

Main effect- Enhance insulin secretion & avoid hypoglycaemia.

- Inhibits glycogen release

- delays gastric emptying

- decrease food intake & normalizes fasting & postprandial insulin secretion

T ½ extremely short- rapidly metabolized by dipeptidyl peptidase-4 (DDP-4)

GLP-1 analogs:

↑ GLP-1 actions up to 10-fold.

Divided into:

Long acting: Liraglutide, albiglutide, dulaglutide, & semaglutide (Under trial)

Short acting: Exenatide & lixisenatide (better post prandial glucose control)

Mechanism of action:

Activation of the GLP-1 receptor (class B GPCRs).

-Expressed in ß cells.

-Activation of cAMP-PKA pathway.

Dipeptidyl Peptideae 4 Enzyme Inhibitor.

DPP-4 inhibitors (also known as gliptins) are a type of oral hypoglycemic that works by blocking the enzyme dipeptidyl peptidase-4 (DPP-4). They are effective in the treatment of type 2 diabetes. The FDA authorised the first drug in the class, sitagliptin, in 2006. [38] DPP-4 inhibitors reduce glucagon and blood glucose levels, while glucagon increases blood glucose levels. DPP-4 inhibitors work by causing incretin levels to rise (GLP-1 and GIP) [39,40,41] This inhibits glucagon release, increasing insulin production, slowing stomach emptying, and lowering blood glucose levels.

Mechanism of action:

Competitively inhibit DDP-4 enzyme

↓

Inhibit the degradation of GIP and GLP-1

↓

Enhance incretin effect

↓

Insulin secretion & glucagon inhibition

E.g., Sitagliptin, saxagliptin, linagliptin & alogliptin (US), Vildagliptin (EU).

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:

-Should not be utilised in type 1 diabetes patients or for diabetic ketoacidosis treatment.

-It is possible to take it with or without food.

-There is no evidence of safety or effectiveness in children under the age of 18.

-Adequate and well-controlled studies in pregnant women are lacking.

Body weight has no influence.

Glycemic management has improved, as has PPG reduction.

Systolic blood pressure dropped.

Lipid profile has improved.

Dose and administration:

The recommended dose is 100 mg once a day.

Can be taken with or without food.

Maximum dose 100 mg daily.

Adverse Reaction:

Upper respiratory tract infection.

Nasopharyngitis.

Headache.

Amylin mimetics:

Amylin is a peptide hormone produced by the pancreatic -cell that is lacking in diabetics. It works as a satiety agent by inhibiting glucagon secretion and delaying stomach emptying. Amylin substitution could therefore help some diabetics improve their glycemic control. Human amylin, on the other hand, has physicochemical features that make it more likely for the peptide hormone to cluster and form amyloid fibres, which may contribute to -cell death in type 2 diabetes. This plainly precludes its usage in pharmaceuticals. However, the addition of amylin agonists to some insulin-treated diabetic people could be an unique way to lower glycemia. The hormone has a signal transduction pathway similar to calcitonin (CT), calcitonin gene–related peptide (CGRP), and adrenomedullin, [45] and the specificity of the amylin receptor has been characterized. Since the description of amylin almost two decades ago, [49,50] The physiological activities of this peptide have been well studied. Amylin is produced in response to dietary stimulation and has a similar 24-hour profile to insulin. [51] Amylin has also been demonstrated to be secreted in a pulsatile fashion, similar to insulin. [52] The peptide circulates in a nonglycosylated (50%) and a glycosylated form, [53] of which the former is the biological active compound. In healthy humans, fasting plasma amylin concentrations are in the range of 4–25 mol/L, and amylin is distributed equally to insulin in plasma and interstitial fluids. In opposition to insulin, it is not eliminated significantly in the liver [54] but mainly through renal metabolism.

Human Studies: Three studies [57,58] have investigated the effects of acute native amylin injection on in vivo glucose metabolism in healthy humans. Despite employing large pharmacological doses that resulted in circulating amylin levels 50–100 times higher than usual postprandial levels, native amylin had no effect on glucose uptake, as measured by a hyperinsulinemic-euglycemic clamp [59] or an intravenous glucose tolerance test. [57,58]. This is in agreement with data of [60] in which no effect on glucose transport in human muscle strips was observed. In terms of impact on β-cell function, only a blunted insulin response was demonstrated at very high doses [58]

Bile acid binding resins:

Type 2 diabetes is a complicated condition that necessitates lifestyle changes as well as pharmacological treatment. To assist control type 2 diabetes, a variety of effective oral antidiabetics medicines are available, allowing doctors to pick specific treatment(s) that fit the individual needs of a patient. This is especially significant for individuals with type 2 diabetes, who frequently have comorbidities that complicate management and limit treatment options pharmacologically. The rationale for using a bile acid sequestrant (BAS) for type 2 diabetes treatment, the clinical effects of the only BAS approved for both glycemic and lipid control in the United States (colesevelam hydrochloride), and the appropriate place for a BAS in type 2 diabetes therapy are all discussed in this review.

Treatment:

BASs were created to treat hypercholesterolemia by decreasing cholesterol levels. The first observation of a glucose-lowering impact of a BAS was reported from a study that examined cholestyramine in individuals with dyslipidemia and type 2 diabetes; 8 g cholestyramine twice daily lowered plasma glucose levels by 13% after 6 weeks. [63]. Several minor studies later shown that colesevelam, colestilan, and colestimide all improved glycemic control in type 2 diabetic patients. [67]. When added to existing antidiabetes therapy, this compound was demonstrated to dramatically enhance glycemic control (while also significantly lowering LDL cholesterol levels) in patients with type 2 diabetic. [68,69,70]. Despite the fact that colestimide is approved in Japan, colesevelam is the only BAS approved for improving glycemic control in individuals with type 2 diabetes in the United States.

Mechanism Of Action:

Bile acid sequestrants are ion-exchange resins made up of polymeric molecules. Bile acid sequestrants substitute bile acids for anions such as chloride ions. They bind to bile acids and sequester them from the enterohepatic circulation in this way. To compensate for the bile acids that have been lost, the liver generates more. Because the body uses cholesterol to generate bile acids, the amount of LDL cholesterol in the blood is reduced. [21] BASs may also influence incretin hormone release, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. Treatment with 1,500 mg/day colestimide raised fasting GLP-1 levels in patients with type 2 diabetes and hypercholesterolemia (22). Similarly, therapy with 3.75 g/day colesevelam increased fasting GLP-1, postprandial GLP-1, and glucose-dependent insulinotropic polypeptide levels (23).

Only approved drug for T2 DM – Colesevelam.

Colesevelam:

Powder (oral sol) or 625 mg tabs.

A/E-GI (constipation, dyspepsia, abdominal pain, nausea), ↑ plasma triglycerides.

Use-T2 DM- adjunct to diet & exercise.

Bromocriptine:

D2 receptor agonist. Long known to improve insulin sensitivity & glycemic control in T2 DM.

Dose- 1.6 – 4.8 mg, taken with food, morning.

SIDE EFFECTS: constipation, diarrhea, bloating, flatulence, bad taste.

EXAMPLES: Cholestyramine, Colestipol (Colestid, Colestipid), Colesevelam.

Potential Drug Therapy:

Newer PPAR agonists-

Agonists for both PPARs (a and Y) Glitazars. (Aleglitazar, muraglitazar) Hyperglycemia and dyslipidemia may be treated with this drug. Glitazars and thiazolidinedione s/e are absent.

In clinical trials, Saroglitazar, a new dual peroxisome proliferator activated receptor (PPAR) agonist, improved lipid and glycemic markers via PPAR-a and y agonist effects, respectively. In 2013, it received marketing approval in India for diabetic dyslipidemia. This study was undertaken to summarise the effects of Saroglitazar in diabetic dyslipidemia patients in real-world clinical studies conducted after the drug was approved for commercialization in India.

Newer Insulins:

Newer/advanced insulin analogues are as follows:

Insulin glargine, Detemir, Degludec.

Insulin glargine:

Insulin glargine, sold under the brand names Lantus and others, is a long-acting insulin used to treat type 1 and type 2 diabetes.[71] It is typically the recommended long-acting insulin in the United Kingdom.[72] It's given as an injection under the skin once a day. [71] The effects usually start an hour after use.[71] Human insulin analogue with a long half-life. pH =4 clear solution Absorption from the injection site is prolonged and predictable. Short-acting insulin formulations cannot be combined.

Advantages over NPH insulin:

More consistent 24-hour insulin coverage than NPH insulin due to sustained absorption (OD) Hyperglycemia risk is reduced (overnight) Applied at any time during the day. Dose- 100 U/ml, 300 U/ml

Mechanism of action:

The insulin receptor binds to insulin glargine. Insulin promotes tyrosine kinase activity via binding to the alpha subunit of IR. Many intracellular substrates, including as insulin receptor substrates (IRS) proteins, Cbl, APS, Shc, and Gab, are autophosphorylated and phosphorylated by bound receptors. Microprecipitates release little amounts of insulin glargine, resulting in a rather consistent

concentration profile throughout 24 hours with no obvious peak. The drug's release mechanism allows it to imitate body-wide insulin levels..[73]

Metabolism:

Metabolized in the liver into two active metabolites with similar activity to insulin:

21a-Gly-human insulin (M1) and 21a-Gly-des-30b- threonine insulin (M2), with M1 being the predominant metabolite.[73]

Insulin Detemir:

Glargine and detemir absorption characteristics are similar, resulting in smoother action and a lower risk of hypoglycemia. Elimination Time to reach half-life: 5-7 hours 60 percent bioavailability (when administered S.C)

Mechanism of action:

Insulins, particularly insulin detemir, work by attaching to insulin receptors to perform their functions. Insulin that is receptor-bound reduces blood glucose by boosting glucose absorption into skeletal muscle and adipose cells and blocking glucose release from the liver.

Degludec:

Insulin degludec, marketed as Tresiba, is an ultralong-acting basal insulin analogue created by Novo Nordisk. [74] It is given as a subcutaneous injection once a day to help diabetics control their blood sugar levels. It has a 42-hour duration of action (compared to 18-26 hours for other marketed long-acting insulins like insulin glargine and insulin detemir), making it a once-daily basal insulin [75-77] that supplies a base insulin level rather than the fast- and short-acting bolus insulins.

Mechanism of action:

Insulin degludec is a long-acting insulin that, unlike insulin glargine, works at a physiological pH. The production of multi-hexamers in subcutaneous tissues is enabled by the addition of hexadecanedioic acid via an amide bond to lysine at the B29 site. [78] This permits a subcutaneous depot to build, resulting in sluggish insulin release into the systemic circulation. [79]

Pharmacokinetics:

Insulin degludec takes 30–90 minutes to start working (similar to insulin glargine and insulin detemir). Because of the gradual release into systemic circulation, there is no peak in activity. Insulin degludec is said to have a longer duration of action than 24 hours. [78] This long (but under 48 hour) duration, when taken at the same time of day, can cause an overlap between doses, resulting in higher insulin action. Because there is a danger of lower blood sugar if the overlap occurs during sleep, it is best to dose in the morning so that the overlap occurs when users are eating and testing their blood sugar. The dose should be titrated during this overlap period as well.

Effectiveness profile:

Patients utilising insulin degludec needed to take much fewer basal insulin doses than those taking insulin glargine U100, according to studies, while reaching equivalent blood glucose levels. Insulin degludec can also be coupled with other insulins, resulting in better glycaemic control. This is not possible with today's long-acting insulins. [80,81]

New And Improved Insulin Delivery Devices:

Types:

A disposable pen: This contains a prefilled insulin cartridge. Once used, the entire pen unit is thrown away.

A reusable pen: This contains a replaceable insulin cartridge. Once empty, a person discards the cartridge and installs a new one.

Advantages:

The ability of a person with diabetes to fine-tune and deliver highly accurate doses using an insulin pen, the portable, discreet, and convenient nature of the pens, small and thin needle sizes that reduce fear and pain, the ability to accurately pre-set doses using a dial, time-saving benefits due to prefilled and pre-set insulin levels, memory features that recall the timing and amount of the previous dose, and a racial bias.

Disadvantages:

Although insulin pens have numerous advantages, they also have certain disadvantages, such as: A restriction on using all forms of insulin through a pen, such as mixing several types of insulin in one injection, being accessible for self-injection only at a higher cost than the vial and syringe method Some insulin is wasted with each usage, and some insurance companies do not give universal coverage..

Insulin Jets:

Insulin jet injectors help diabetics to avoid using needles when injecting insulin. Many individuals, however, are wary of these little devices since they can be costly and difficult to operate. Continue reading to learn how they function and their benefits and drawbacks.. [82]

Working of Insulin jets: Insulin jet injectors provide the pressure needed to push the insulin through the pen and into your skin using a compressed spring or a compressed gas cartridge. More compressed springs are being employed. They're small, light, strong, and inexpensive. Nitrogen or carbon dioxide are commonly found in compressed gas cartridges. They can provide greater pressure than compressed springs, but they are more expensive, heavier, and require more frequent replacement.

Advantages:

Patient compliance due to lack of needle, Faster delivery of insulin, it may use less insulin.

Disadvantages:

Expensive, requires device maintenance, isn't as simple to use, Risk of incorrect dosage, skin damage or pain, and infection.

Insulin Pumps

Safety features, durability, availability of manufacturer service, capacity of supplier to provide training, ease of use, clinically desirable features, and cosmetic attractiveness to the user should all be considered while choosing an insulin pump. Nontechnical people may not be able to assess the safety and dependability of a new pump's engineering, so prescribers should only recommend or utilise pumps that have been field tested. Insulin for insulin pumps Insulin infusion pumps work well with rapid-acting insulin analogues (such as lispro). The insulins' stability in pumps has been established.

Safety: When approved procedures are followed, pump therapy is just as safe as multiple-injection therapy. With CSII, undetected disruptions in insulin supply may cause ketotic episodes to occur more frequently and faster, which is especially concerning during pregnancy. Infections or inflammation at the needle site can make CSII therapy more difficult, but they can be avoided with good hygiene and frequent site changes. As with conventional therapy, hypoglycemia can occur in insulin pump users. [84,85]

Insulin Inhalers:

Injected insulin, according to researchers, clinicians, and people with diabetes, is an effective way to treat the disease. They'll probably also argue that injecting insulin into your body without using a needle is preferable. You can't take insulin as a tablet, but you can inhale it.

Inhaled insulin mechanism: Inhaling insulin is a concept that has been around for decades. Researchers didn't make it practicable until the 1990s. You breathe tiny insulin powder into your lungs using an inhaler similar to those used by asthmatics. It enters your bloodstream through tiny blood vessels there.

Inhaled Insulin in June 2014, the FDA approved Afrezza.

It's a pre-measured, rapid-acting insulin inhaler that you take before meals. It isn't intended for diabetic crises like diabetic ketoacidosis (DKA). Low blood sugar, cough, and a scratchy or painful throat are common inhaled insulin side effects. If you have type 1 diabetes, you'll need to take long-acting insulin as well to keep your blood sugar under control. Inhaled insulin should not be used if you smoke or have a respiratory ailment such as asthma or COPD.

Insulin Inhaled Early Exubera, the first inhaled insulin, was approved by the FDA in September 2006. It could be used by those with type 1 or type 2 diabetes. However, the drug's manufacturer pulled it from the market in October 2007 when it failed to gain traction with patients. The inhaler was criticised for being too large and cumbersome. (The Afrezza inhaler is a fraction of the size.) Exubera was later linked to lung diseases, including cancer, according to the FDA.

Summery:

Diabetes is one of the world's most difficult health concerns. Insulin resistance and insulin secretory malfunction are important factors in the development of type 2 diabetes. Another important idea in diabetes pathophysiology is GLP-1 insufficiency, which contributes to:

Deficiency in insulin secretion. Excess glucose in the blood. Hyperglycemia after eating. Incretin mimetics are a novel treatment option for type 2 diabetes. Exenatide is the first drug in this class, and it is given twice a day by injection. Exenatide has the unusual virtue of producing weight loss in addition to improving glycemic control. DDP-4 prevents a 2- to 3-fold increase in GLP 1 levels. The first DPP-4 inhibitors are sitagliptin and vildagliptin. A single medicine, Colesevelam, is approved for type 2 diabetes in bile acid binding resins exclusively. Both hyperglycemia and dyslipidemia may be treated with newer PPAR agonists.

Conclusion:

A variety of drugs are being developed for the treatment of type 1 and type 2 diabetes. All of these medications appear to help with glycemic control, but it's unclear whether they'll affect the course of the disease or the micro- and macrovascular implications of uncontrolled diabetes. Although the latest medicines will thrill doctors with their innovative mechanisms of action, they are exceedingly expensive and may have major side effects if used long term.

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