A REVIEW ON PREPARATION AND DRUG DELIVERY SYSTEMS OF INSULIN

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Abstract:

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by chronic hyperglycemia. It is a metabolic disorder of glucose metabolism, and it is the most commonly occurring endocrinal disorder which affects almost each and every cell of the human body. It is mainly associated with insulin resistance to the body cells or by increased synthesis of glucose in the body or insufficient insulin production by pancreatic β-cells. There are approximately 3.5crore diabetics in India and this figure is expected to increase up to 5.2crore by 2025. The major types of DM are IDDM (Type-1) and NIDDM (Type-2).Insulin is a hormone containing 51 amino acids having 2-chains. Chain-A have 21 amino acids and chain-B have 30 amino acids. Insulin preparations are the mainstay in management of type-1 and type-2 DM. Available insulin preparations are short acting, long acting or mixed action to mimic the physiological insulin secretion. Insulin drug delivery systems that currently available for administration are syringes, insulin infusion pumps, jet injections. Insulin syringe is most commonly used & and most economical of all the delivery devices. The purpose of this review is about the efficacy and safety of various insulin preparations for management of DM are discussed. In addition the drug delivery systems are in use and various applications of various insulin devices and to focus more on insulin as a prim drug for the glycemic control.

Key words**: **Diabetes mellitus, Devices, DM, Insulin, Insulin drug delivery systems, Type-1 & Type-2, Short acting, long acting insulin

Introduction:

Diabetes mellitus is a commonest endocrinal disorder characterized by deficiency in insulin in body. It is the common disorder that affects more than 100million people worldwide. It is a chronic disorder of carbohydrates, fats and protein metabolism [1]. This Diabetes mellitus is a chronic disorder of protein metabolism and fats along with carbohydrates. A defect or deficient insulin secretory response, which translates into impaired carbohydrates (glucose) use and it is a characteristic feature od DM, as it is the result of hyperglycemias.

It is a chronic disorder, metabolic disorder characterized by elevated levels of blood glucose levels[2].Diabetes mellitus is found to damage the many body systems particularly blood vessels, eyes, kidneys, heart, and nerves. Diabetes mellitus is generally referred to "sugar" [3]. It results either due to; Insufficient insulin production, Inability of body to utilize the insulin produced, Increases synthesis of glucose in body. Insulin and glucagon are the hormones both are secreted by the beta (β) cells and glucagon is secreted by the (α)cells both are located in islets of Langerhans's. Insulin decreases the glucose levels by glycogenesis and transports glucose in to muscles, liver, and adipose tissues in addition to increases risk of obesity, metabolic and cardiovascular disorders and malignancy in future life of fetus after delivery. The international diabetes federation (IDF) estimates the total no. of diabetic subjects to be around 40-9 million in India and this is further set to 69.9million by the year 2025[3].Metformin hydrochloride is the biguanide class of oral antihpeglycemics improve glucose tolerance in diabetic patents and it is most widely used and most accepted drug for diabetes [4].

Classification of Diabetes mellitus:

The mostly accepted classification of Diabetes mellitus was published by WHO in the year 1980[5] & It is modified in the year 1985[6]. The classification describes to the clinical stages and etiological types of DM and other categories of Diabetes [7].

This new classification of DM contains stages which reflects the various degrees of hyperglycemia in individual subjects with any of disease process which leads to diabetes mellitus [8,9]. The classification system contains four types of DM. Type-1(IDDM), Type-2(NIDDM), gestational diabetes mellitus and other specific types.

1. **Insulin dependent diabetes mellitus/Type-1 DM:** This type of diabetes mellitus is also called as autoimmune diabetes and previously known as juvenile onset DM or ketosis prone diabetes. This is mainly seen in children as well as young adults. The onset can be usually sudden and life threatening [10]. It is associated with less secretion of glucose due to damage of β-cells due to unknown cause of self-antibodies damage our body tissues. The onset of symptoms is rapid in Type-1 DM. The rate of disruption of β-cells is quite variable among the individuals; it can be occur rapidly in some individuals and slow in others [11]. The exact cause of Type-1 diabetes mellitus is not known. Although in most people , there is evidence of an autoimmune mechanism involving auto antibodies that destroy the beta islet cells and leads to type-1 DM[10].
2. **Non –Insulin dependent diabetes mellitus/Type-2 DM:** This type of diabetes mellitus is also known as adult onset diabetes. This type of diabetes mellitus occurs due to relative insulin deficiency or resistance or both. The onsets of symptoms are slower and less marked then type-1 diabetes mellitus. People with type-2 DM are frequently resistance to action of insulin [12]. The causes are multifunctional and predisposing factor includes obesity, sedentary life style, increasing age, genetic

factor and such patients are at increased risk of developing macro vascular and micro vascular complications [13, 14].

3. Gestational Diabetes mellitus: The glucose intolerance occurring for the first time or diagnosed during pregnancy is referred to as gestational diabetes mellitus [3] .Women that develop type-1 diabetes mellitus during pregnancy and women with undiagnosed asymptomatic type-2 DM that is disorder during pregnancy is classified as gestational diabetes mellitus. The gestational diabetes mellitus may develop during pregnancy and may disappear after delivery.

4. Other specific Type (monogenic type): The most common type of diabetes which is developed changes associated in chromosomes and with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1a. These forms of diabetes mellitus are frequently characterized by onset of hyperglycemia at an early age. These are also referred as maturity-onset diabetes in youth (MODY) [14]. These comprise less than 0% of diabetes mellitus cases.

Diagnosis of Diabetes mellitus:

For screening diabetes mellitus the fasting glucose concentration should be used according to American diabetes association. Postprandial blood sugar test, random blood sugar and glucose tolerance tests, renal threshold of glucose, urine sugar, and oral glucose tolerance tests used for bold sugar determination.

The criteria used for diagnosis of diabetes mellitus are:

1. Symptoms of diabetes like polyuria, polydipsia &casual bold glucose concentration=11.1 mol/L or 200mg/Dl.
2. Fasting plasma glucose =70-110mg/Dl.

The diagnosis of insulin was shown in table no-1.

Table.1:Diagnosis of diabetes mellitus

Type	Diagnosis	Plasma glucose concentration
Normal	Fasting & 2hr post prandial	≤6.0mmol/m,≤7.8mmol/m
Diabetes	Fasting &2hr post prandial	≥7.0mmol/m,≥11.1mmol/m
Impaired glucose tolerance	Fasting and post prandial	≤7.0mmol/m,708-11.0mmol/m
Impaired fasting glycaemia	Fasting	6.0-6.8mmol/m

Signs and Symptoms of Diabetes mellitus:

In case of diabetes mellitus cells fail to metabolize glucose in the normal manner, effectively become starved [3]. The long term effect of DM which includes potential blindness, renal failure, and risk of foot ulcer, sexual dysfunction and people with diabetes are at increased risk of disease. The characteristic features and symptoms of diabetes mellitus was shown in table no-2.other symptoms are observed due to 1. Amino acids and body protein form gluconeogenesis, leading to muscle wasting, breakdown of tissues and further blood glucose levels are increased.2. Fat catabolism, releasing some of it's energy and ketone bodies are produced [3].

Table.2:Characteristic features and symptoms of Diabetes mellitus

S.no	Types of Diabetes mellitus	Characteristic features	Symptoms
1.	Type-1	Less secretion of glucose due to damage of β cells due to unknown cause self-antibodies damage our body tissues.	Excessive hunger, excessive thirst, blurred vision, fatigue, frequent urination, dramatic weight loss, rapid breathing, flushed face, nausea,.
2.	Type-2	Insulin scantiness due to insulin resistance. Failure of insulin secretion genetically due to impairment of β cell function.	Increased hunger, increased thirst, increased urination, blurred vision, tiredness.

Epidemiology:

Approximately 5-10% of patients suffer from type-1 diabetes mellitus and majority (90-95%) suffer from type-2 DM. Type-1 usually occurs in younger population below 30years of age, the incidence being very high in girls between 10-12years of age and in boys between 12-14 years of age.

Type-2 DM occurs mainly in older people that are above 40years. About half of the total patients newly diagnosed with type-2 DM are above 55years and approximately 18% are 60 years (or) above.

Aetiology of DM:

Abnormality in beta cells of gluco receptors leads to increased glucose concentration and beta cell deficiency. β- Cells failure may occur when insulin secretion is impaired [16].

1. Damage to pancreatic β-cells of islets of Langerhans leads to deficiency of insulin (type-1).

2. Secretory problems may leads to deficiency of insulin or insulin resistance.
3. Genetic problems may leads to DM.
4. Some diseases like cystic fibrosis, neoplasia, and trauma leads to DM.
5. Increased secretions of counter-regulatory hormones (glucagon, growth hormone) may leads to DM.
6. Other factors like obesity, advanced age, emotional stress, and vacuities in highly perfused tissues like kidneys, eyes etc., and may leads to DM.

Management of DM:

DM is a incurable disease the prime objective of DM is to normalize the elevated levels of bold glucose level and to abolish the occurrence of associated acute as well as chronic complications.

To eradicate DM in the patents has to take care of their symptoms to slow down the developing the risk factor which include BP, Glycaemia and control of lipids which decrease the macro vascular risk, stoppage of smoking[15].

Objectives:

The objectives of treatment of DM are

- To attain normal levels of glucose and glycosylated hemoglobin.
- To inhibit the presence of glucose in urine.
- To educate the patents to control the disease by themselves.
- To minimize or eliminate the cardiovascular risk factors like obesity, tobacco use and hypertension etc.

Treatment: The DM is treated by

a. Insulin
b. Oral hypoglycemic agents

Insulin:

Insulin is the primary treatment for type-1 and type-2 DM. It is essential for life which is called as insulin dependent DM. It is most effective in lowering blood glucose levels and maintains glucose levels in normal range. It is observed that this hormone is absent or deficiency in diabetic people [16].Insulin is given in the form of injections and pumps. Various types of insulin's like long acting, intermediate acting and short acting insulin's are used. Insulin is a animal hormone produced by the β-cells of islets of Langerhans in the pancreas. It regulates blood glucose levels and various anaerobic activities such as glycogenesis and lipid synthesis.

Physiologically insulin consists of two constituents namely Basal (a constant background level of insulin during the fasting and post absorptive period) and Bolus (prandial spikes of insulin after eating) the key objective of insulin therapy in diabetes is to accomplish rigid blood glucose management by stimulating insulin secretion of normal pancreas. Insulin is biosynthesized in significance quantities only in β-cells of islets of Langerhans in the pancreas from perproinsulin. Perproinsulin is a single chain precursor and is the primary translation product of the insulin gene(MRNA).It is composed of 40 amino

acid residues and is relatively inactive first it has to be processed in to inactive proinsulin and then into the active insulin hormone. The perproinsulin undergoes translocation through the membrane of the rough endoplasmic reticulum and after losing 24 amino acids residues from the N-terminal gives rise to proinsulin. The pro insulin is a single polypeptide of 86 amino acid residues. The three portion of proinsulin are;

Chain A-carboxy terminal (25 amino acids)

Chain B-amino terminal (30 amino acids)

Chain C-connecting peptide (35 amino acids)

Pro insulin is exposed to several specific end peptidases in the endoplasmic reticulum. The endopeptidases remove the chain ‘c’ peptide from the proinsulin and generate the bioactive form of insulin. The biosynthesis of insulin was shown in figure no-1.

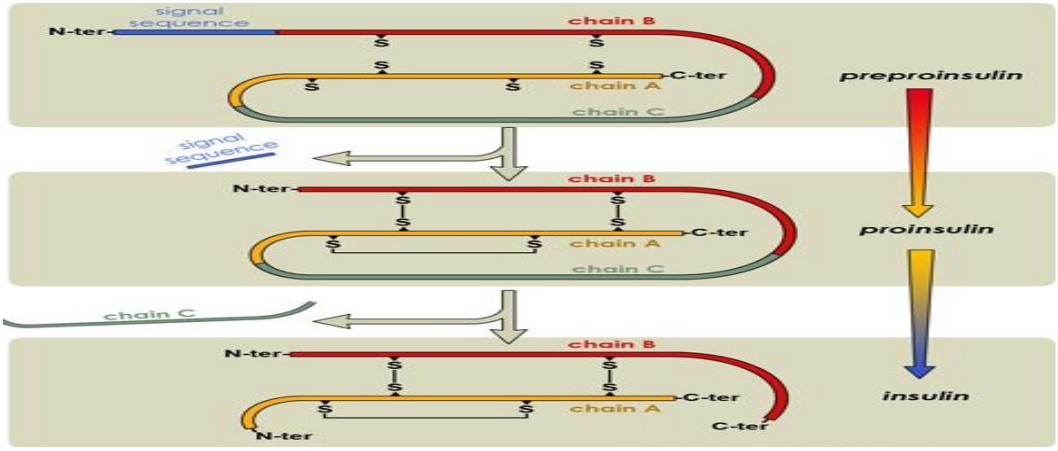

Figure no-1: Biosynthesis of insulin

Structure of insulin:

Insulin is composed of two polypeptide chains; chain A and chain B. Chain B consist of 30 amino acids residues whereas chain A consist of 21 amino acid residues with an interchain disulphide bridge between the amino acid residue 6 and 11. Both the polypeptide chains (A and B) are linked together by two disulphide bridges. The structure of insulin was shown in figure no-2.

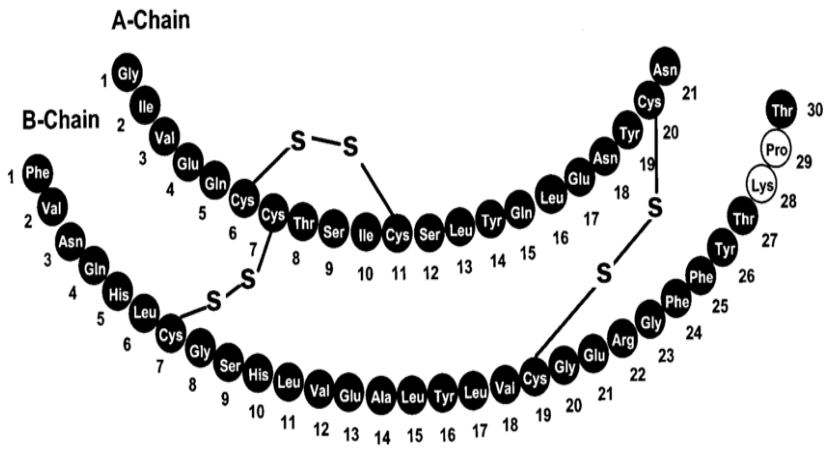

Figure no-2: Structure of insulin

Mechanism of action of insulin:

Insulin mediates its action by acting on it's specific membrane-bound receptors found on almost all the body cells. Basically, insulin receptor comprises of two subunits α and β which are linked via two disulphide bonds. The mechanism of action of insulin was shown in figure-3.

1. Binding of insulin to it's α –subunit stimulates the tyrosine kinase activity of the β- subunit.
2. Phosphorylation cascade results in translocation of Glut-4(and some galut-1) transport proteins into the plasma membrane.
3. It includes the transcription of several genes resulting in increased glucose catabolism and inhibits the transcription of genes involved in gluconeogenesis.
4. Insulin promotes the uptake of K+ ions into cells [14].

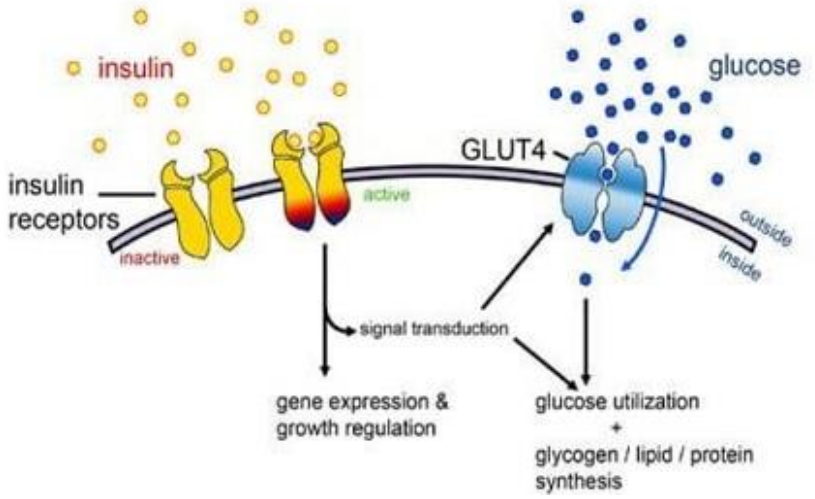

Figure no-3: Mechanism of action of insulin

INSULIN PREPARATIONS:

Insulin was first isolated and extracted successfully in 1921 opened an important factor in the management of diabetes mellitus especially for patents with deficiency of insulin. Insulin was the first protein to be sequenced (in 1995) and it became the first human protein to be manufactured through human recombinant technology [17]. It was introduced into clinical practice in 1982 as synthetic human insulin with the advantage of being less allergenic than animal insulin preparations. Human insulin eventually replaced all of the animal insulin preparations are currently generated by recombinant DNA technology. Insulin preparations consist of the amino acid sequence of human insulin or variations there of (Insulin analogues). There is great variability in the time of onset of action of insulin among individuals and even with repeated doses in the some individuals depending on the dose size, the injection site, desire and the circulating anti insulin antibodies [18].

The repeated exposure to hydrophobic surfaces causes changes in insulin stability leading to formation of insoluble fibrils [19]. This phenomenon mainly affects dips required in acute situations that in IV and subcutaneous infusion in insulin therapy. Many techniques are evolved to avoid it such as addition of Glycerol [20], and albumin [21] addition, patents serum [22] addition and blood [23] addition but none of them approved that are safe and physiological. At temperature above room temperature that is 25˚C, chemical distillation due to polymerization may occur [24]. Vials for daily use can therefore be kept in temperature at 2-8 ˚C. Current insulin formulations ensure stability of hormones at below 25 ˚C for a month.

Rapid acting Insulin preparations:

The rapid acting insulin include human insulin and three insulin analogues namely lispro, aspart and glulisine. These are rapid acting insulin reach peak serum values with in 1 hour and have reduced duration of acting in contrast to regular human insulin. The rapid acting insulin when given subcutaneously the analogues rapidly gets dissociated into monomer and rapidly absorbed due to their low propensity for self-aggregation [25]. These agents show greater stability and consistency and superior pharmacokinetic profile upon injection.

Insulin lispro:

It is produced by the exchange of proline and lysine at B28 and B29 positions on carboxy terminals of human insulin. It is administered as subcutaneous bolus by pen or subcutaneous infusion using selected external controlled infusion devise in insulin lispro injection should be dispensed in the original unopened ,multiple dose vial, disposable injection pen or injection cartridge supplied by manufacturer. If the product exhibits discoloration, turbidity, unusual viscosity, the cartridge or vial should be discarded since the changes indicate contamination [25]. The insulin lispro has quick onset of action and shorter duration of action. The examples of insulin lispro is Humalog-100u/ml injection.

Insulin aspart:

It is a single substitution of proline by aspartic acid at position B28 [26].It has lower tendency for self-aggregation. Generally it is inserted concomitantly with certain long acting insulin (Eg-NPH) to meet basal insulin needs in diabetic patents. The fixed dose of combination of insulin aspart protamine with insulin (70/30) is meant only for subcutaneous administration and should not be given IV. It is better in control of meal time glycaemia. The example of insulin aspart is Novolog, novorapid 100u/ml injection.

Insulin glulisine:

Insulin glulisine is different among all the human insulin as the amino acid aspargigine at location B3 is exchanged by lysine and the lysine in location B29 by glutamic acid. It was sold under the trade name of apidra. It is when injected subcutaneously it appears in the blood earlier than human insulin when used as meal time insulin. The dose to be administered with in 15min before or 20min after starting a meal. It is administered using a conventional insulin syringe or in injection pen. Insulin glilisine formulation is stable in infusion sets up to 48hrs [25]. It also given by continuous subcutaneous infusion into the abdominal wall via infusion devise and it is compatible with ringer's solution or dextrose solution.

Short acting Insulin's:

The short acting insulin's are mostly used to cover the mealtime requirements of patents for insulin .An insulin formulation with an onset between 30min to 1hr this medication should be administered 30min before meal. It can be administered Intravenous or subcutaneously and may be used to treat diabetic ketoacidosis. These are all so known as soluble insulin's or regular insulin's. Short acting Insulin is unmodified stored at neutral pH and simply contains an additive (phenol or m-cresol) which prevents the growth of microorganisms in preparation overtime [27].

Regular insulin: It is a product of zinc crystalline having the strength of 100 or 500 USP insulin unit/ml. The major limitations of regular insulin are post-prandial hypoglycemia and late post prandial hypoglycemia. This injection should be administered 30-45 min before meals [28]. The onset time, peak effect and duration of regular insulin dose dependent. It can be administered by IV to treat diabetic ketoacidosis. It is also known as neutral insulin and soluble insulin and used to treat type-1 and type-2, gestational diabetes mellitus. The onset of action is 30min and duration of action is 8hours.Examples of regular insulin include Actrapid 100 IU/ml.

Intermediate acting Insulin:

Intermediate acting insulin is used to control glucose levels between meals and these are given in combination with short acting insulin's. [29] A human made form of insulin often taken in combination with short acting insulin. Its action is typically initiated with in the first hour of injecting followed by a period of peak activity lasting up to seven hours. Intermediate acting insulin also referred as Isophane or NPH (Neutral protamine hagedorn) insulin's.

Example: NPH (Humalin-N, Novolin-NPH)

Insulin NPH (Humalin, Novolin-N) is intermediate acting insulin that is a suspension of crystalline zinc insulin combined with the positively charged polypeptide protamine. Unlike short acting insulin's NPH has a long duration of action. These NPH are packed in 10 ml multiple dose container or in vials having the strength of 100 unit /ml.These NPH dose generally ranges in between 10-80unit of subcutaneous route[25].The NPH is most quickly absorbed from abdominal fat and comparatively slow from upper arm and lateral thigh area and from superior buttocks area[30]. Insulin is also available in combination with regular insulin. They are in a fixed combination of either 70% or 75% of NPH and 25% or 30% of regular insulin.

Long acting Insulin Analogues:

These long acting insulin analogues are indicated for treating diabetes in children and adults. This insulin formulation is administered subcutaneously either once or twice daily patents once-daily schedule should self-administer this drug with the evening meal or at bedtime. The onset of action is 30-60min and duration of action is 16-24hrs. The long acting insulin can control blood sugar levels for an entire day. The action is similar to the action of insulin normally produced by pancreas to help control blood sugar levels between meals. Long acting insulin's is also called basal background insulin's.

Insulin Glargine:

Insulin glargine is different among normal insulin's because the aspargine is changed by glycine at amino acid 21 of the insulin-A chain and to aspargine residues are added to the carboxyl terminal of the B-chain. The onset of action begins within 1-2 hours. It's duration of action is basal insulin secretion extends up to 24 hours .It is mainly used in management of type-1 and type-2 diabetes mellitus. Since it contributes only to the basal secretion , it is frequently used in combination with other insulin's or oral hypoglycemic agents occasionally the higher strength preparation (300 unit/ml) has been approved by the US – Food and drug Administration (FDA) [31]and it is under the list of who essential medicines .Example include Lantus optist-100u/ml.

Insulin Detemir:

In this type of insulin analogue the theorine amino acid at position of B30 has been detached and myristic acid is attached to the lysine at position 29[25]. Insulin detemir is a type of long acting insulin in those coats slowly over 24 hours. This insulin detemir can be used with another type of insulin or with oral diabetics medicine to keep blood sugar levels under control. The onset of action this insulin ranges from 3-4 hours observed between 6-8 hours [24]. All these features indicate that the insulin glargine meet the pharmacokinetic characters and it is necessary to ensure basal insulin requirement in type-1 DM and many clinical trials shown that insulin Glargine provides good control of glycemic levels. It is long acting insulin used to treat both type-1 and type-2 diabetes and it is used by injection under the skin. The extended duration of action of soluble insulin detemir is due to slow systemic absorption by virtue of short self-association and albumin binding .Duration of action of insulin detemir is dose dependent.

Insulin Degludec:

It is an ultra-long acting basal insulin analogue that was developed by NOVO nordisk under brand name Tresiba. The long duration of action (about 42 hours)is due to multi hexamers depot formed at injection site and slow release of monomers. In this B-30 threonine is deleted and B-29 conjugated to hexadecanedioic acid [25]. It includes the essential medicine in WHO. It is available as degludec-100 unit/ml in combination with 3.6 mg/ml of liraglutide solution for injection and administered via subcutaneous route.

Table-3: Pharmacokinetic properties of insulin preparation

Type of Insulin	Onset of action	Peak effect	Duration of action
Rapid acting Insulin(Insulin analogues)	5-15min	30-60min	2-5hrs
Short acting insulin's(soluble and regular insulin's)	30min	1-3hrs	4-8hrs
Intermediate acting insulins(Isophane/NPH)	1-2 hrs	4-8hrs	8-12hrs
Long acting insulins(Glargine)	30-60min	No peak	24hrs
Insulin detemir	30-60min	6-8hrs	6-24hrs
Ultra long acting insulins(Degludac)	1-2 hrs	No –peak	42hrs

ORAL HYPOGLYCEMIC AGENTS:

The most effective management of DM is demands an professional approach involving the life style as well as modification with diet and exercise and pharmacologic therapies are needed to control glycemic levels. The clinicians encourages patents to combine life style with Oral hypoglycemic agents [32].These oral hypoglycemic agents are have been the employed mainly for treating type-2 diabetes mellitus(type-2 DM) for numerous decades given their efficacy and convenience. These agents reduce blood glucose levels and are effective orally. These are effective when insulin gets degraded in GIT and these have longer duration of action than insulin and it's preparations. The oral hypoglycemic agents are mainly used to treatment of type-2 Diabetes mellitus when it can't be controlled by diet and exercise. The last two decades have witnessed the introduction of many classes of these agents and their optimal and side effects are gradually recognized. The types and examples of oral hypoglycemic agents were shown in tale no-4.

The approved hypoglycemic agents are eight clases majorly. The oral hypoglycemic agents currently available are Biguanides (MET), Sulfonylureas, Glinides (GLN), Thiazolidinedione's (TZD), Alpha-glycosidase inhibitors(AGI), Dipeptidyl peptidase-4-Inhibitors(DPP-4I), and the most recent sodium glucose contrasporter 2-inhibitors(SGL-T-2I), Glucagon like peptide-1(glp-1)agonists.

Table-4:Oral hypoglycemic agents

Drug classes	Examples	Dosage	Side effects
Biguanides	Metformin	1-3gm	Nausea Mild diarrhea
Sulfonyl urea's	Gliclazide Glimepride Glyburide Glypizide	40-32mg 1-6mg 2.5-15mg 2.5-40mg	Increased weight Hypoglycemia Hypersensitivity Headache
Glinides	Nateglinide Repaglinide	180-540mg 1-16mg	Headache Increased weight Dyspepsis
Thiazolidine diones	Pioglitazone Rosiglitazone	15-30mg 4-8mg	Headache Increased weight Mild anemia
Alpha glucosidase inhibitors(AGI)	Acarbose Miglitol	25mg a day 25mg a day	Flatulence Abdominal discomfort GI upset
Diphrnyl pepdase-4 inhibitord(DPP-4I)	Linagliptin Saxagliptin Sitagliptin Alogliptin	5mg-OD 5mg-OD 100mg-OD 50mg-OD	Angeoodema Pancreatitis
Glucagon like peptide(GLP-I)agonist	Exenatide Liraglutide Dulaglutide	2mg 0.6mg-OD 0.75mg once a week	Nausea Nasopharyngitis Headache
Sodium glucose contrasporter-2 Inhibitors(SGLT-2)	Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Empagliflozin	50-300mg/day 2.5-10mg/day 5-10mg/day 12.5-100mg/day 1-50mg/day	Decreased weight Dehydration Genitourinary infections

Insulin delivery devices:

Insulin pens:

Insulin pens look similar to oversized ink pens, making them a potentially convenient and discreet way of carrying insulin. These insulin pens are extensively used over traditional vial and syringe method for insulin administration worldwide. The introduction of the insulin pens was a milestone in insulin delivery [33]. An insulin pen has three components an insulin cartridge a disposable short needle and an incremental one click per unit dosing. The device can be either reusable or disposable. Reusable insulin pens have a replaceable cartridge. Disposable pens have a replaceable cartridge. The disposable pens have a prefilled cartridge and are discarded after the use. Currently cartridges of insulin preparations such as lispro, Aspart and glargine are existing for reusable pens; similarly disposable prefilled pens are available for regular insulin (U100 and U500) and most of the insulin preparations.

The Novopen was launched by Novo nordisk in 1985, followed by Novo pen 2 in 1988[33]. In general insulin pens are simple accurate and convenient in insulin delivery compared to syringes. In 1989 Novo presented the world's first disposable, prefilled insulin pen 'Novolet'[34]. Insulin absorbs on to the plastic surface of the prefilled pens over time and a precise concentration can be achieved by proper mixing. Hence these pens are increased the dose accuracy and blood glucose stability between cartridge changes[35].Compared to syringes pens offer more flexibility, accuracy and long term cost effectiveness ,contributing to improved treatment and adherence. First generation insulin pens are available in the market from the 1990's. The most popular insulin pen in this category are multiple generations of durable pens of the Novopen family, Allstar (sanofi), Humalog pen, Kwikpen (Eli lilly)and Solostar (sanofi). Novopen 3 is a durable pen allowing a max dosage of 70U was launched in 1992. Novopen 1.5 a shorter version of Novopen-3 was launched in 1996.Flexpen a prefilled insulin pen was introduced in 2001, in 2005 The Novopen -4 was launched, Kwikpen and SOLOSTAR (sanofi) were launched in 2007 and 2008 respectively and in 2008 next generation Flexpen was introduced. Sanofi India launched its first indigenously developed reusable insulin pen Allstar. Specifically designed for diabetic patents in India in 2012[33]. In 2017 junior Kwikpen a half unit insulin pens have advanced safety features such as audible clicks with each dose as well as ergonomic features to reduce the physical efforts of the injection and confer more user friendliness, accuracy and flexibility[36].

Insulin Inhalers:

Insulin inhalers allow patents to allow in fine inhalable insulin into the lungs. Inhaled insulin was introduced and approved by FDA in January 2006. The pulmonary route of insulin administration was closer to physiologic portal delivery and therefore the first substitute for the subcutaneous route of insulin delivery [37]. The first inhalable insulin Exubera developed by Pfizer was approved by FDA in 2006 and the product was withdrawn from the market in 2007 because of high cost and dose inaccuracy [38,39].Then Afrezza is developed and approved by FDA IN 2014[40] which is small and handy. The use of Afrezza has provided a significant glycemic control and shows hypoglycemia in tpe-1 DM and the use of insulin inhalers are reduced and limited due to safety concerns.

Insulin pumps:

These are known as continuous subcutaneous insulin infusion. Pumps are advanced method for the delivery of insulin and can all so be used for dispensing insulin in any patent who expresses their interest to initiate pump therapy [41]. These insulin pumps are also used in diabetes management which requires careful handling. Various insulin pumps are currently available in the market. The pump is a small device which consists of an insulin reservoir, the program chi, the keypad, and the display screen. The insulin reservoir is connected to the infusion set and catheter to continuously deliver insulin to meet the daily requirement. The pump has specific in built programs to dispense insulin at basal rates and incremental doses before meals. The continuous subcutaneous insulin infusion (csii) or the insulin pump was introduced in late 1970's,originally to treat type-1 diabetes mellitus.[33] the most suitable site for continuous delivery is abdomen, although other regions like thigh is also used. One should remember to change the reservoir tubing and infusion set on 2-3 days in a sterile environment. A high accuracy insulin pump is an ideal choice for children with type-1 diabetes mellitus as they require very low basal rates. However the cost for insulin therapy by this device is relatively expensive.

The new generation external pumps released in the year 1990's are comparatively small, compact, handy and effective. The currently popular insulin pump models on the global market are Medtronic minimed, Omnipod (Insulet), T: Slim (Tandem), Accu-chek solo micro pumps (Roche) [42]. In 2003 medtronic introduced the first ever "Intelligent" insulin pump. Diabetic management with insulin pumps provides better glycemic and metabolic control in patients with diabetes. The use of insulin pumps effectively contributes to the patents quality of life. Insulin pumps are mostly used for insulin replacement In both type-1 and type-2 Diabetes mellitus but widely accepted by type-2 DM [43].

Insulin Syringes:

Insulin syringes are disposable and reusable for one time use these help to make the needle reusable and sterile to avoid the risk of infection from used needles. Insulin syringes come in multiple sizes with different doses of insulin and number lines on insulin syringe is measured in ml as 0.3ml, 0.5ml, and 10ml respectively. These insulin syringes allow more flexibility if dose need to be adjusted [44].Insulin syringes are reusable needles had to be sterilized by boiling to effective reuse. Initially big and heavy reusable syringes with plungers, barrels and long large-bore needles were used for insulin delivery. The first specialized insulin syringe for insulin injection was manufactured by becton Dickinson in 1924 Novo nordisk launched its first insulin syringe, the 'Novo Syringe' in 1925[33]. In 1954 the disposable glass syringe was introduced. The plastic monoject injection was introduced in 1955.In 1970 BD manufactured the first one-piece insulin syringe with an integral needle. In 1983 the British diabetic association recommended a change from commonly practiced two insulin strengths to single strength insulin. The U-100 plastic insulin syringe with units marking down the side of the syringe came into use. FDA approved a U-500 specific insulin syringe designed by BD in 2016.In place of long, large bore sized and reusable needles the small bore sized and short length neeedels are used for insulin injection.

Jet injectors:

Insulin jet injectors are designed to overcome uncomfortable feeling associated with insulin injection. These are designed to send a fine spray of insulin through the skin using high pressure air mechanism. [45]The jet injector that uses a high pressure narrow jet of injection liquid instead of a hypodermic needle to penetrate the epidermis. The jet may produce high pressure of injection and a tiny hole in the surface of skin and the medication travels through the hole. The injector disperse insulin into the subcutaneous adipose tissue compartments with efficiency over 90%.This jet injector technology was introduced in 1860s.The new generation , disposable dose chambers and nozzles were launched in the 1990s[33].The jet injectors are the solution for the patients with needle phobia. These jet injectors are less painful since a needle is not used and it can be carried anywhere and has better acceptance and highly expensive.

CONCLUSION:

DM is one of the leading cause of several chronic diseases, including renal complications. The disease predominantly offers individuals of all age irrespective of gender. As the number of patents with DM increases every day, it is becoming a challenge for health care professional to treat them. The development of novel technologies must focus on patient centered needs and improved clinical outcomes for a broad spectrum of diabetic population. The continued improvements in continuous glucose monitoring technique facilitated both direct benefits to the case of type-1 diabetic patents and paved the way of developing the devices for insulin delivery. Through there were available devices, many of those are prohibitively expensive along with some disadvantages. The ultimate dream is to develop an artificial pancreas capable of 100%TIR and 0% time below range and affordable to everyone for diabetes management.

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