



CONTEMPORARY APPROACHES IN INSULIN ADMINISTRATION FOR THE TREATMENT OF DIABETES

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Abstract: Diabetes mellitus is a metabolic disorder, caused by dysfunction of insulin secretion or insulin function or both, leading to persistent hyperglycemia and other vascular complications as the disease progresses. Several factors contribute to the progression of the disease, such as family history or genetics, environmental factors, and various genetic disorders. A sedentary lifestyle, unhealthy diet, physical inactivity, and obesity are the major responsible factors. Treatment of diabetes is started with the use of drugs such as metformin, Sulfonylureas, thiazolidinediones, SGLT-2 inhibitors, DPP-4 antagonists, etc. Moreover, cell-based treatments such as the pancreas or pancreatic cell transplantations are being explored broadly for the treatment of type-1 diabetes mellitus. Whereas, insulin is the major player in the treatment of diabetes mellitus. For several decades, insulin has been administered as a subcutaneous injection, several times a day. However, the subcutaneous route has several limitations, such as pain at the injection site, infections due to improper administration/self-administration, hypertrophy due to deposition of insulin at the site of injection, patient discomfort; fail to achieve blood glucose control in several patients. This led to the exploration of alternative routes for insulin delivery, soon after its discovery. Various non-invasive and novel routes have been studied, including oral route, nasal route, pulmonary, transdermal route, and buccal, ocular, intrauterine, and rectal routes. These routes have proven successful up to some extent and several complications are also associated with these novel delivery systems. Toxicity associated with long-term use, safety and efficacy studies, feasible formulation of these delivery systems for efficient human use, still need to be explored deeply. In this review, we will study diabetes mellitus, alternative insulin delivery routes, and various advantages and disadvantages associated with formulations of these routes.

Index Terms – diabetes mellitus, insulin delivery, insulin, novel drug delivery

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder caused by defect in insulin action or insulin secretion deficiency or both. In addition, insulin deficiency contributes to persistent hyperglycemia with carbohydrates, protein and fat metabolism disorders. Tissue and vascular damage occurs as disease progresses, leading to major diabetic complications such as retinopathy, (1) (2) neuropathy, (3) nephropathy, (4) cardiovascular complications (5) and ulceration. (6) Diabetes thus covers a wide range of heterogeneous diseases. (7) The International Diabetes Federation (IDF) reports that the overall prevalence of diabetes mellitus in 2011 was 366 million, which is predicted, would increase up to 552 million by 2030. (8) (9) In 21st century, diabetes mellitus long considered as disease of minor importance to global health is now one of the key threats to human health. (10)

Asia is the major site of a fast growing diabetes epidemic. Some estimates based on population growth, ageing and rate of urbanization in Asia shows that India and China will remain two countries with the largest number of people with diabetes (79.4 million and 42.3 million, respectively) by 2030. (11) (12) In the last few years, developing countries such as India have seen the highest increases. In the rural population, the present prevalence of diabetes is 2.4% and in urban population, 11.6%. It has been projected that India will have largest number of diabetic people in world by 2025. (13) (14) India is currently facing an uncertain future in terms of potential burden that diabetes can place on the country. (15)

Until quite recently, international health organizations and national governments have been ignoring the growth and rise of diabetes and other non-communicable diseases. In comparison to the funding for the control of communicable diseases, funding for the prevention and control of such diseases including diabetes has been low priority. (16)

II. CLASSIFICATION OF DIABETES MELLITUS

A single classification system of diabetes is ideal because it facilitate three main purposes: clinical care, aetiopathology and epidemiology. With this in mind the expert group decided that defining a classification system that prioritizes clinical care and assists medical professionals in deciding whether or not to initiate insulin therapy especially at the time of diagnosis, was the best option. (17)

The National Diabetes Data Group (NDDG) published its first diabetes classification in 1979. (18) in 1980, World Health Organization (WHO) endorsed this recommendation, which was updated in 1985. The NDDG classification of diabetes was based on pharmacologic treatment used and it was divided into two major groups:

- Type-1 diabetes mellitus (insulin dependent)
- Type-2 diabetes (non insulin dependent)

The NDDG also sub-categorized diabetes into three types: Gestational diabetes, Malnutrition related diabetes mellitus and some other types. (19)

Table: 1 classification of diabetes (19)

S. no	Type name
1.	Type-1 diabetes mellitus
	a.) Autoimmune/ immune-mediated/ type-1A b.) Idiopathic/ type-1B
2.	Type-2 diabetes mellitus
3.	Other detailed types
	a. Single gene defects of β -cell function b. Single gene defects in insulin function c. exocrine pancreas diseases d. Endocrinopathies e. Drug or chemical induced diabetes f. Infections g. Rare forms of diabetes (immune mediated) h. Some genetic syndromes causing diabetes

2.1 Type-1 diabetes mellitus

Also named as juvenile diabetes is characterized by an autoimmune mechanism that damage beta-cells, resulting in absolute insulin deficiency. (20) When insulin is not sufficient, patient can develop ketoacidosis, fall into coma and eventually die. (19) Therefore to maintain normglycemia, all type-1 patients will require insulin therapy. (20) T1DM is linked with development of auto antibodies months or years before symptoms occur. These are not pathogenetic but serve as biomarkers for progression of autoimmunity. (21) T1DM was once thought to be primarily a disorder affecting children and adolescents, however, perceptions have shifted in the last decade, so that age at symptom onset is not a limiting factor (22) (23) type-1 diabetes is further sub-classified into: Type-1A and Type-2B.

2.1.1 Auto-immune/ immune mediated/ type-1A

The main histocompatibility locus on chromosome 6 determines a genetic predisposition to this organ specific autoimmune disorder. (24) The disease's origin can be traced back to a genetically predisposed person who is exposed to an environmental stimulus that contributes in T-cell mediated destruction of pancreatic β -cells. This type of diabetes mellitus affects only 5-10% of people with diabetes. Though patients with this form of diabetes are rarely obese, the existence of obesity is not incompatible with diagnosis. (25)

2.1.2 Idiopathic/ type-1B

Some forms of type-1 diabetes have no known etiologies. This type of diabetes is strongly inherited. There is no proof of beta cell autoimmunity discovered immunologically. (25)

2.2 Type-2 diabetes mellitus

Type-2 diabetes is characterized by relative insulin deficiency caused by pancreatic β -cell dysfunction and insulin resistance in target organs. (26) it is a pervasive and severe global health problem that has arisen as a result of rapid cultural, economic and social shifts as well as ageing populations, unplanned urbanization, dietary changes, obesity, decreased physical activity, an unhealthy life style and number of other factors. T2DM is most common in adults but is rapidly growing in children and adolescents. (17) Because of hyperglycemia and insulin resistance syndrome, people with T2DM are at high risk for both micro vascular (retinopathy, nephropathy, neuropathy) and macro vascular (cardiovascular comorbidities) complications. (27) The true mechanism of this form of diabetes is uncertain, but it is thought to be combination of both genetic and environmental factors, culminating in a very heterogenic phenotype. (19)

Women with previous gestational diabetes the third form of diabetes as well as those with hypertension or dyslipidemia are more likely to develop T2DM. (28) The genetics of T2DM are not yet defined clearly as these are quite complex.

2.3 other specific types of diabetes mellitus

Diabetes mellitus types with different identified etiologies are grouped together in this heading. People with genetic defects in β -cell function or insulin action, people with exocrine pancreas disease such as pancreatitis, or cystic fibrosis, people with dysfunction associated with other Endocrinopathies, and people with pancreatic dysfunction caused by drugs, chemicals, or infections account for less than 10% of diabetic cases. (20)

2.3.1 Single-gene defect of function of β -cell

MODY (maturity onset of diabetes of young), permanent neonatal diabetes (PNDM), transient neonatal diabetes (TNDM), and genetic syndromes in which insulin deficient diabetes is associated with specific clinical features are all clinical manifestations of monogenic defects in β -cell function. (29) (17)

2.3.2 Genetic defects in insulin function

Insulin resistance caused by monogenic factors is less common than beta-cell defects caused by monogenic defects. In the absence of obesity, they commonly exhibit insulin resistance symptoms such as hyperinsulinemia, acanthosis nigricans, polycystic ovarian disease and virilization. (30) (17)

Mutations in the insulin receptor cause a variety of clinical sign and symptoms as well as varying degrees of hyperglycemia. (31) Leprechaunism and Rabson-Mendenhall syndrome are two pediatric syndromes characterized by intense insulin resistance, dysmorphism, serious intrauterine retardation and mortality due to mutations in the insulin receptor gene. (32) (17)

2.3.3 Disease of exocrine pancreas

Diabetes can be caused by a variety of acquired processes, including pancreatitis, pancreatic cancer, and pancreatectomy. (28) any processes that damage the pancreas can cause diabetes. (33) while removal of 90% of pancreas doesn't cause diabetes, but it has been reported in very small pancreatic carcinomas. (34) (19)

2.3.4 Endocrinopathies

Several hormones like growth hormone, cortisol, glucagon, and epinephrine antagonize insulin action. (35) Whereas, disease such as acromegaly, Cushing's syndrome, glucagonoma can cause diabetes as these cause excess secretion of these hormones. (17)

2.3.5 Drug or chemical induced diabetes

Insulin secretion may be hampered by variety of medications. These medications do not induce diabetes on their own, but they may hasten the development of diabetes in people who have insulin resistance. (25) some toxins like pyrinuron, a rat poison, and pentamidine can destroy pancreatic beta cells permanently. (36) (17)

2.3.6 Infections

Certain viruses are associated with causing diabetes. For example, in genetically predisposed individuals, rubella and coxsackie B viruses have been linked with autoimmune destruction of beta cells and causing diabetes. (37) (38) (19)

2.3.7 Uncommon forms of immune mediated diabetes

Some forms of diabetes have different etiology and pathogenesis than T1DM. These forms are associated with specific immunologic diseases. In rare cases, individuals who produce insulin auto antibodies spontaneously develop hyperglycemia extreme enough to meet the requirements for diabetes. (39) Insulin receptor auto antibodies interact with insulin receptor; prevent binding of insulin with target tissues, hence causing diabetes. (40) on rare occasions, insulin receptor auto antibodies have been discovered in patients with systemic lupus erythematosus and other autoimmune disorders. (41) (17)

III. PATHOGENESIS/PATHOPHYSIOLOGY OF DIABETES

3.1 Type-1 diabetes mellitus

Type1A is induced by cell mediated autoimmune attack on β cells, whereas type1B is far less common, has no known cause, between intermittent episodes of ketoacidosis, is often seen in people of Asian or African origin who have varying degrees of insulin deficiency. (42) (43)

T1DM is distinguished by autoimmune destruction of insulin producing cells in the pancreas by infiltrating CD4+ and CD8+ T-cells and macrophages. (44) (45) when islet-reactive lymphocytes come into contact with cognate antigen in the pancreatic lymph nodes, they become activated and migrate to the pancreas. Lymphocytes surround the islet first (peri-insulinitis), then enter the islet core (destructive insulinitis), causing beta cell degeneration and eventually T1DM. It develops in genetically susceptible individuals, with the median onset age of 10-14 years. (46) (47)

Alleles or genetic variants linked to type-1 diabetes increases susceptibility or protect against disease. (Devendra et al., 2004) diabetes that appears before age of 5 years is a marker of high familial risk, implying that genetic factors play a significant role. (Gan et al., 2012) according to the studies on monozygous twins, the concordance rate between the two individuals is approximately 50%. (Tesauro & Mazzotta, 2019) this shows that some environmental factors are also associated with onset of disease, but the precise triggers remain unknown. T1DM is recognizably a polygenic disorder, with nearly 40 loci implicated in disease susceptibility. (Atkinson et al., 2014) (Noble et al., 2010) the class II human leukocyte antigen (HLA) genes, found on the short arm of chromosome 6, have been linked to the highest risk of developing the disease. (Tesauro & Mazzotta, 2019)

Autoimmunity in T1DM, the destruction of pancreatic cells due to autoimmunity is referred to as insulinitis. T1DM inflammation is typically described by a severe decrease or absence of insulin producing β -cells and also immunological infiltrates composed of macrophages, T-lymphocytes, natural killer cells, and B-lymphocytes. (Tesauro & Mazzotta, 2019) (Tudies et al., 2009)

Although, the clinical picture of type-1 diabetes has been known for over a century as a progressive loss of beta cell function over time and the need for daily insulin treatment for patient survival, the precise immunologic, genetic and physiological events that control disease initiation and progression are still being elaborated. (48) (49) (50)

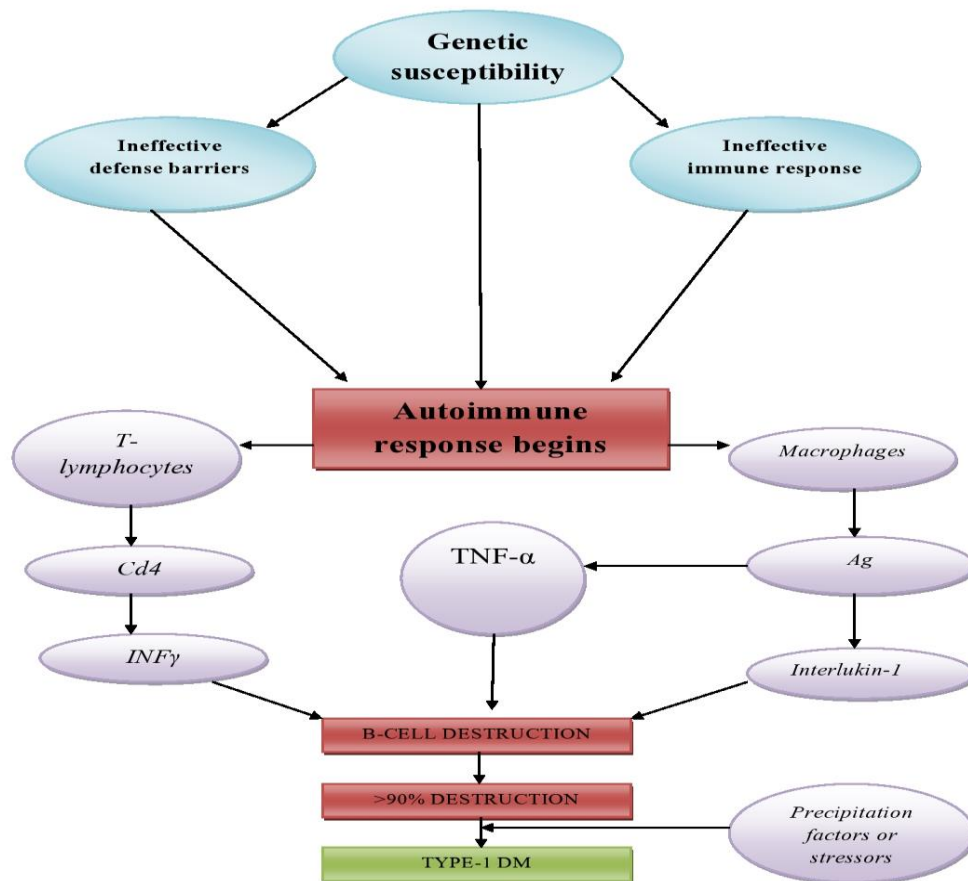


Figure-1: Type-1 diabetes mellitus pathogenesis (51)

3.2 Type-2 diabetes mellitus

Type-2 diabetes is a bipolar disorder caused by a defect in both insulin action and insulin secretion whose complex interaction contributes to a gradual increase in plasma glucose levels. (52) (53) type-2 diabetes is distinguished by hyperinsulinemia, insulin resistance, and pancreatic β -cell failure, with up to 50% cell loss at time of diagnosis. (26) (54) type-2 diabetes risk factors include a complex web of genetic, metabolic and environmental factors that interact and contribute to disease's prevalence. Ethnicity, family history, obesity and physical inactivity are some other factors that can also contribute in occurrence of disease. In terms of disease's pathophysiology, a breakdown of feedback loops between insulin action and insulin secretion results in abnormally high blood glucose levels. Insulin secretion is reduced in case of β -cell dysfunction limiting body's ability to maintain physiological glucose levels. Insulin resistance, on the other hand, contributes in increasing glucose production in liver while decreasing glucose uptake in the muscle, liver and adipose tissue. (55) (56) Impaired α -cell function has recently linked to pathophysiology of the disease. (57) (58)

Genetic factors involved a family history linked to development of type-2 diabetes. The significantly higher concordance rate between monozygotic twins than between dizygotic twins suggests the involvement of genetic factors role. (59) When the mother has a disease, the risk of developing type-2 diabetes is higher than the father having disease. (27) (60) many genetic loci and over 220 genes have been identified in genome-wide association studies that may confer an increased risk of developing type-2 diabetes. (61) (62)

- Impaired insulin secretion: patients with type-2 diabetes have various insulin secretion abnormalities. (56) insulin is produced by β -cells, which is synthesized as pre-proinsulin. During the maturation process, pre-proinsulin undergoes a conformational change with the assistance of several proteins in the endoplasmic reticulum to produce proinsulin. (55) (63) proinsulin is then transported from the endoplasmic reticulum to Golgi apparatus, where it enters immature secretory vesicles and is cleaved into C-peptide and insulin. (64) (65) insulin is matured and stored in granule until insulin release is triggered. Insulin release is primarily triggered in response to high glucose concentrations. (55) Because of difference in their genetic susceptibility, β -cells are vulnerable to toxic pressures such as inflammation, inflammatory stress, ER stress, metabolic/oxidative stress, and amyloid stress which have potential to lead to islet integrity loss. (66) but in order for β -cells to respond to metabolic needs, proper islet integrity must be maintained. The mechanisms mentioned above may cause islet integrity to be disrupted under pathological conditions, which impair optimal communication of cells within pancreatic islets, which leads to poor insulin and glucagon release and eventually exacerbating hyperglycemia. Defects in the synthesis of any insulin precursor or insulin itself as well as disruption in secretion mechanism, can lead to insulin secretory dysfunction which is primary cause of beta cell failure and a foundation of type-2 diabetes mellitus. (55)(67)

- Insulin resistance: when insulin in body is not able to exert sufficient action proportional to its blood concentration, a condition called insulin resistance develops. Insulin resistance in major target organs such as liver and muscles is a common pathophysiological feature of type-2 diabetes. It develops and spreads prior to the onset of disease. (59) obesity and physical inactivity increase the risk of insulin resistance, which, in combination with a genetic predisposition, place stress on β -cells resulting in cell failure and progressive decline in insulin secretion. (27) (68) (69) defects in insulin signaling, glucose transport, glucose Phosphorylation, glycogen synthesis, pyruvate dehydrogenase complex activity and mitochondrial oxidative activity; all contribute to insulin resistance in muscles. (27) (70) insulin resistance in conjunction with insulin deficiency, hyperglucagonemia, increased glucagon sensitivity, increased substrate (fatty acids, lactate, glycerol and amino acids) delivery, leads to increased gluconeogenesis in the liver which is responsible for increased basal rate for glucose production and fasting hyperglycemia. (71) (72) fasting hyperglycemia is also caused by insulin resistance in kidney and augmented renal gluconeogenesis. (73) (27)

This insulin deficient signaling (insulin resistance) is caused by a number of alterations such as, mutations, post translational modifications in the insulin receptor, IRS (insulin receptor substrate) or downstream located effector molecules. The most common insulin resistance alterations include decreased number of insulin receptors and their catalytic activity, an increase in serine/threonine Phosphorylation state in insulin receptors and IRS, an increase in tyrosine phosphatase activity, primarily PTP-1B (protein tyrosine phosphatase-1B) which participates in receptor and IRS dephosphorylation, a decrease in PI3K (phosphoinositide 3-kinase) and Akt activity and defects in GLUT-4 expression and function. Reduced glucose uptakes in muscular and adipose tissue, promotion of alterations at metabolic levels are caused by these alterations. (74) (75) (76)

Table: 3 main hallmarks to differentiate type-1 and type-2 diabetes (77)

s. no	Type-1 diabetes	Type-2 diabetes
1.	AUTO-ANTIBODIES	
	Present	Absent
2.	HLA (human leukocyte antigen)	
	present	Absent
3.	C-PEPTIDE	
	low	Normal
4.	COMPLICATIONS ASSOCIATED	
	Early micro vascular	Micro and macro vascular
5.	INSULIN DEFICIENCY	
	Absolute deficiency	Relative deficiency

Both genetic and heredity diabetes genes, environmental factors such as lifestyle contributes to beta-cell defects which leads to type-2 diabetes. Also, lipotoxicity and glucotoxicity contributes in beta-cell defects as shown in fig. 2

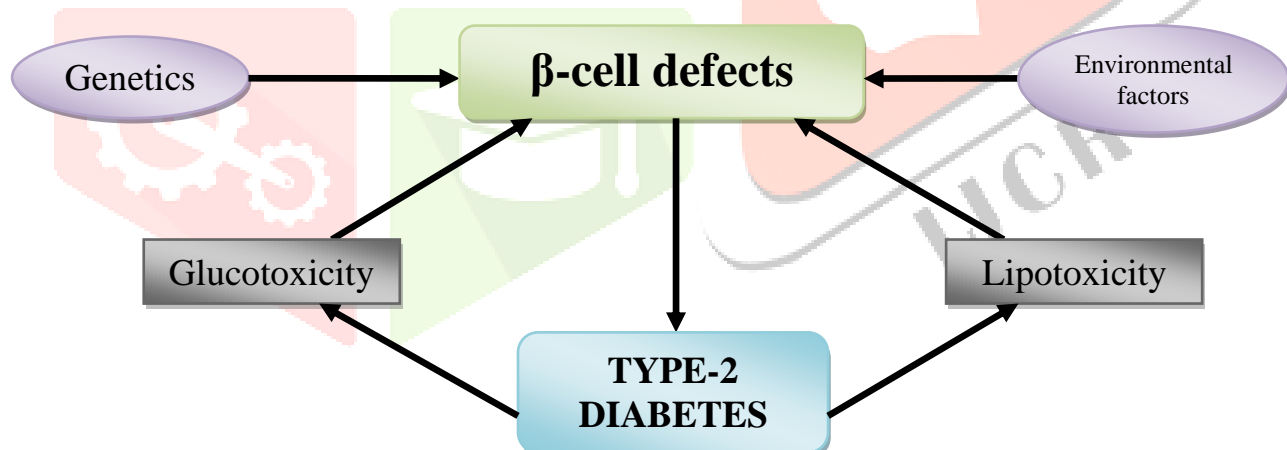


Figure: 2 pathophysiology of type-2 diabetes (78)

IV. DIAGNOSIS AND TREATMENT OF DIABETES

At least one of the criteria must be met in order to diagnose the diabetes:

- Diabetes symptoms like polyuria, polydipsia, unexplained weight loss etc, as well as casual plasma glucose concentration of 11.1 mmol/L (200 mg/dL)
- Fasting plasma glucose= 7.0 mmol/L (126 mg/dL) with no food intake for at least 8 hours. (7)

After diabetes has diagnosed, treatment has to start. In patients with type-1 diabetes, insulin replacement therapy is mainstay of the treatment whereas type-2 diabetes should be considered a potentially preventable disease. Diet and lifestyle changes are regarded as the cornerstones of type-2 diabetes treatment and management. Oral hypoglycemic agent can also help in treating type-2 diabetes. When diet, weight loss, exercise and oral medications are ineffective in controlling blood glucose levels, insulin can be used as an alternative approach for diabetes treatment. (7) metformin, sulfonylurea, glinides, thiazolidinedions, α -glucosidase inhibitors, glucagon like peptide-1 (GLP-1) receptor agonists, dipeptidyl-peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors are currently used antidiabetic drugs. (79)

4.1 Metformin

Metformin, the only type of biguanide approved for clinical treatment of diabetes, (80) remains the first line treatment, particularly for obese patients. (81) (82) (79) metformin's hypoglycemic mechanism is still not fully known. (83) (84)

4.2 Sulfonylureas

It is an enhancer of insulin secretion. Sulfonylureas stimulate the insulin release from pancreatic β -cells via mechanism that involves blocking of ATP sensitive potassium channels (K_{ATP}). Recently α -endoslfine, an 18-kD protein that displays sulfonylurea binding to β -cell membranes, inhibit cloned K_{ATP} channel and stimulate insulin secretion, has been proposed as endogenous ligand for the sulfonylurea receptor. (85) (86) these drug include two generations. Tolbutamide, tolacarburea, chlopropamide and hexahydrourea acetate are examples of first generation agents while glibenazide, glipizide, glizide, and glimetazide are examples of second generation agents. Second generation drugs have stronger effects, longer duration of action and fewer side effects as compared to first generation drugs. (79) (87)

4.3 Glinides

Glinides like repaglinide, nateglinide, mitiglinide are a type of fasting insulin secretagogue that can mimic early phase insulin release allowing for better postprandial glucose control. (79) (88) through binding to its distinct sites on the pancreatic β -cell membrane, glinides displayed a faster and briefer insulinotropic activity as compared with Sulfonylureas. (79) (89) in clinical trials, glinides have shown effective lowering of HbA1c levels in patients with type-2 diabetes, both as monotherapy and in combination therapy. (79) (90) (91)

4.4 Thiazolidinedions (TZD)

These are insulin sensitizing agents that act as agonists of the nuclear factor peroxisome proliferator-activated receptor- γ (PPAR- γ), improving insulin sensitivity particularly in peripheral tissues. Thiazolidinedions can boost glycogen synthesis while inhibiting gluconeogenesis in liver. Furthermore, they can enhance glucose oxidation and promote fat conversion in adipose tissues. (79) (92)

4.5 Sodium glucose cotransporter-2 (SGLT-2) inhibitors

The kidneys contribute to glucose homeostasis through gluconeogenesis, glucose use and glomerular filtrate glucose reabsorption. (93) (94) SGLT-2 inhibitors lower blood sugar levels by increasing glucose excretion from the kidney. SGLT-2 is responsible for transport of d-glucose and is expressed specifically on proximal renal tubules. (79) (95) in diabetic patients, SGLT-2 in the proximal tubule is over expressed and glucose reabsorption is increased, resulting in elevated blood glucose levels. (96) (97) (79) by competitively inhibiting SGLT-2 mediated glucose absorption, SGLT-2 inhibitors lower the renal threshold for glucoseuria. patients can eliminate 20-30% of the glucose filtered (about 50-100 mg glucose/day) (98) (99) and thus hypoglycemic effect is achieved by using SGLT-2 inhibitors. In addition to hypoglycemic effect, SGLT-2 inhibitors can improve insulin resistance and islet beta-cell function, rise plasma glucagon levels, and improve glomerular hyper filtration in the early stages of diabetic kidney disease. (79) (100) (101)

4.6 Dipeptidylpeptidase-4 (DPP-4) inhibitors

In 2007, dipeptidylpeptidase-4 inhibitors, also known as gliptins became available. They increase the incretin effect to increase the glucose stimulated insulin secretion and have other effects that help with glycemic control. (98) (102) DPP-4 inhibitors were introduced in year 2006. Sitagliptin, saxagliptin and linagliptin are some drugs used as DPP-4 inhibitors. Fasting and postprandial hyperglycemias as well as HbA1c are significantly reduced by DPP-4 inhibitors. (79) (103)

4.7 GLP-1 RAs

Incretin is a hormone that plays important role in glucose homeostasis. By increasing glucose dependent insulin secretion, decreasing glucagon secretion, delaying gastric emptying and increasing satiety, incretin mediates the effects of low glucose. (79) (104) (105) their mechanisms of lowering glucose levels are similar to DPP-4 inhibitors. There are currently six GLP-1 RAs approved for the treatment of type-2 diabetes: twice daily exenatine, once daily liraglutide, lixisenatide, once weekly extended release- dulaglutide, albiglutide, and semaglutide. (79) (106) (107)

4.8 Combination or multi drug therapy

The goal of primary therapy is to achieve ADA guidelines for glucose control, which can begin with a Sulfonylureas or metformin. Because diabetes is a progressive disease, combination therapy is used if treatment with single drug fails to achieve this goal, i.e., monotherapy fails to achieve glycemic levels goal due to non compliance. (108) a sulfonylurea plus metformin, sulfonylurea plus α -glucosidase inhibitor, a sulfonylurea plus a thiazolidinedione, metformin plus repaglinide, biguanide plus α -glucosidase inhibitor and metformin plus thiazolidinedione, all are reasonable combinations of drugs used as combination therapy. (109) (110) if combination therapy also fails to induce glycemic control, insulin should be initiated.

4.9 Cell-based treatments for type-1 diabetes

Type-1 diabetes mellitus is a single-cell disease in which the pancreatic β -cells in islets of Langerhans are destroyed irreversibly due to an autoimmune assault, resulting in potentially fatal metabolic dysfunction due to low levels of insulin in blood. Recent clinical trials have shown that human islets of Langerhans transplantation can provide a cure for type-1 diabetes mellitus. (111) (112) (113) islet β -cells from other species, called xenografts can be used to treat type-1 diabetes mellitus. Using islets of Langerhans from other species is an obvious way to provide the large amount of functional tissue required for diabetes transplantation therapy. The majority of efforts in this area have been focused on use of pig islets. (111) (114) stem cells can also be used as substitutes for beta-cells. Although interesting experimental procedures have been developed, pancreas and islet transplantations are limited by a small number of donors, chronic immunosuppression, and the recurrence of autoimmunity/onset of alloimmunity. Furthermore, pancreas transplantation has only been partially successful. (115) (116)

4.10 Insulin in treatment of diabetes

The major breakthrough in medicine and therapy in patients with diabetes was marked by the discovery of insulin in 1922. Long before insulin was discovered, it was believed that the pancreas secreted a substance that regulated the carbohydrate metabolism. (117) (118) the direct synthesis of insulin's polypeptide chains was available in 1950, but due to difficulties in obtaining an appropriate chemical combination of A and B chains, the total synthesis of the molecule was obtained in 1966; the preparation obtained was 70% pure and only limited clinical studies on humans were conducted. (119)

Use of insulin is most important aspect of diabetes treatment. Almost all insulin treatments now are human insulin or analogues synthesized using recombinant DNA technology. Insulins are categorized based on duration and onset of action. (98) Insulin is available as rapid, intermediate and long-acting formulations which can be injected separately or mixed in the same syringe. (120) lispro, aspart, glulisine are currently available rapid acting Insulins; detemir and glargine are currently available long-acting analogue basal Insulins. (121) (122) type-2 diabetes patients are typically started on a basal once-daily, long-acting insulin, twice-daily, intermediate acting insulin or twice daily premixed insulin. Whereas, to mimic the normal insulin profile as

closely as possible, type-1 diabetes patients are started on a basal-bolus insulin regimen. (98)

V. DELIVERY OF INSULIN

5.1 Current approach

Many diabetics are currently reliant on multiple doses of subcutaneous insulin injections every day to maintain the blood glucose levels and it is regarded as the standard treatment of diabetes. Poor patient compliance, injection site discomfort, infection due to self-administration/improper administration, insulin disposition at injection site causing hypertrophy, cost-effectiveness and inadequate blood glucose regulation are some limitations that are associated with subcutaneous delivery of insulin. (123) (124) (125) therefore, alternative routes of administration have been extensively researched in order to improve the pharmacokinetic profile of the insulin and reduce the pain and inconvenience associated with the subcutaneous injections, thereby improving patient comfort. (126) (127)

5.2 Novel approaches

To overcome the drawbacks of subcutaneous insulin delivery, extensive research has been conducted to identify non-invasive routes that would provide at least comparable glucose control while improving patient compliance. For many of these, clinical use has been already begun. (128) (129) in order to improve pharmacokinetic profile of insulin, alternative routes of administration have been broadly studied. (126) (127)

Novel routes of insulin delivery include transdermal, oral, nasal, rectal, ocular, buccal, vaginal, pulmonary, etc. some these are discussed here.

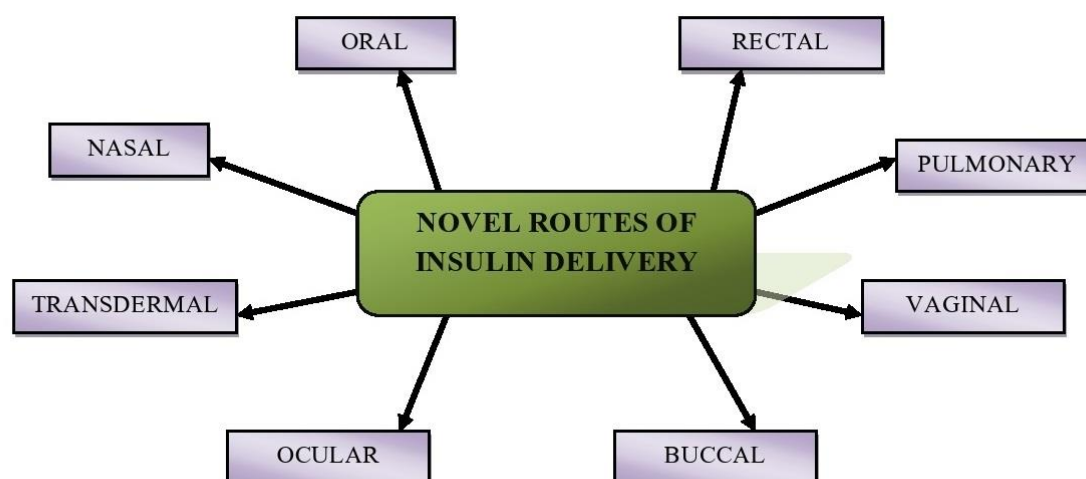


Figure: 3 various routes of insulin administration

5.2.1 Oral route

For chronic therapy, oral route is regarded as the most acceptable and convenient route of drug administration. Because of the knowledge explosion in biotechnology industry, extensive research is being conducted to achieve successful blood glucose control via oral delivery system. Furthermore, oral insulin is advantageous because it is delivered directly to liver, its primary site of action, via portal circulation, a mechanism very similar to endogenous insulin; subcutaneous insulin on the other hand, does not replicate the normal dynamics of endogenous insulin release resulting in failure to achieve long-term glycemic control in patients. (130) (131) (132)

5.2.1.1 Challenges to oral delivery of insulin

Peptides and proteins, in general, cannot be administered via oral route due to rapid enzymatic degradation in the stomach, inactivation and degradation by proteolytic enzymes in intestinal lumen and poor permeability across intestinal epithelium due to their high molecular weight and lack of lipophilicity. As a result, the oral bioavailability of most peptides and proteins is less than 1%. The goal here is to increase bioavailability between 30-50%. (130) (133)

- **Enzymatic barrier:** insulin degrades due to harsh environment of GIT. This is due to the fact that digestive processes are designed to breakdown the proteins and peptides without any discrimination. Insulin is thus degraded enzymatically by pepsin and pancreatic proteolytic enzymes such as trypsin and α -chymotrypsin. Moreover, some cytosolic enzymes such as insulin-degrading enzyme also contribute in degradation of insulin. (130) (132)
- **Intestinal transport of insulin:** another major impediment in absorption of hydrophilic macromolecules like insulin is their inability to diffuse across epithelial cells through lipid-bilayer cell membranes into bloodstream. Insulin delivery in the mid-jejunum, on the other hand, protects insulin from gastric and pancreatic enzymes, and release from the dosage form is aided by intestinal microflora. (130) (134) various other strategies are being studied to enhance absorption of insulin in intestine; some of these are successful in overcoming this barrier.
- **Dosage form stability:** because insulin is a sensitive polypeptide hormone, any conformational change in its structure would have an effect on its biological activity. (135) (136) there can be physical or chemical degradation during dosage form development. Physical degradation involves the modification of the native structure to a higher order structure, whereas chemical degradation results in the formation of a new product due to bond cleavage. (130) (132)

A number of different strategies have been explored for oral insulin delivery. Improved insulin absorption has been achieved with varying degrees of success by increasing its chemical stability, protecting it from the proteolytic enzymes, incorporating insulin into liposomes and increasing permeability of intestinal mucosa by using surfactants or emulsions. (137) the potential toxicity or local damage is an obvious disadvantage of using agents like permeation enhances. Insulin has also been encapsulated

within enteric capsules or microspheres. These can shield insulin from the harsh environment of GI tract. The major pitfalls of microsphere formulations are their variability and potentially harsh fabrication methods which can easily lead to denaturation of insulin. (136)

However some of the agents such as, GIPET 1, ORMD 0801 or CapsulinIR which contain either regular insulin or analogues have progressed to phase-2 clinical trials. Tregopil, an insulin analogue tablet, recently demonstrated rapid absorption (20 minutes) and runoff (90 minutes) potentially making it suitable for postprandial glucose control. Although a solution is not apparent in the near future, the oral route remains a promising non-invasive route that will most likely be developed significantly in coming years. (128) (138)

5.2.2 Nasal route

Because of the larger surface area of nasal epithelium and the presence of microvilli, as well as the fact that it inhibit first-pass metabolism, is not affected by gastric enzymes, is highly vascularised and has fewer side-effects, this route of administration for delivery of proteins and peptides has been studied as an alternative to the subcutaneous route. (123) (139) rapid mucociliary clearance of drug from site of deposition, which result in short time span available for absorption and low permeability of nasal membrane to peptides, are some of the disadvantages associated with this route of administration. (140) numerous enhancers have been tested for decades to improve the insulin absorption with minimum local toxicity. Bile salts (1-4% sodium glycocholate and deoxycholate), fusidic acid salt (8% 9-laureth), phospholipids (2% didecanoyl-phosphatidyl-choline) and cyclodextrins are among them. The kinetics profile of the insulin administered via nasal route has been studied in both healthy and type-1 diabetic patients. These studies revealed a rapid increase in insulin concentration with a peak at 10-20 minutes, as well as a rapid decrease in insulineaemia (In about 2 hours). (141) (142) however bioavailability is low at about 10%. (126)

5.2.2.1 Advantages and disadvantages of nasal route

Some of the advantages of intranasal delivery include rapid onset of action as compared to injection, large surface area of nasal mucosa, lower enzymatic activity than GI tract. Endothelial membrane is porous and relatively high permeability of nasal epithelial membrane. The possibility of obtaining pharmacokinetic properties that mimic insulin's pulsatile secretion opens doors to developing more effective insulin replacement therapy. But, nasal mucosa has low permeability. Rapid clearance of administered formulation due to mucociliary mechanism, moreover, transferase, reductase, esterase, monoxygenase and some proteolytic enzymes including exopeptidases such as mono and diaminopeptidases, endopeptidases such as serine and cystine, are all found in nasal cavity leading to possibility of enzymatic degradation of insulin. (123)

5.2.3 Pulmonary route

The respiratory tree has the largest surface area available for drug delivery, about 140 m². Unlike the columnar epithelium of GI tract and nasal cavity, the alveolar epithelium, which accounts for 95% of the absorptive surface, offers an appealing option for systemic drug and polypeptide hormone delivery. The epithelium is thin (0.1-0.2 μm), highly permeable and densely vascularised, with only a few mucociliary clearance mechanisms present. (137) in a recent study of diabetic patients, an insulin containing aerosol generated by raindrop nebulizer achieved approximately 80% deposition of inhaled insulin in the lungs. In another study, guinea pigs were given nebulizer poly (lactic-co-glycolic acid) (PLGA) nanospheres. This resulted in significant blood glucose reduction and hypoglycemia prolongation. (143) (144)

5.2.3.1 Absorption and distribution

Inhaled insulin is likely transported through the alveolar capillary barrier via a transcytosis mechanism. Insulin enters the systemic circulation 10 minutes after the inhalation and reaches its peak effect after about 60 minutes, which is comparable to insulin analogue, lispro and earlier than subcutaneously injected regular insulin, which reach its peak effect after 120-360 minutes after administration. Furthermore, because inhaled insulin has a shorter duration of action, than regular subcutaneous insulin, it may reduce the risk of hypoglycemia occurring 2-3 hours after meals or at night. Inhaled insulin bioavailability was found to be 10-20 % with good intra-individual variability. The dose to be administered can be adjusted by varying the amount of insulin powder in inhaler as well as number of breaths taken. (126) (145)

5.2.3.2 Efficacy

Clinical studies of inhaled insulin conducted in type-1 and type-2 diabetes patients have shown drop in glycated hemoglobin to 7.9 and 7.7% which was 8.5% at the beginning. Patients with type-1 diabetes had 5.5 mild to moderate hypoglycemic episodes per patient.month and 0.08 severe episodes per patient.month. The incident of mild to moderate hypoglycemia in patients with type-2 diabetes mellitus was 0.83 per patient.month, with no cases of severe hypoglycemia recorded. (126) (146) (147)

5.2.3.3 Formulations

Innovative inhaler systems can produce insulin particles of sufficient size: <6μm, for deep penetration into the lung which is required for transport across the pulmonary epithelium into the blood stream. (126) a wide variety of inhaler devices are currently in use.

- Inhale/Exubera inhaler: excepients primarily mannitol, in inhale therapeutic systems fine dry powder formulation stabilize insulin during spray drying and storage.
- AER_x iDMS inhaler: the AER_x iDMS pulmonary insulin delivery system combines single use liquid insulin strips with a breath activated, microprocessor-controlled device that is designed to minimize variability due to patient technique.
- The AeroDose inhaler: Aerogen developed the AeroDose inhaler, a breath-activated, "liquid-insulin delivery" device.
- Technosphere-insulin: The Pharmaceutical Discovery Corporation has developed the Technosphere-insulin, a dry powder formulation containing recombinant human insulin and a diketopiprazine-derivative enhancer. (137)

5.2.4 Transdermal route

In comparison to painful hypodermic injections, a transdermal delivery strategy that transports insulin across the skin barrier represents a minimally invasive and appealing method of insulin delivery. It also has several advantages over other administration methods. Insulin can avoid chemical and enzymatic degradation in GI tract when administered via transdermal route. (148) (149) (150) however, skin does offers an effective barrier, limiting the penetration of large, hydrophilic polypeptides such as insulin. This impermeability is caused due to the upper layer of skin, stratum-corneum because of its lipid-rich matrix. (141) (151)

5.2.4.1 Advantages

It avoids first-pass metabolism, GI tract degradation and have possibility of controlled release over time. Encourage patient compliance because a transdermal formulation is easy to apply and remove, making it more appealing alternative to subcutaneous insulin delivery. (123)

5.2.4.2 Disadvantages

As mentioned above, skin offers an efficient barrier for molecules like insulin. Also, there is possibility of enzymatic and other sorts of degradation, poor reproducibility of delivering a dose leading to potential toxicity. (123)

Various approaches have been investigated physically or chemically to improve the transport efficacy of the insulin molecule across the skin in order to overcome the skin barriers in transdermal insulin delivery. (148) the recent advancements in transdermal insulin delivery systems are shown in fig. 4.

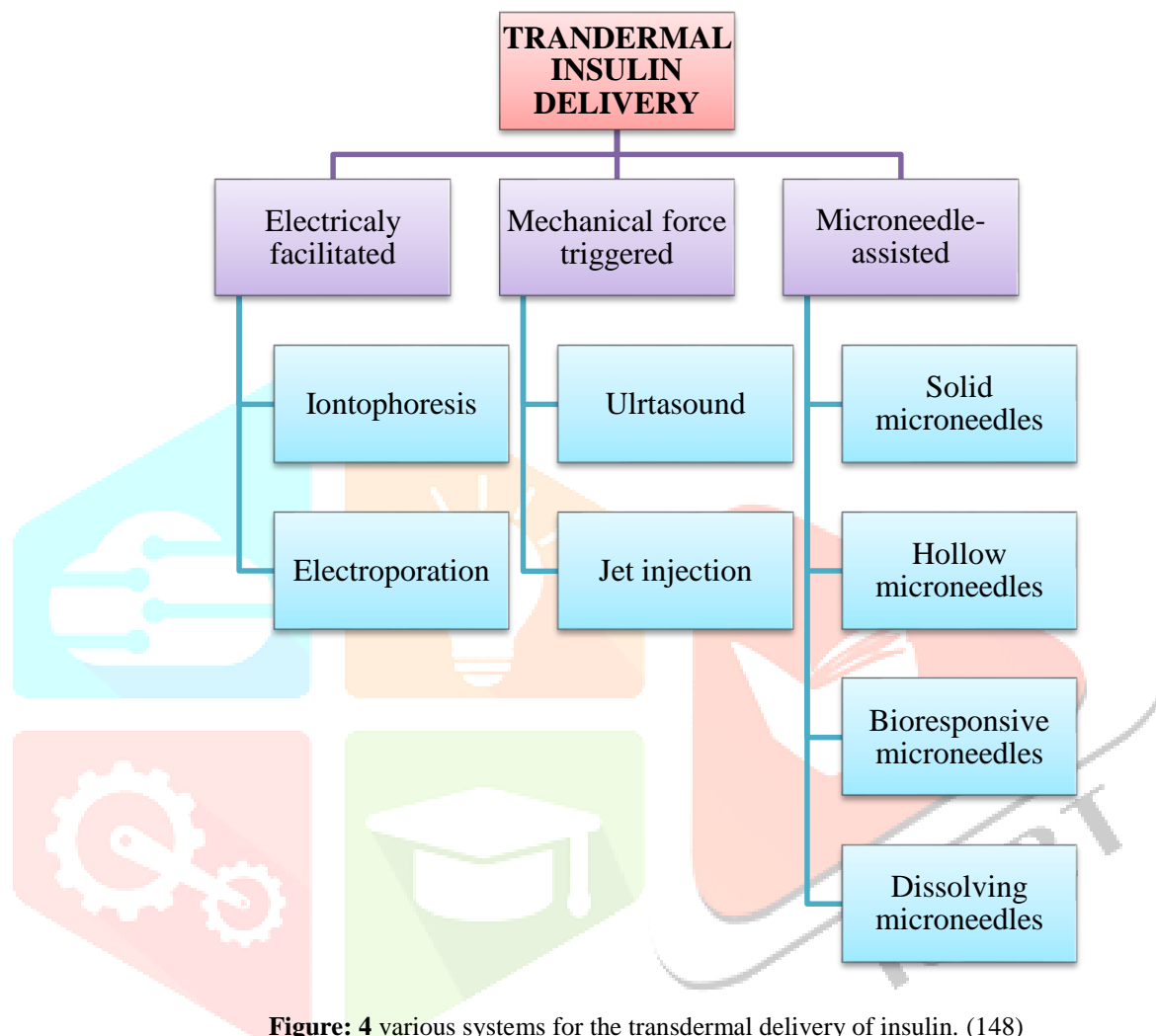


Figure: 4 various systems for the transdermal delivery of insulin. (148)

Chemical enhancers, external instruments and microneedle devices have shown a considerable potential in increasing insulin permeation by disrupting the skin barrier as compared to passive transport through the skin. Furthermore, transdermal strategies such as power jet, heat or megnetophoresis-assisted administration routes could be investigated for needleless delivery of insulin. (148) (152) (153) transdermal delivery of insulin is successful to a greater extent but some limitations like safety in long-term use, its reliability and efficacy of delivery are also there. More research needs to be done in this context.

5.2.5 Buccal route

The buccal tissue that lines the inner mucosal side of the cheeks is made up of a non-keratinized and stratified epithelium with a surface area of about 50 cm². The dense network of blood vessels beneath the basement membrane, as well as lack of tight junctions of buccal epithelium, facilitates the drug's journey. Direct jugular vein access to the systemic circulation allows for rapid onset while completely bypassing the first-past effect and avoiding extensive drug metabolism and degradation. (154) (155) (156) transcellular and paracellular pathways are two major mechanisms for transport of drug through buccal mucosa. Peptides that cross the buccal epithelium via paracellular pathway come across the extra-cellular enzymes such as aminopeptidases, resulting in insulin degradation. (123) insulin is delivered as an aerosol into the oral cavity, where it is absorbed through the inner surfaces and enters the systemic circulation. (140)

5.2.5.1 Advantages and disadvantages

Buccal delivery of insulin bypasses the first-pass metabolism leading to high bioavailability, ease of accessibility of this absorptive site, have low enzymatic activity. This route have high patient compliance because of painless administration, easy drug withdrawal and can be self administered. It also saves insulin from degrading environment of stomach.

Use of absorption enhancers often causes irritation of buccal mucosa. The bitter taste of absorption enhancers used in buccal compositions, such as bile-acid salts. As a result, the use of bile-acid containing formulations on a regular basis is hardly acceptable for long-term administration. Moreover, barrier properties of mucosa and small area available for drug absorption are some of the limitations. (123)

Only twice the buccally delivered insulin reached clinical trials, with neither test drug able to overcome translational barriers. In the case of GenereX Biotechnology's Oral-lyn™, insulin is delivered in micellar oral spray via the RapidMist™ system. The

clinical trial in India was halted due to lack of clinical efficacy. MSL-001 was mucoadhesive polymeric film that was non-covalently bound to glycan-coated gold nanoparticles for transbuccal delivery of recombinant human insulin (GNPs). Due to low insulin bioavailability, this joint venture between MonoSol Rx (PharmFilm®) and Midatech (GNPs) was dissolved. (154) (157)

While designing the buccal delivery system, all these constraints are taken into considerations. An ideal buccal systemic drug delivery system requires intimate contact with the buccal mucosa in order to maintain its position in mouth for desired period of time. Furthermore, the system or its components should facilitate insulin absorption through the mucosa while protecting it from environmental degradation. Thus, the permeability and local environment of the mucosa can be manipulated to facilitate insulin permeation with the proper formulation and dosage form design. (158)

5.2.6 Ocular route

The ocular route is another non-invasive route of insulin delivery in which insulin is delivered into the systemic circulation by installing eye-drops into the eyes. The conjunctival and, in particular, the nasal mucosa are the primary systemic absorption sites for drugs delivered via this pathway. Convenient administration of drug as eye drops, faster absorption, more economical than injections are some of the advantages of ocular route. Moreover, insulin is able to avoid GI tract environment as well as first-pass metabolism. (123) despite these benefits, the development of systemic delivery via the ophthalmic route is hampered by the lachrymal drainage system's dynamic. This system delivers tear fluid and any installed formulation from the pre-corneal region to the nasal cavity and mouth, where it is swallowed and ingested into the GI tract. This high elimination rate leads to a short duration of drug contact with its absorption sites (i.e. Conjunctival and nasal mucosa) and ultimately results in low bioavailability. (159) recently, an eye device made of acidified GelFoam® (an absorbable gelatin sponge) was studied, and findings indicates that insulin is absorbed efficiently in the system, at least in rabbits. (141) however, more efficient research and investigations has to be done for this route to be clinically useful.

5.2.7 Intrauterine and rectal route

Intrauterine is an effective route for delivery of drugs because of its large surface area, dense network of blood vessels and high elasticity due to presence of smooth fibers in the muscular coat. The main advantages of the intrauterine route are that insulin avoids first-pass metabolism, degrading environment of GI tract, large surface area and high permeability of vagina. Despite all these benefits, the vaginal route remains an underutilized route for systemic delivery due to gender specificity, local irritation, and cultural sensitivities etc. moreover cyclic changes in vagina cause variability in rate and extent of absorption of drug. Presence of cervical mucus and the amount of vaginal transudate can also alter the pH of vagina. (123) Attempts have been made to administer the lysophosphatidylcholine-containing insulin intra-vaginally to sheep as an aqueous solution and as a lyophilized powder with bioadhesive starch microspheres. Similar attempts were made in rats to place the insulin via intrauterine-delivery; thus insulin was discovered to be absorbed in a biologically active form in the uterus of rats. (143)

For several years, the rectal route of drug administration has been used as drugs are easily introduced and retained in the rectal cavity. When patients are prone to nausea, vomiting, convulsions, and in particular, disturbances of consciousness, the rectal administration maybe viable alternative to oral administration. On the one hand, because of extensive rectal vasculature, presence of lymphatic vessels in rectal region, rectal drug delivery is efficient. Patient acceptability, on the other hand, is much lower and the drug absorption maybe affected by defecation. (160) the absorption mechanism of the drug from rectum is same as that of the other parts of GI tract. The main absorption mechanism here is passive diffusion. Drug levels in the systemic circulation, on the other hand maybe greatly influenced by the anatomical differences in the hemorrhoidal venous drainage of the rectum. (161)but, the rectal route is independent of factors like enzymatic degradation, intestinal motility, gastric emptying time, or the presence of diet. Moreover, there is avoidance of first-pass metabolism. (143) since significant concentration of insulin is absorbed from the rectum and penetrate directly to the portal vein, insulin suppositories could regulate the postprandial glycemia in a more physiological manner than the conventional insulin therapy. (140) rectal formulations for insulin administration are made with use of absorption enhancers. The effect of salicylates on insulin rectal absorption in dogs was investigated, and sodium salicylate and 5-methoxysalicylate were found to increase the insulin rectal absorption. (162) although these routes are effective to some extent, but much lower patient compliance is a major drawback for their effective clinical use in diabetes treatment.

VI. CONCLUSION

Diabetes mellitus is a metabolic disorder that is caused mainly due to defects in insulin function or insulin secretion or both. It is one of the most prevalent disorders affecting around 400 million people globally. Its two major types are T1DM and T2DM. several factors can lead to diabetes such as genetic factors or family history, environmental factors, sedentary lifestyle, unhealthy diet; physical inactivity, etc. major treatment approaches include the use of drugs such as metformin, Sulfonylureas, SGLT-2 inhibitors, DPP-4 inhibitors, thiazolidinediones, etc. these drugs are used individually or as combination therapy. Moreover, cell-based treatments like the pancreas or pancreatic cell transplantations are being studied extensively. Whereas, insulin is a key factor in diabetes treatment. Insulin is widely used as a subcutaneous injection, but several limitations lead to inefficient blood glucose control, which is a major requirement of the treatment. Patient discomforts, infections, pain at the injection site are some of the boundaries of this route. Therefore several other routes were taken into consideration by the researchers for the fulfillment of the blood glucose control. These novel delivery routes include oral route, nasal route, and pulmonary route, transdermal route, and ocular route, buccal, intrauterine, and rectal route. These routes are much more efficient in terms of their delivery comfort, efficacy, bioavailability, protecting insulin from enzymatic degradation in the GI tract. Several formulations are prepared by the researchers that are currently being used. But certain gaps need to be filled for the effective clinical usage of some of these routes which, in the future can change the paradigm of the treatment of diabetes mellitus. In the future, there is scope for exploration of safety and efficacy studies, formulating insulin in affective dosage forms without any degradation or structural alterations, long-term use of certain preparations, and effective clinical use of the novel routes of insulin delivery in patients with diabetes.

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