Chapter 1
INTRODUCTION

1.1 Diabetes

Changes in lifestyle and dietary habits, particularly looking at and adapting to various cultures, have resulted in changes in health and disease status. According to WHO diabetes is described as an endocrine condition characterised by improper glucose, lipid, and protein metabolism in the body. Diabetes is referred to as "Madhu meha" which literally 'madhu' means 'honey' and 'meha' means passing through excretion. The word 'Diabetes' is derived from the Greek word 'siphon' and 'Mellitus' from the Latin 'sweet like honey' (Ritu, 2013). Diabetes mellitus is regarded as one of the most common chronic diseases globally. Diabetes mellitus is thought to cause varied organ failure like kidneys, eye, heart and alternative important organs (WHO, 1999). Illness needs attention because the deadly disease can only be controlled however has no cure. Despite the advanced technology within the medical fields for treatment of varied diseases, like pathophysiology, management and findings, the incidence of diabetes mellitus has been continuously increasing since times immemorial. Diabetes mellitus, a chronic medical condition, has earned a worldwide pandemic standing over the previous few decades moving uncountable folks. The signs and symptoms of DM aren't best-known in some cases and therefore referred to as 'silent killer' (Campbell, 2001). Historical texts reveal that since 200 BC, diabetes mellitus has been acknowledged as a disease in India and has been classified into two types: a hereditary problem and dietary disorder i.e. Type 1 and Type 2 diabetes were recognized as separate conditions for the first time by the India physicians Sushruta and Charaka in 400-500 BCE. The prevalence of metabolic illnesses such as diabetes mellitus has reached epidemic levels. The incidence of polygenic disease has been increasing with age of population and manner changes related to industry and urbanization from the previous few decades. There will be a substantial increase in each T1DM and T2DM worldwide that is anticipated to lift 439 million adults by 2030 (Shaw et al., 2011). Due to changing demographics, it is predicted that there will be 578 million cases of diabetes worldwide in 2030 and 700 million cases by 2045 (International diabetic federation,

2020). Republic of India because the largest developing country within the South Asian region is at Associate in treatment accumulated risk of developing polygenic disease compared to alternative. In step with the International Diabetes Federation (IDF) in Republic of India 2019 Associate in treatment assessable that 77 million folks were living with polygenic disease, with an estimated prevalence of 8.9% among adults. (Ranasinghe et al., 2021, IDF International Diabetes Federation 2019). As per the World Health Organization (WHO) report, the Indian continent has the foremost burden of heart-related diseases and therefore the largest patient base for polygenic disease within the world the number of diabetic patients in Republic of India, China, Russia, and Brazil is 31.7, 20.8, 4.6, and 4.6 million, severally. This additionally burdens the country as productivity loss (estimated to be 0.85% of the GDP) on account of mortality in 2004 and accumulated to 1.2% for Republic of India as per the present state of affairs for nutrition-related disorders. In step with the report, nearly half-hour and thirty fourth of the population in urban areas and rural areas, severally area units in pre-diabetic stage due to the high intake of calories and fewer micronutrient-rich foods. http://www.who.int/healthinfo/global_burden_disease/GobalHealthRisks_report_part2.pdf accessed on 18th January 2021. Diabetes is approximately six times more common in metropolitan areas than in rural areas. In the previous 20 years, the leading causes of diabetes mellitus have been decreased activity, increased weight and tension, dietary changes, malnutrition, alcohol intake, and viral infection. Female diabetes patients have a higher prevalence than male diabetic patients because hormones and inflammation behave differently in women. Diabetes disorders affect less educated people more than highly educated ones (Verma et al., 2018).

1.2 Anatomy and physiology of pancreas

One of the biggest digestive glands is the pancreas (Figure 1.1). Its principal role is exocrine, secreting enzymes involved in lipid, carbohydrate, and protein breakdown. It also has an endocrine role that is generated from clusters of cells distributed throughout the gland and is involved in glucose homeostasis as well as the control of upper gastrointestinal tract motility and function. The pancreas has a lobulated surface with a mild to firm hardness and is yellow in colour. The pancreas is divided into four sections: the head, neck, body, and tail. The pancreatic head generally has a prominent uncinate process. The pancreas in adults is 12 to 15 cm long and fashioned like a flattened 'tongue' of tissue lying in the retroperitoneum, thicker at the medial end (head) and thinner at the lateral end (tail). The head is placed within the curve of the duodenum, and the remaining gland travels transversely and

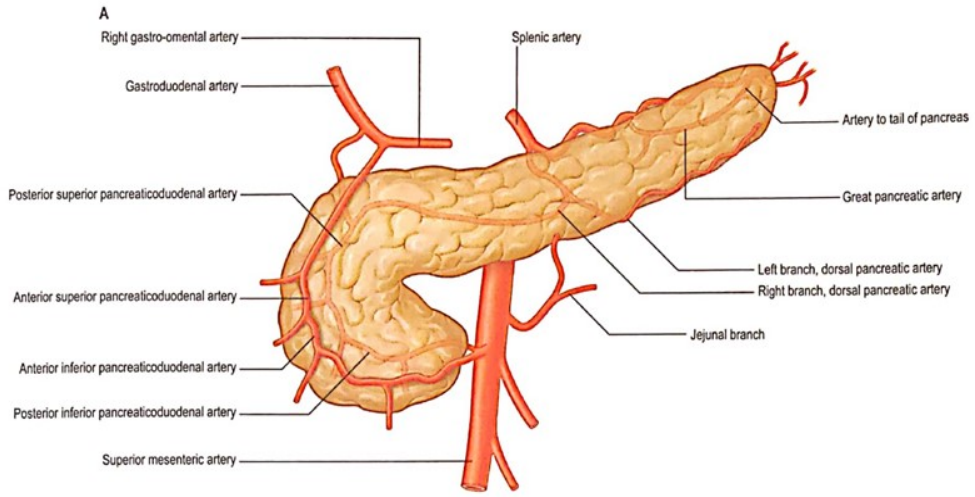

Figure 1.1: Anatomy of Pancreas (Adopted from Gray's Anatomy: the Anatomical Basis of Clinical Practice, 42nd Edition by Standring et al., 2020)

somewhat cranially through the retroperitoneum and posterior to the stomach to the splenic hilum. The inferior vena cava, hepatic portal vein/superior mesenteric vein, and splenic veins are 'draped' with it. It has an average capacity of 70-80 cm^3 in adults. The volume of the pancreas grows with age, peaking in the fourth decade. The front (ventral) side of the pancreas is covered by the parietal peritoneum, which has an inferior border that faces the root of the transverse mesocolon. The anterior (ventral) surface of the pancreas is covered by parietal peritoneum, which has an inferior border that abuts the root of the transverse mesocolon. The upper and lower borders of the pancreatic head are superior to the horizontal segment of the duodenum and continue the uncinate process. Posteriorly, the bile duct is partly immersed inside the head of the gland at the main duodenal papilla, just prior to its connection with the pancreatic duct. The lower side of the head of the pancreas is anterior to the inferior vena cava, which is located at the level of the right gonadal vein termination.

1.2.1 Uncinate process

The uncinate process is a hook-shaped extension of the infero-medial section of the pancreatic head.

1.2.2 Neck

The pancreatic neck is roughly 2 cm broad and joins the body's head. The posterior neck is grooved by the hepatic portal and superior mesenteric veins. In one-third of

people, the inferior mesenteric vein confluences with the superior mesenteric and splenic veins. The pancreatic body is the longest section of the gland, running from the neck to the tail and becoming increasingly thinner.

1.2.3 Anterior surface

The peritoneum covers the anterior surface, and the omental bursa divides the pancreatic anterior surface from the stomach.

1.2.4 Posterior surface

The posterior surface of the pancreas is devoid of peritoneum. The left crus of the diaphragm, the left suprarenal gland, the superior pole of the left kidney enclosed by the renal fascia, the left renal vein, and the fusion of Toldt prior to the abdominal aorta are where it is located. The splenic vein travels directly on this surface of the gland from left to right, indenting it to varying degrees ranging from a shallow groove to virtually a tunnel.

1.2.5 Superior border

The superiority of the pancreatic body is rounded to the right, while it gets narrower and sharper to the left. An omental eminence often projects from the right end of the superior border above the level of the stomach's lower curvature. The superior borders are situated anterior to the celiac trunk and its branches, as well as those of the typical hepatic and splenic arteries.

1.2.6 Inferior border

The artery known as the superior mesenteric passes posteriorly to the gland at the centre of the pancreatic neck's inferior border. In the lateral direction, it extends dorsally to the lower border, where it connects with the splenic vein or at the junction of the splenic and superior mesenteric veins.

1.2.7 Tail

The pancreatic tail is the gland's thinnest, most left-lateral component, and it is continuous with the body. In adults, it is 1.5 to 3.5 cm long and located between the splenorenal ligament and the splenic hilum. It either ends at the splenorenal ligament's base or continues into the splenic hilum. The splenic artery and its branches, along with the splenic vein and its limbs, are found posterior to the tail.

1.2.8 Pancreatic ducts

The pancreatic duct of Wirsung often travels through the gland slightly diagonally

from left to right, from a more inferior to a more superior point in the brain. The duct is created by the confluence of several lobular (secondary) ducts in the tail. It increases in size within the pancreatic body as more lobular ducts connect virtually at right angles to its long axis, generating a herringbone pattern. As it enters the gland's neck, the pancreatic duct flows inferiorly and posteriorly towards the bile duct, which drops through the pancreas's head. The two ducts join and enter the duodenum's descending wall obliquely. A few mucosal folds in the pancreatic duct's terminal portion prevent pancreatic juice reflux. The length of the common pancreaticobiliary channel varies and can range from 5-7 mm in most people.

The superior area of the anterior section of the pancreas head is drained by the auxiliary pancreatic duct (of Santorini). It is much smaller than the pancreatic duct and is formed within the head of the pancreas from several lobular ducts. It generally interacts with the pancreatic duct around the gland's neck or near its first inferior branch.

1.2.9 Pancreatic secretion

The pancreas, which runs parallel to the stomach, is a big complex gland with an internal structure similar to that of the salivary glands. The pancreatic acini release pancreatic digesting enzymes, whereas the small ductules and bigger ducts flowing from the acinar cells secrete enormous volumes of sodium bicarbonate solution. The combined enzyme-sodium bicarbonate product then travels through an extended pancreatic duct that usually connects to the hepatic duct immediately prior to elimination into the duodenum through the papilla of Vater, which is covered by the sphincter of Oddi.

Pancreatic juice is released most frequently in reaction to the presence of chyme in the upper sections of the small intestine, and the types of food in the diet impact the properties of pancreatic juice to some extent, insulin is also secreted by the pancreas, although not by the same pancreatic tissue that secretes intestinal pancreatic juice. Instead, islets of Langerhans, which are located in islet patches throughout the pancreas, generate insulin straight into the blood rather than the gut.

1.3 Types of diabetes mellitus

According to American Diabetes Association (2018), diabetes mellitus can be classified into the following general categories:

1.3.1 Insulin dependent diabetes mellitus (IDDM) or T1DM

Insulin dependent diabetes mellitus or T1DM is additionally observed as

autoimmune disorder within which Islets of Langerhans within the exocrine gland square measure destroyed and so fails to provide internal secretion leading to internal secretion dependency of the patient. T1D persons have the next risk of cardiopathy, stroke, nephropathy, high pressure, blindness, nerve injury, and gum diseases.

1.3.2 Non-insulin dependent diabetes mellitus (NIDDM) or T2DM

This is a specific type of metabolic illness that frequently includes obesity and insulin resistance. T2DM happens because of impaired hypoglycaemic agent secretion by the β-cells and endogenous aldohexose output. It was previously referred to as non-insulin-dependent diabetes mellitus or adult-onset diabetes. T2DM is by far the most prevalent type of diabetes, accounting for 85 to 95% of cases in industrialized countries and an even larger percentage in underdeveloped countries as stated by the International Diabetes Federation. This condition might take years or decades to manifest. It is generally preceded by pre diabetes, in which This refers to a condition where blood glucose levels are elevated beyond normal levels but haven't reached the threshold for a diagnosis of diabetes. People with prediabetes can frequently delay or avoid the progression to type 2 diabetes by decreasing weight via improved activity and nutrition as the Diabetes Prevention Program and other research projects have demonstrated. The causes of type 2 diabetes are complex, anxiety, stress, advanced age, obesity, sedentary lifestyle, inconsistent food, and so forth. Obesity has been linked to around 55% of type II diabetes, and lowering saturated fat consumption has been linked to a reduction in type II diabetes. T2DM typically seen in adults and previous aged.

1.3.3 Gestational diabetes (GD)

Diabetes that develops during pregnancy is known as gestational diabetes mellitus. This frequent issue refers to the first time a high blood glucose level is diagnosed during pregnancy. Gestational diabetes affects around 3-5% of pregnant women. If this can be left untreated, it will cause complications for both mother and baby.

1.3.4. Secondary diabetes

These type of diabetes is generally caused by:-

i. **Genetic defects of beta - cell function**:- This kind of diabetes was previously known as Maturity Onset Diabetes of Young (MODY). It has poor insulin secretion with little or no insulin deficiency.

ii. **Endocrinopathies:-** Growth hormone, cortisol, glucagons, and adrenaline are among hormones that can inhibit insulin activity. Diabetes can be caused by

diseases related to increased hormone production.

iii. **Exocrine pancreatic disorders:-** Diabetes is caused by any event that injures the pancreas in a diffuse manner, including pancreatitis, trauma, infection, pancreatic cancer, and pancreatectomy.

iv. **Drug or chemical-induced diabetes:-** Many medicines can affect insulin secretion, these drugs may not cause diabetes on their own, but they may trigger diabetes in those who already have insulin resistance.

v. **Other genetic Syndromes:-** Down syndrome, Diabetes insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness (DIDMOAD) and myotonic dystrophy may also cause diabetes.

1.4 Type 1 diabetes mellitus

1.4.1 Embryonic defect in β cell development

The immune system and T1DM were linked together for the first time in 1973, when HLA antigens were shown to be associated with insulin-dependent diabetes mellitus but not insulin-independent diabetes mellitus. Following that, other investigations revealed that HLA genes account for up to 50% of the inherited risk of T1DM. Seroconversion of islet autoantibodies to insulin, glutamate decarboxylase, insulinoma antigen 2, or zinc transporter 8 represents the first visible sign of autoimmunity, and their combined presence in serum remains the best predictor for both loss of immune tolerance and clinical manifestation of T1DM. However, it is still unknown how these antibodies affect the death of beta cells. (Roep et al., 2021).

Beta cell dysfunction or a lack of sufficient beta cell mass can cause neonatal diabetes that requires lifelong insulin therapy to survive. Permanent neonatal diabetes has been linked to mutations in a small number of genes, including insulin promoter factor (Ipf-1/Pdx-1), forkhead box P3 (FoxP3), ATP-sensitive potassium channel Kir6.2 (Kcnj11) and glucokinase (Gck). These genes encode key components that control β cell development and function. A novel type of chronic neonatal diabetes related to the human Wolcott-Rallison syndrome has recently been found as a loss of expression of PERK, eIF2a kinase (EIF2AK3). In PERK-deficient people, serum insulin insufficiency and decreased beta cell mass are related to an increase in neonatal diabetes. The reason for inadequate β cell mass was unknown; it might be related to a lack of PERK activity in β cells and/or other cells and organs that support β cell development and survival. For example, insulin-like growth factor 1 (IGF-1) is known to promote b cell proliferation and survival (Zhang et al., 2006).

1.4.2 Biochemical changes in type 1 diabetes mellitus

i. Thiamine, a member of the vitamin B family, is required from exogenous sources for maintaining different kinds of functions in the body because it cannot be synthesized by the human body for normal functioning of the heart, muscles, and nerves. To treat certain metabolic disorders, the human body needs thiamine. Diabetic individuals have been shown to have mild thiamine insufficiency or reduced plasma thiamine concentrations (Daghri et al., 2015).

ii. When glucose is unavailable to cells, fatty acids become the primary fuel, resulting in another alteration in diabetes: excessive but incomplete β oxidation in the liver. The TCA cycle cannot completely oxidize the acetyl CoA produced by β oxidation because the high ($NADH/NAD^{+}$) ratio created by β oxidation prevents the formation of acetyl CoA in the cycle, resulting in the overproduction of ketone bodies. β hydroxybutyrate and acetoacetates, which cannot be utilized by extrahepatic tissues as quickly as they are produced in the liver. Diabetes patients blood also includes a trace quantity of acetone, which arises from endogenous decarboxylase autoacetate.

iii. Epinephrine predominantly affects muscle, adipose tissue, and liver tissue. It stimulates the liver glycogen to become blood glucose fuel for anaerobic molecular activity by activating glycogen phosphorylase and inactivating glycogen synthase via CAMP-dependent phosphorylation of the enzymes. Epinephrine also stimulates glycolytic ATP production by promoting the anaerobic breakdown of muscle glycogen via lactic acid fermentation. A study has been conducted to determine the responses to epinephrine between healthy subjects and T1DM patients. Glucagon responses to epinephrine were absent in T1DM patients and significantly reduced when compared to healthy subjects, implying that there are physiological differences in epinephrine action at the liver, muscles, adipose tissues, pancreas, and cardiovascular system between T1DM patients and healthy subjects. (Guy et al., 2004).

iv. Most of the fatty acids synthesized or injected by organisms have one of two phases, depending on the organism's needs. The incorporation of triacylglycerols into the body for the storage of metabolic energy or incorporation into the phospholipid components of the membrane in humans maintains the amount of body fat over long periods, though there will be minor shortened changes as calorie intake fluxes and the biosynthesis and degradation of triacylglycerols are regulated to meet the metabolic requirements of the moment. The activity of various

hormones regulates the rate of triacylglycerol production. Insulin, for example, stimulates carbohydrate conversion to triacylglycerols. People with severe diabetes are unable to utilize glucose correctly and also fail to synthesize fatty acids from carbohydrates or amino acids due to a lack of insulin secretion or action.

v. Acetyl CoA produced during fatty acid oxidation in humans and most other animals can either join the citric acid cycle or be converted to ketone bodies, acetone, acetoacetate, and β hydroxybutyrate for export to either tissue. Untreated or uncontrolled diabetes causes the liver to overproduce ketone bodies, which has various negative health consequences, when insulin levels are insufficient in untreated diabetes, additional hepatic tissues cannot adequately take up glucose from the blood, either as fuel or as fat. Under these conditions, malonyl coenzyme levels decrease, carnitine acyl transferase 1 inhibition is shown, and fatty acids enter mitochondria to be reduced to acetyl CoA. However, because cycle intermediates have been taken off for use as substrates in gluconeogenesis, this acetyl CoA cannot transit through the citric acid cycle. The subsequent buildup of acetyl CoA promotes the release of ketone bodies into the blood, which exceeds the ability of extrahepatic organs to oxidize them.

vi. If fat deposited in adipose tissues is to be utilized as energy in other parts of the body, it must first be transferred from the adipose tissue to the other tissue in the form of a few fatty acids. This transport is accomplished by hydrolyzing triglycerides back into fatty acids and glycerols. At least two types of stimuli play key roles in inducing this hydrolysis. When the amount of glucose available to the fat cell is insufficient, one of the glucose break-down products, glycerol phosphate, is insufficient because this substance is required to maintain the glycerol portion of triglycerides, resulting in triglyceride hydrolysis. Second, many hormones from the endocrine glands can activate a hormone-sensitive cellular lipase, which promotes the fast breakdown of triglycerides. In the presence of live fat cells, fatty acid ionizes quickly in the plasma, and the ionic protein instantly interacts with albumin molecules of plasma proteins. To distinguish them from other fatty acids in the plasma that exist as esters of glycerols, cholesterol, and other compounds, free fatty acids or non-esterified fatty acids are used. Conditions that enhanced the rate of fat use for cellular energy also raised the concentration of free fatty acids in the blood. The concentration can occasionally increase fivefold to eightfold as a result of malnutrition or diabetes mellitus.

vii. The capacity of body cells to store glucose as glycogen is usually limited, with

only a little amount of glycogen stored across the liver, skeletal muscles, and all other tissues combined. Conversely, adipose tissue can store many kilograms of fat, allowing fat production to serve as a mechanism for storing energy reserves for future use. When there is insufficient insulin, as seen in individuals with severe cases of DM, fat synthesis is significantly impaired or may not occur at all for the following reasons:

a) In the absence of insulin, glucose cannot effectively enter fat and liver cells, leading to a limited supply of acetyl CoA and NADPH required for fat synthesis.

b) The lack of glucose in fat cells reduces the supply of β-glycerol phosphate, hindering the synthesis of triglycerides in tissues.

1.4.3 Physical structure in type 1 diabetes mellitus

Growth retardation, pubertal delay due to poor glycemic control, and related multiple disorders or illnesses are common in type 1 diabetes patients. Gender, genetic endowment, age at diagnosis, diabetes duration, puberty, metabolic management, growth hormone status, insulin-like growth factor, and IGF-binding proteins are all variables that influence growth. Insulin modulates the expression of hepatic growth hormone receptors, influences IGFs and IGFBPs binding proteins and synthesis via altering growth hormone post-receptor events, and boosts insulin IGF-I bioactivity considerably. T1DM is characterized by low portal insulin, hypersecretion, low circulating IGF-I, and high circulating insulin growth factor-binding protein (Virmani A 2015).

1.4.4 Mechanism of type 1 diabetes mellitus

T1DM develops in a person as a result of the adaptive immune system destroying insulin-producing cells in the pancreas, known as cells. Overexpression of human leukocyte antigens, or HLA class molecules DR4, DQ8, and DQ2, and susceptibility are found to be increased in approximately 90% of T1DM patients, and one or more environmental factors cause beta cell components to be recognized as autoantigens, which the immune system mistakenly detects as foreign, resulting in an autoimmune response. Some autoantigens have been found, including insulin B chain peptide and beta cell secretory granules containing glutamic acid decarboxylase 65, protein phosphatase-like IA-2 (islets antigen 2), and transmembrane Zn transporter. The presence of any of these autoantibodies increases the chance of developing T1DM. These autoantigens are presented to

diabetogenic autoreactive T lymphocytes via HLA molecules and major histocompatibility complexes (MHC) I and II on antigen presentation cells (APCs). Autoantibody-producing CD4 T cells stimulate APCs, including B cells, which produce high-affinity autoantibodies against beta cells. Autoreactive CD4 T cells aid diabetogenic CD8+ T cells in cytolytic activity and assault beta cells via the secretion of cytokines such as tumour necrosis factor TNF- and IFN-, Fas cells, and perforin/granzyme. This cytokine also activates macrophages and other innate immune cells, causing beta cells to be further damaged. (Giwa et al., 2020).

1.4.5 Psychological features of T1DM (American Diabetes Association)

Diabetes distress, depression, anxiety and disordered eating, nervousness, guilty, morning sadness, suicide thoughts.

1.5 Type 2 diabetes mellitus

1.5.1 Pathology of T2DM

Type 2 diabetes is characterized by a more intricate pathology compared to type 1 diabetes. It involves both insulin resistance in the liver and muscles and impaired β-cell function, leading to insulin deficiencies.

i. Natural history:- prevalence increases with age, affecting around 10% of those over the age of 65, with half of these people being aware that they have the disease. The increased frequency was due to impaired glucose-induced insulin secretion and resistance to insulin-mediated glucose.

ii. Glycosuria:- As the renal threshold for glucose grows with age, glycosuria may not manifest until the glucose concentration reaches a significantly elevated level.

iii. Pancreatic Tumor:- Diabetes can develop at an elderly age, resulting in weight reduction and appetite loss.

1.6 Complication of diabetes mellitus

1.6.1 Diabetic retinopathy

Diabetes retinopathy has become one of the most common and dangerous disorders that diabetes patients used to suffer from, leading to blindness in individuals aged 30-65 in industrialized nations. All diabetes patients must have regular examinations with their pupils thoroughly diluted.

1.6.2 Pathogenesis

Hyperglycemia increases retinal blood flow and metabolism, as well as having a

direct influence on retinal endothelial cells and pericytes loss and vascular autoregulation. Uncontrolled blood flow often directs capillaries and stimulates the synthesis of vasoactive chemicals and endothelial cell proliferation, causing capillaries to break down. This factor causes retinal damage, stimulates the production of growth factors such as vascular endothelial growth factors (VEGF), and promotes endothelial cell proliferation, resulting in the formation of new blood vessels and increased vascular permeability, which causes retinal leakage excitation.

1.6.3 Clinical features of diabetic retinopathy

Microaneurysms (inner arteries). They appear as small, discrete, round, dark red patches that are close to yet appear to be distinct from the retinal vessels. They appear to be hemorrhages; however, pictures of injected retinal preparations revealed that they are infected with minute aneurysms coming from the venous end of the capillary near capillary-closer locations.

1.6.4 Hemorrhages

This most important feature occurs in the shape's deeper layer and is referred to as blood hemorrhages. The smaller ones may be difficult to distinguish from microaneurysms. If the patient has high blood pressure, a fling-shaped hemorrhage may form in the nerve fibre layer.

1.6.5 Exudates

These can range in size from tiny spores to substantial confluence pairs and are frequent in diabetic retinopathy. They are especially prevalent in the macular region. Exudates form as a result of plasma leaking from defective retinal capillaries and overlap regions of neuronal degeneration.

1.6.6 Cotton, Wall spots

These are comparable to hypertensions and occur more frequently in 5-disc diameters. They are artery occlusions that produce retinal ischemia and are thus a characteristic of proliferative diabetic retinopathy, and they typically contribute to rapidly growing retinopathy or a link with uncontrolled hypertension.

1.6.7 Intra retinal micro vascular abnormalities

Intra-retinal microvascular anomalies are diluted torso capillaries that reflect the surviving patent capillaries in a region where the majority have been occulted and are a marker of severe pre-proliferative retinopathy.

1.6.8 Neovascularization

This can occur as a result of the venous circulation responding to an ischemic retina, either in the optic disc or in the retina. The initial manifestation of neovascularization is the production of thin tufts of fragile vessels on the surface of the retina, although they are incomplete and prone to inhibition, resulting in the formation of hemorrhage, which may be pre-retinal or into the vitreous. This new vascular system's serous product connecting is accountable for the stimulation of the connective tissue response, which is known as glycolysis. This first shows as white clouds within the network of new arteries, and the surrounding retina is coated by dense white sheets. Although bleeding is less prevalent at this stage, retinal detachment can occur because of the adhesion constriction between the vesicles and the retina.

1.6.9 Venous changes

This involves vascular dilation, beading (calibration change in sausage), and increased density. These latter modifications show white distinct capillary no perfusion and are characteristics of advanced preproliferative retinopathy.

1.6.10 Rubeosis

The most severe manifestation of retinopathy can involve the development of new blood vessels on the internal eye surface. Secondary glaucoma may occur when these vessels obstruct the drainage angle of the eye, leading to impaired outflow of aqueous fluid.

1.7 Prevention of Diabetes

1.7.1 Glycaemic and blood pressure control

Good glycemic control, particularly in the early stages of diabetes, minimizes the chance of developing retinopathy. Early diagnosis followed by effective treatment is utmost important. In many cases it has been seen that the diagnosis of retinopathy is confirmed only when a patient visits the eye specialist for some high trouble or for checkup. Hyperglycaemia increases retinal hypoperfusion, and a rapid decrease in blood glucose levels may cause early retinopathy by generating relative ischemia. Gradual enhancement in glycemic control is therefore recommended. The rate of retinopathy progression is still much lower in aggressively treated individuals. Lowering blood pressure has been shown to be beneficial for hypertensive individuals. Elevated plasma cholesterol levels are linked to diabetic retinopathy.

1.7.2 Screening

Regular retinal screening is crucial for diabetic individuals, but it is more vital for those with risk factors. Diabetes with an early start and a long duration, hypertension, poor glycemic control, pregnancy, use of oral contraceptives, smoking, alcoholism, and other signs of microangiopathy, such as neuropathy and proteinuria, fall into this category. Train people to conduct screening in a structured and audited program. They choose screening photographic methods with reference to ophthalmology inspection by slit lame or microscopy if required. The problem is that many diabetics do not attend tests and are not closely monitored.

1.8 Diabetic nephropathy

i. Diabetes is a risk factor for developing diabetic nephropathy.

ii. Inadequate blood glucose management

iii. Diabetes for an extended period of time

iv. Presence of other microvascular complication

v. Ethnicity (Asian Pima Indians)

vi. Innate hypertension

vii. Ancestry of diabetic Nephropathy

Diabetic nephropathy is a leading cause of renal failure in developed countries. Management of diabetic nephropathy, in conjunction with either microvascular or macrovascular complications, has shown to be difficult and lethal in long-term episodes. After 20 years, around 30% of diabetic patients developed diabetic nephropathy, although the risk declined to less than 1% per year after that, and the danger did not apply to all patients from the start. The thickening of the glomerular basement membrane and the formation of metric material in the mesangium are the first signs of diabetic nephropathy. Following that, modular deposits appear and glomerular sclerosis develops.

1.8.1 Screening of microalbuminuria

i. Nephropathy in type I and type II diabetes was discovered, as
was a predictor of macrovascular disease in type II diabetes.

ii. Elevated blood pressure, inadequate glycemic control, and smoking all pose as risk factors.

iii. Urine albuminuria may be estimated using random urine samples (3-30 mg/mM)

(27-270g/mg). Male values larger than 2.5, female values greater than 3.5.

iv. If feasible, validate with an albumin excretion rate of 20-200 mg/min (30-300 mg/24 hours), needed length of urine collection (overnight or 24 hours).

v. Patients with type I diabetes are evaluated every year, beginning five years after their diagnosis.

vi. Patients diagnosed with type II diabetes should undergo annual evaluations.

1.9 Diabetic neuropathy

i. Both myelinated and unmyelinated fibres experience axonal degeneration.

ii. Axon shrinking in the early stages

iii. Axonal fragmentation occurs later.

iv. Schwannoma vassal lamina thickening.

v. Demyelination is patchy and segmental.

vi. Basement membrane thickening and microthrombi formation in intraneural capillaries.

1.9.1 Classification of diabetic neuropathy

i. Somatic Polyneuropathy:- Symmetrical, mostly sensory and distal, Asymmetry, mostly motor and proximal, with amyotrophy.

ii. Mononeuropathy

iii. Glycerol (autonomy)

iv. Cardiovascular

v. Gastrointestinal

vi. Genitourinary

vii. Sudomotor

viii. Vasomotor

ix. Pupillary

a) Symmetrical sensory polyneuropathy:- Vibrating sensor are diminished distally along with lose tandem reflection in the lower limbs. Sensory abnormalities are mainly found in clinical presentation. In severe cases, paresthesia (high pain) in the feet, discomfort in the lower limbs discovered in the front part of the leg,

burning sensation in the soles and feet, an unnatural gate usually coupled with feet numbness, weakness in the muscle occurred. Toes may clot due to interosseous muscular atrophy.

b) *Asymmetrical motor diabetic neuropathy:- Substantial wasting of the lower* limb's proximal muscles is frequently accompanied by substantial discomfort, mainly in the foot in the anterior portion of the leg, as well as hyperaesthesia and paresthesia. Significant weight loss may occur, and the patient may seem seriously ill. Tendon reflexes on the afflicted side may be missing.

c) *Mononeuropathy:*- A single peripheral or clinical nerve can be impaired by either motor or sensory function. There are 31 pairs of clinical nerves- C1- C7 - 8 cervical nerves. T1-T12-Thoracicnerve, L1- L5 - 5 lumbar nerve pairs, S1- S5 - 5 cervical nerves and one coccygeal nerve. Mononeuropathy is a severe and rapidly developing disease that gradually recovers.

d) Autonomic neuropathy

e) Erectile dysfunction: - Affects 30% of diabetic males are mainly affected by erectile failure.

f) Neuropathy and vascular reasons are prominent, but psychological problems such as melancholy, anxiety, and decreased libido may also play a role.

1.9.2 Clinical features of diabetic neuropathy

i. Cardiovascular:- Hypertension caused by posture, tachycardia during rest, and a fixed heart rate.

ii. Gastrointestinal:- Dyspepsia caused by esophageal atoms, abdominal fullness, vomiting, unstable glycemic state caused by delayed stomach emptying (gastroparesis), nocturnal dysuria (facial in continuous), and constipation caused by colon atomic.

iii. Possible issues include sexual dysfunction and retrograde ejaculation.

iv. Sweating is caused by sudomotor-gustatory stimulation.

v. Nocturnal sweats without Hypoglycemia.

vi. Anhidrosis

vii. Vasomotor - Cold feet caused by decreased skin vascular responses.

viii.Pupillary- pupil size reduction.

ix. Resilience to Mydriatics- Medicine made of the pupil eye dilute.

x. Delayed or absent reflex to light.

1.9.3 Diabetic foot ulcer

1.9.3.1. Clinical features:- Symptoms

i. Neuropathy- Paraesthesia, Pain, Numbness.

ii. Ischemia- Claudication, Rest pain.

1.9.3.2 Structural damages

i. Neuropathy- Osteomyelitis, infection, and ulcer.

ii. Digital gangrene- Charcot joint

iii. Claudication- Muscle pain due to lack of oxygen.

iv. Charcot joint- Is characterized by bones and joint fragmentation of foot and ankle.

v. Ischemia- Ulcers, sepsis, gangrene.

1.9.3.3 Management:- Aims of dietary management: -

i. Good nutritional management decreases hyperglycemia and prevents hypoglycemia.

ii. Aid in weight control.

iii. Reduced the likelihood of macro and microvascular complications.

iv. Ensured enough nutritional intake.

v. Prevent autogenic diets or ones that exacerbate complications, such as high protein consumption in nephropathy.

1.10 Complication of diet

1.10.1 Carbohydrates

People with diabetes, particularly type I, are asked to maintain a consistent carbohydrate intake throughout the day. The progress of modern insulin regimens, particularly those using insulin analogues or continuous subcutaneous insulin infusions, has been observed and has resulted in some adaptability in meal scheduling as well as carbohydrate content. Using a specialized approach known as DAFNE dosage adjustment for normal eating, the quantity of carbohydrate in a meal can be adjusted using a given amount of short-acting insulin. To maintain

such dietary habits, mainly carbohydrates, the proper education of diabetic patients is highly essential. It is critical for people with type II diabetes to avoid refined sugars and limit their overall consumption.

1.10.2 Glycemic index

The glycemic index of carbohydrate-containing foods contributes significantly to the change in blood glucose after two hours of injection of a specific food compared to the reaction to a reference food having a comparable amount of carbohydrate. The effect of different meals on postprandial glycemic control can be rated.

i. *Fats:*- Total dietary fats should be limited to less than 355 of total calorie intake, with 10% as saturated fat and 10%–20% as monounsaturated fat from oil and spreads derived from olive, grapeseed, or groundnut oil. Because they improve the plasma lipid profile, monounsaturated fats are advocated as the primary source of dietary fat. Polyunsaturated fat should not exceed 10% of total fat consumption (Table 1.1). This kind of fat decreases total and LDL cholesterol as well. Omega-3 fatty acids, found mostly in oily fish such as salmon and mackerel, have been demonstrated to aid in the secondary prevention of cardiovascular disease.

ii. *Weight management:*- Weight management is critical for a patient with type II diabetes because a large proportion of those with the disease are overweight or obese, and several diabetes medications or insulin promote increased body weight. Obesity, specifically abdominal obesity characterized by a bigger waist, has been linked to insulin resistance and an increased chance of cardiovascular disease. Weight loss can be accomplished by reducing energy intake while increasing energy expenditure through physical exercise. An extremely low-calorie diet of less than 800 kilocalories per day may generate good results, but it is difficult to sustain and

Table 1.1: Recommend composition of diet for people with diabetes.

Components	Recommendation
Carbohydrate	45-60%
Sucrose	up to 10%
Fats (total)	>35%
N-6 polyunsaturated	>10%
N-3 polyunsaturated	Eat oily fish once or twice
Mono saturated	10-20%
Saturated	>10%
Protein	10-15% (don’t exist 1 g/kg/BW)

may result in the behavioural changes needed for long-term weight control as well as nutritional shortfalls. In addition to calorie restriction, overweight adults should be encouraged to engage in regular exercise for 30 minutes per day, such as walking, swimming, or cycling, since this may improve insulin resistance, lipid profile, and blood pressure.

iii. *Alcohol:-* Moderate alcohol consumption is acceptable if there is no medical concern that necessitates abstinence. Alcohol inhibits gluconeogenesis and can either induce or protect against hypoglycemia, especially in people taking insulin or sulfonylurea.

iv. *Salts:-* The sodium intake should not exist 6 grams daily. The person suffering from diabetes along with hypertension should be restricted > 3 gram daily.

v. Diabetic foods and sweeteners:- Type II diabetes patients benefit from calorie deficit diet. Most of the food prone to cause diabetes contain sorbitol with high calories, and may cause gastrointestinal side effects; thus, they are not recommended as part of a diabetic diet. Most diabetic meals contain sorbitol, are high in calories, and may cause adverse effects related to gastrointestinal tract.

vi. *Normal glucose and fat metabolism:-* By homeostatic mechanism the blood glucose level is tightly regulated. There is also a equilibrium among the circulatory entry of glucose from the lower intestinal absorption after meals, peripheral uptake of glucose and particularly skeletal muscles. The brain requires a constant supply of glucose since it is a critical physiological component, and if there is any deficiency, oxidation of free fatty acids will not occur because of glucose dependency of the as its primary source of metabolic energy. When intestine absorption decreases between meals, counter-regulatory hormones such as glycogen and adrenaline boost glucose production from the liver. The liver generates glucose by gluconeogenesis and destroys glycogen. Glycerol and amino acids are the primary substrates for gluconeogenesis. The insulin level in the blood rises after meals. Insulin is an anaerobic hormone that controls glucose, protein, and fat metabolism. Insulin is produced by pancreatic cells and released into the portal circulation, where it is raised in response to an increase in blood glucose levels.

1.11 Insulin

1.11.1 History of insulin

Banting and Best discovered insulin in 1921 who explained the hypoglycemia. of a pancreas extract that was made after the exocrine portion of the organ degenerated

due to the ligation of the pancreatic GLUT. According to Sanger, insulin is a polypeptide with 51 amino acids and a molecular weight of 6,000. The A-chain has 21 amino acids, whereas the B-chain contains 31. Insulin is produced in islet cells as a single-chain peptide termed preproinsulin, from which 24 amino acids are obtained and from which proinsulin is initially extracted. Proteolysis in the Golgi apparatus removes the connecting, or C peptide. Insulin and C-peptide are both stored in granules in the cell. Along with insulin, the C peptide is released into the circulation.

1.11.2 Insulin preparation

In the United States, most insulin is formulated as U-100 (100 units/mL), short-acting insulin is formulated as U-200 (200 U/ml, lispro), and acting insulin is formulated as U-300 (300 units/mL, glargine) to limit injection volumes for patients with high insulin requirements. In individuals with extreme insulin resistance, regular insulin manufactured as U-500 (500 units/mL) is occasionally given. Distinct pharmacokinetics have been developed for human insulin (regular and neutral protamine; Hagedorn (NPH) insulin contains the native insulin amino acid sequence) or to modify insulin absorption and therefore insulin activity. Insulin is divided into two types: short-acting insulin and long-acting insulin. Insulin lispro is a short-acting insulin formulation that uses rDNA technology to reverse the insulin analogue across amino acids 28 and 29 on the insulin B chain. Insulin analogues created through genetic engineering that resemble lispro are insulin aspart and insulin glulisine. These insulin mimics have complete physiologic activity but a lower propensity for self-aggregation, leading in faster absorption, initiation of effect, and duration of action. The decrease in plasma following a meal is linked to the decay of insulin action, so a shorter duration of activity seems to be associated with fewer episodes of hypoglycemia. In many individuals, insulin aspart, lispro, or glulisine is made instead of normal insulin for postprandial coverage. Human insulin glargine is distinct from hormonal insulin in that two arginines are added to the C terminal of the B chains and asparagine is substituted with glycine at amino acid 21, resulting in the formation of microparticles in subcutaneous tissue at the physiological pH level. In comparison to NPH insulin, the beginning of insulin glargine action is delayed and less strong. A reduced prevalence of hypoglycemia, particularly at night. Long insulin mutations (NPH insulin, insulin glargine, insulin detemir, or insulin short-acting insulin attempt to minute physiology insulin released with meals) meet basal insulin needs.

1.11.3 Insulin regimes

The peak and duration of insulin action vary considerably among patients. Long-acting insulins such as NPH, glargine, and detemir serve as basal insulin, while regular insulins function as prandial insulin. Short-acting insulin analogs should be administered prior to meal (10 minutes), while regular insulin should be injected 30-45 minutes beforehand. However, the current insulin regimen has a flaw: injected insulin reaches the systemic circulation immediately, whereas endogenous insulin is released into the portal venous system. Consequently, exogenous insulin treatment exposes the liver to physiological insulin levels. None of the current insulin regimens replicate the ideal pancreatic islet insulin secretion pattern. Nevertheless, most physiological regimens are employed until excessive insulin doses, increased reliance on short-acting insulin, and more frequent self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) become necessary. Individuals with T1DM typically require 0.3-0.7 units/kg) of insulin each day, split into numerous doses of around 50%.

1.11.4 Synthesis and storage

Biochemical research has provided information on the synthesis, storage, and release of insulin by DF Stainer and his colleagues. They incubated human pancreatic tumors or pancreatic tumor islets, which have the potential to produce an excessive quantity of insulin, with radioactive leucine and phenylalanine. The pancreatic tumor creates two radioactive protein products that can bind to pure insulin-specific antibodies. One was to be established as being insulin itself, but the other, which clearly resembled insulin since it reacted with anti-insulin antibody was subsequently larger in molecular weight than insulin, was treated with trypsin and carboxypeptidase to cause cleavage of a number of peptide bonds and the formation of a compound that was proved to be identical with native insulin. Further chemical and enzymatic research revealed that the big insulin-like molecule formed by the pancreas, now known as proinsulin, is made up of a single polypeptide chain with between 81 and 86 residues, depending on the species of origin. It contains both A and B insulin. The A chain is the carboxyl and the B chain is the amino ends of the proinsulin molecule. The C chain connects the A and B chains. Two basic amino acid pairs divide the A and B chains from the C chain. The proinsulin molecule has three disulfide cross connections in the same locations as native insulin in its A and B segments. The amino acid sequence of the C chain of different species of proinsulin exhibits several replacements; its mutation rate is many times larger than

that of the A and B chains. The biosynthetic precursor of insulin is proinsulin, which has just a modest degree of insulin-like action. Each conversion to insulin appears to be completed by the action of peptide in the islets tissues. Proinsulin, which is the precursor to insulin, is first produced on the ribosomes and then transported to the golgi apparatus via the endoplasmic reticulum. The concentration of man's blood and tissues is so low that normal chemical methods of bioassay procedures are insufficient for investigations of secretion and use. The average human pancreas contains around 10 mg of insulin, but only 1 to 2 mg is released into the blood. The pancreas releases insulin in response to blood glucose levels and other variables. When blood glucose levels rise considerably over the typical range of roughly 80-90 mg/100 ml after a meal, the contents of secretion vesicles adjacent to the plasma membrane of β cells are released into the blood. After a meal, insulin concentrations return to normal within an hour or two. An insulin molecule in the blood has a half-life of roughly 3–4 minutes. As a result, pancreatic insulin production is extremely sensitive to variations in blood glucose levels. Increased amounts of certain amino acids, as well as chemicals produced by the stomach and intestine, boost insulin secretion.

1.11.5 The action of insulin on target tissues

The most conspicuous effect of insulin administered to mammals is the prone reduction of the blood glucose level, which is believed to be enhancement of transport of glucose to blood across the plasma membrane of muscles and fat cells into the intercellular space. It is also responsible for the inactive form of glycogen synthesis to active form and it inhibits lipolysis because of this process in the peripheral tissue there is enough conservation of blood glucose and into glycogen and lipids and there is also increased oxidation to glucose and carbon dioxide. Glucose is responsible for the synthesis of protein from amino acids responsible for the enhancement induction of glucokinase and phosphofructokinase and suppresses the formation of certain enzyme gluconeogenesis. These enzymes are pyruvate, carboxylase and fructose diphosphatase. Insulin appears to have a generalized action on the plasma membrane of its target cell leading to enhanced entry not only of glucose but also of amino acid, lipids and potassium followed by biosynthesis of protoplasm and storage product.

1.11.6 Insulin receptors

The idea that insulin binds to specific receptors in or its target cell was first proposed many years ago. However, experimental proof of such receptors did not

come until late 1960, when it was found that radioactive insulin is bound with very high affinity to specific receptors of muscle and fat cells in time and temperature dependent manner. The binding of insulin is accompanied by characteristic metabolic effect on fat cells, particularly increased synthesis of triacylglycerols from glucose and decreased enzymatic hydrolysis of lipids. Binding of insulin takes place outside the surface of the cell; it was experimentally proven by P. Cuatrecases (1960). An agarose bed is an inner polysaccharide material used in affinity chromatography. The insulin receptor proteins have a molecular weight 30000. Its affinity for insulin is very high; the dissociation constant of the insulin receptor complex is about 10^{-10}.

1.11.7 Regulation of insulin secretion

The human pancreas normally secretes one unit of insulin each hour; however, a much higher amount is released after each meal. Chemical, hormonal, and neurological variables all influence insulin production in cells.

i. *Chemical*:- The cell possesses a glucose sensing system that is dependent on glucose entrance into cells via GLUT 4 and phosphorylation by glucokinase. The glucosensor causes a partial depolarization of the cell and enhances intracellular insulin dipositivity (owing to increased inflow, decreased efflux, and the release of insulin intracellular reserves). Exocytosis may also be induced by amino acids, fatty acids, and 10 ketone bodies, while glucose is the major regulator and boosts insulin production as well. Within 2 minutes, glucose induces a minor increase in insulin production, which is mediated by a delayed but more continuous second phase of insulin release. Glucose entrance into cells indirectly inhibits ATP-sensitive adenosine triphosphate potassium channels, causing membrane depolarization and calcium-dipositive-mediated exocytosis of insulin storage granules. Glucose and other foods aid in insulin release by increasing chemical signals from the stomach that act on pancreatic cells to trigger anticipatory insulin release. Gut glucagon secretion, gastrin, gastric inhibitory polypeptide, vasoactive intestinal peptide (VIP), pancreozymin-cholecystokinin, and other incretins are implicated; however, various incretins may convey signals from various foods. Glucagon and various peptides improves insulin secretion in cells by increasing the production of cyclic AMP (cAMP).

ii. *Hormonal*:- Many hormones, including growth hormone, corticosteroids, and thyroxine, impact secretion of insulin. Intra-islet paracrine interactions between hormones secreted by different kinds of islet cells are significant, and prostaglandin

has been discovered to inhibit insulin. The cells are the most prevalent cell type and form the core of the islets. The cells that surround the core and generate glucagon account for 25% of the islet cell mass. Somatostatin-producing cells are dispersed throughout the cells. There are additional cells that contain pancreatic polypeptides.

a) Both the release of insulin and glucagon are inhibited by somatostatin.

b) Glucagon stimulates the release of insulin and somatostatin.

c) Insulin reduces glucagon secretion.

iii. *Neural:-* The islets are abundant with sympathetic and vagal nerves.

a) By blocking cell adenylyl cyclase, adrenergic α2 receptor activation reduces insulin release.

b) Adrenergic β2 activation promotes insulin release by increasing βcell adenylyl cyclase.

c) Cholinergic—ACh-induced muscarinic activation or vagal stimulation increases insulin secretion in cells via IP3/DAG-increased intracellular Ca2+.

Because the blocking medications have opposing effects, these neural inputs appear to affect both vascular and induced insulin secretion. The hypothalamus is the primary central locus for insulin secretion regulation; stimulation of the ventrolateral nuclei causes insulin release, whereas activation of the ventromedial nuclei inhibits or limits insulin release.

1.11.8 Actions of insulin release

i. The hormone insulin facilitates the transport of glucose across cell membranes, with skeletal muscle and adipose tissue exhibiting particular sensitivity to insulin. However, glucose utilization in these and other tissues is constrained by its intracellular availability. In contrast, glucose entry into the liver, brain, red blood cells (RBCs), white blood cells (WBCs), and renal medullary cells occurs independently of insulin. Diabetic coma can be exacerbated by ketoacidosis, which impedes glucose metabolism in the brain. Muscle activity promotes glucose uptake into muscle cells without necessitating insulin. Additionally, the intracellular pool of vesicles containing GLUT1 and GLUT4 of the glucose transporter is in a constant state of flux, with GLUT vesicles dynamically interacting with the membrane. Insulin controls the equilibrium state in order to promote membrane translocation.

ii. The first stage in intracellular glucose use is phosphorylation, which produces

glucose 6-phosphate. Insulin enhances this process by stimulating the production of glucokinase. Additionally, insulin activates glycogen synthase, facilitating conversion of glucose to glycogen. Furthermore, it inhibits phosphorylase, thereby reducing glycogenolysis in the liver.

iii. Insulin blocks gluconeogenesis in the liver by decreasing phosphoenolpyruvate carboxykinase synthesis via gene regulation. In instances of insulin deficiency, proteins and amino acids are redirected from adjacent organs to the liver, where they undergo conversion into glucose and urea. As a result, glucose is underused and overproduced in diabetes, resulting in hyperglycemia and glycosuria.

iv. Insulin inhibits lipolysis and stimulates triglyceride synthesis in adipose tissue. Diabetes causes an increase in free fatty acids and glycerol in the blood due to the uncontrolled activity of lipolytic hormones (glucagon, Adr, thyroxine, etc.), which are taken up by the liver to form acetyl-Coenzyme (acetyl-CoA). Acetyl-CoA is normally converted into fatty acids and triglycerides; however, in diabetics, this phenomenon is disrupted, and acetyl-CoA is misdirected to the formation of ketone bodies. Ketone bodies enter the bloodstream and are used as an energy source by the muscles and heart; when their capacity increases, ketonaemia and ketonuria develop.

v. Insulin stimulates the transcription of vascular endothelial lipoprotein lipase, which increases the clearance of VLDL and chylomicrons.

vi. In muscles and most other cells, insulin increases AA entry and protein synthesis while inhibiting protein breakdown. Protein breakdown occurs as a result of insulin deficiency. AAs are broken down in the blood and absorbed by the liver, where they are converted into pyruvate, glucose, and urea.

1.11.9 Mechanism of action of insulin

Insulin interacts with specific receptors present on the cell membranes of nearly all cells, albeit with varying densities depending on the cell type. The density of insulin in the liver and fat cells is high. The insulin receptor was isolated and fused to produce a heterotetrameric glycoprotein with two extracellular and two transmembrane subunits connected by disulfide bonds. The subunits include insulin-binding sites as well as tyrosine protein kinase activity. The binding of insulin to its subunits triggers receptor aggregation and the internalization of the insulin bound molecules. This stimulates the tyrosine kinase activity of the subunits, which phosphorylate tyrosine residues of the subunits, resulting in the activity of these subunits to phosphorylate tyrosine residues of insulin. Subsequently, a cascade of

phosphorylation and dephosphorylation events is initiated, magnifying the signal and leading to the activation or inhibition of enzymes responsible for insulin's swift metabolic effects.

The activation of a certain enzyme produces certain secondary messengers, such as phosphatidylinositol triphosphate (PIP3). Phosphatidylinositol triphosphate kinase also mediates the insulin effect on metabolic enzymes. Insulin enhances glucose transport across cell membranes via ATP-dependently translocating and activating the glucose transporters GLUT4 and GLUT1. It also increases the expression of genes involved in the direct synthesis of GLUT-4 over time. Insulin has been demonstrated to control the genes for a wide range of enzymes and carriers, primarily by mitogen-activated protein kinase (MAP). Internalized receptor-insulin complexes are either eliminated intracellularly or liberated extracellularly. The importance of these two processes varies across different tissues, with the liver having the highest degradation and the vascular endothelium having the lowest.

1.11.10 Fate of insulin

Insulin is just found outside of cells. It is peptide breakdown in the gut or orally given insulin or pancreatic release that is largely created in the liver and muscles. During the initial passage through the liver, over half of the insulin entering the portal vein from the pancreas is inactivated. As a result, they are exposed to much greater insulin concentrations than other tissues. Insulin has a plasma half-life of 1–9 minutes.

1.12 Synthetic medicines for diabetes mellitus

1.12.1 Mechanism of action of Sulfonylurea

Monotherapy promotes rapid insulin release from the pancreas by acting on sulfonylurea receptors on the pancreatic cell membrane. This mechanism induces depolarization by diminishing the conductance of ATP-sensitive potassium channels. In type II diabetes, insulin secretion rate rises at any glucose concentration, but the dynamics of insulin release in response to glucose or meals are delayed and suppressed. The sulfonylurea predominantly boosts phase I insulin secretion while having little effect on phase 1. They do not cause hypoglycemia in pancreatectomized animals, and their indirect effect via the pancreas is verified in type I diabetics. A minor action reducing glycogen and increasing somatostatin secretion has been observed. The rate of hepatic breakdown may be slowed.

a) *Extra pancreatic action*

Long-term treatment diminishes the insulinotropic effect of sulfonylureas, likely attributed to the down-regulation of sulfonylurea receptors in β cells, even though glucose tolerance enhances. During this phase, they prepare the target tissues for insulin action. This is due to more insulin receptors being activated and improved receptor activation and translation. It has been suggested that the long-term enhancement in carbohydrate tolerance results in a reduction in glucose concentration in the blood, which reverses the downregulation of insulin receptors. Sulfonylureas appear to be associated with an increase in insulin receptors on target cells and inhibition of gluconeogenesis. a linear fashion.

b) Pharmacokinetics

Orally, everything is well absorbed. An has at least a 9% plasma protein binding rate and a modest volume of distribution of 0.2–0.4 l/kg. Some are extensively hydrolyzed and may generate active metabolites. Others are majorly removed without damage to the urine. As a result, in individuals with liver or renal disease, they should be administered with care.

1.12.2 Biguanides Mechanism of action

They do not trigger the release of insulin, but their action requires the presence of some insulin. There hypoglycaemic actions are-

a) Inhibits liver glucose production and hepatic gluconeogenesis.

b) Improves glucose absorption and Uptake in skeletal muscle and fat facilitated by insulin. Glut 1 transport from the intracellular site to the plasma membrane is improved, despite the fact that it has no effect on Glut 4 translocation. The activity is the same as that of insulin.

c) Interferes with the mitochondrial respiratory chain, leading to heightened anaerobic glycolysis and increased peripheral glucose utilization. Metformins that bind less strongly to mitochondrial membranes decrease oxidation phosphorylation.

d) Inhibits the uptake of glucose, other hexoses, amino acids, and vitamins B12 in the intestine.

e) Pharmacokinetics- Forming incompletely but adequately absorbed clearance of metformin approximately glomerular filtration rate.

1.12.3 Meglitinide analogous

Meglitinide is based on the glibenclamide sulfonylurea moiety. They bind to the cell's sulfonylurea (Sur) I receptor with lower affinity and stimulate insulin release in

the same way. Unlike repaglinide, nateglinide has a greater effect on insulin secretion as plasma glucose levels rise, leading to a mild augmentation of insulin secretion during fasting. These medications have a quick onset of action and a short duration of action, and they are given within 30 minutes of main meals.

a) *Pharmacokinetics*

Both Nateglinide, Repaglinide is metabolism in the level and has a life of 1-2 hours.

1.12.4 Thiazolidinedione

This novel class of oral anti-diabetic medications specifically activates the nuclear peroxisome proliferator-activated receptor (PPAR), increasing the transcription of numerous insulin-responsive genes. They appear to promote glucose entry and muscle fat by boosting Glut4 expression and translocation. The activation of genes in adipose tissue that control fatty acid metabolism and lipogenesis may result in insulin sensitivity. In type II diabetic patients, improved glycemic management leads to a reduction in circulating insulin. Pioglitazone lowers blood triglyceride levels while boosting HDL levels without changing LDL levels. Rosiglitazone's impact on the lipid profile is unclear.

1.12.5 Reactions to insulin

a) Hypoglycaemic:- This is the most prevalent and possibly deadly response seen in individuals with type 1 diabetes whose insulin needs change unexpectedly. Hypoglycemia can develop in any diabetic after an unpleasant tend injection in large quantities, avoiding a meal, or participating in vigorous exercise. Symptoms include sweating, anxiety, a headache, dizziness, behavioural changes, eyesight issues, weakness, weariness, and, in rare cases, a dip in blood pressure.

b) Local reaction:- Swelling, erythema and stagnating sometimes occur especially in the beginning.

c) Allergy:- This is unique because it contains proteins that are extremely rare in humans and extremely pure insulin.

d) Edema:- Some patients developed acute depended edema (due to sodium retention) after onset of insulin therapy.

1.13 Herbal treatment for diabetes

According to Ayurveda, various medicinal plants have been known to possess anti-

diabetic properties. The majority of herbal remedies derived from these therapeutic plants are said to have few or no negative effects (Piero et al., 2011). The World Ethnobotanical Organization reports that 800 medicinal plants are used to prevent diabetes mellitus. Only 450 medicinal plants have been scientifically proven to have anti-diabetic properties, with 109 medicinal plants having a broad mode of action (Prabhakar et al., 2011). As per WHO, the global population relied upon traditional herbal medicines for their primary healthcare requirements (WHO, 2003). Since ancient times, Asia's nations, particularly India and China, have employed herbal medicines. (Ahmed and Goldstein, 2006; Adeghate and Singh, 2014). The World Health Organization also supports the consumption of traditional medicines that are efficacious and safe for human use (WHO, 2013). Traditional medicine, also known as traditional or folklore medicine, is made up of knowledge systems that emerged over many centuries throughout numerous cultures prior to the arrival of advanced medicine. By the development of up-to-date cure, herbaceous medicine custom has deteriorated but still it continues to be expected to be used in many parts of the experience. This is due to many reasons, some of them being their effectiveness and better security sketches. Moreover, study on traditional curative herbs has been recommended by WHO Expert Committee on diabetes (Bailey & Day, 1989). Many scientists suggest the diversified systems possessed by an herbaceous drug are expected to be the reason for their beneficial belongings in constant ailments. Because of the combination of synthetic elements present in plants, they may expend synergistic effect and may also possess numerous mechanisms increasing insulin sensitivity, protecting beta cells, and lowering hepatic glucose production, anti-oxidant, anti-inflammatory, anti-hyperlipidemic activity etc. However, the side effects, long-term usage, and cost-effectiveness of the existing hypoglycemic drugs have resulted in a great demand for complementary and alternative medicine, which has fewer side effects and more cheap agents for the treatment of diabetes. The primary benefits of anti-diabetic herbal formulation include natural healing, long-term effects, improved immunity, metabolism, and nutrition. In India, many diabetics are dependent on natural medications. Despite such widespread acceptance, the number of standardized herbal medications is extremely low due to a lack of regulatory standards and implementation methodology. Despite the fact that many plants have been used in antidiabetic herbal formulations, only few plants have been scientifically validated, and no one official herbal medicine is now available for widespread use (Rahul et al., 2022).

1.14 Anti-oxidative properties of plants

It has been established that oxidative stress plays a vital role in the development of both types of DM (Ighodaro, 2018). Previous research has connected a rise in reactive oxygen species (ROS) to pancreatic cell death, which affects insulin production (Newsholme et al., 2019). To stop additional cellular damage, it is therefore a useful therapeutic approach to introduce substances that increase antioxidant capacity (Sandireddy et.al 2014). A large number of traditional medicinal herbs have been proven to have anti-oxidative threat skills in their biological systems. The antioxidant properties of these plants have also been scientifically proven using a range of in-vitro and in-vivo testing procedures (Rochette et al., 2004; Salem et al., 2017).

1.15 Concept of Glucose Transporters in the field of Diabetes Mellitus

1.15.1 Glucose transporter (Gould et al., 1993)

i. Lefeure in 1948 was the first person to postulate the human body to transfer glucose across the bilayer.

ii. In vivo try to explain the glucose uptake mechanism as a mobile carrier across sheep placenta.

iii. In 1970, it was assumed that glucose transporters were controlled by a protein inserted into the plasma membrane of erythrocytes and that they could be partly purified and functionally rebuilt into proteoliposomes.

In 1985, the cloning of copy DNA and coding the rate-cell glucose transporters happened, and 13 related membranes of SLC to the GLUT) protein family 13 were later found in humans. The Glut family is a member of the large facilitative superfamily, and approximately 5,000 families of the major facilitative superfamily have been found so far. GLUT proteins employ unidirectional substrate transport and can be either symmetric or asymmetric. GLUT proteins are composed of 500 amino acids and have transmembrane-spanning alpha helices as well as a single N-linked oligosaccharide.

1.15.2 GLUT 1 the erythrocyte-type glucose transporter

Many investigations on GLUT-1 human membranes have been conducted. This transporter is abundant in erythrocytes, accounting for around 3–5% of the total. Lienhard and his colleagues identified this protein in 1980. The GLUT-1 protein and its mRNA are found in a variety of tissues and cells; it is most abundant in the

brain and is also found in blood-tissue barrier cells, the placenta, the retina, and other tissues. It is also found in muscle and fat, which showed acute insulin-stimulated glucose transport. It is found in lesser concentrations in the liver.

1.15.3 GLUT 2 the liver-type glucose transporter

GLUT 2 has a high K_m for glucose (17 mM) and is expressed at a high level in pancreatic cells as well as the basolateral membranes of the intestine and kidney, epithelial cells, and hepatocytes. The pace of glucose metabolism is controlled by this cell at the glucose phosphoregulation phase. Thus, modulation of GLUT 2 surface expression has no effect on metabolism unless it is used to limit glucose excess to hexokinase, as occurs in diabetic cells in the intestine. GLUT 2 may also reach the apical portion of the cell in the presence of an elevated luminal glucose concentration to increase flux absorption. A rise in blood glucose concentration causes insulin production in pancreatic cells, while a rise in blood glucose concentration causes glycolytic and lipolytic enzymes to be expressed in hepatocytes. The procedure mentioned earlier will not occur in the absence of GLUT 2. GLUT 2 has been shown in certain investigations to operate as a glucose sensor in the hepatorenal vein and the central nervous system. This sensor appears to regulate eating behaviour, glucagon secretion, insulin secretion, and peripheral glucose absorption.

1.15.4 GLUT 3 the brain-type glucose transporter

Through immunological investigation of human tissues, it was shown that GLUT 3 is present at high levels in the brain, placenta, heart, liver, and kidney. The mRNA level of GLUT 3 in the kidney and placenta is around half that found in the brain. It is the essential neuronal glucose transporter found in dendrites and axons, and its levels of expression in different parts of the brain are determined by the cerebral glucose concentration at 1.5 mM. At the blastocyst stage, GLUT 3 is present in the trophectoderm of the embryo. GLUT 3 is expressed in monocytes, macrophages, lymphocytes, and platelets. Upon cellular activation, it can be translocated and fused to the plasma membrane, resulting in enhanced glucose absorption and metabolism.

*1.15.5 GLIUT 4 The insulin-responsive glucose transporter (*Tiannan Wang et al., 2020)

GLUT 4 has gained increasing attention in the first field of study and in the scientific community as a result of its relevance in whole-body glucose homeostasis, its active participation in the mechanism of insulin control, and this harmony in insulin

resistance issues such as obesity and type 2 diabetes. To investigate the mechanism of glucose stimulation, antibodies targeting the glucose transporter protein were created. In 1988, a specific antibody was developed against GLUT sample preparation, which led to the identification of molecules encoding and insulin-induced GLUT from mouse adipocytes. It was shown that insulin stimulation causes GLUT-4 translocation from intracellular vesicles to plasma membranes. When insulin stimulates the transport of GLUT-4-containing vesicles to the cell membrane, the concentration of GLUT-4 in the plasma membrane rises, and more and more GLUT-4 enters the cell without any GLUT-4-specific action. GLUT-4 recycling occurs regularly during insulin stimulation. When the insulin is withdrawn, the quantity of GLUT-4 on the plasma membrane decreases, and the rate of movement returns to its baseline level. GLUT-4 is a 509 amino acid protein that is encoded by the SLC2A4 gene in the human genome and is found mostly in adipocytes and skeletal muscles. GLUT 4 has a Km of roughly 5 mM/L.

1.15.6 GLUT 5 the small-intestine sugar transporter (Veronique Douard and Ronaldo 2008)

The transporter GLUT 5 transports GLUT 5 across cell membranes in a passive manner. GLUT 5 is primarily responsible for the transport of fructose, although it may also transport glucose or galactose. The small intestine regulates fructose absorption from dietary sources as well as its availability to other tissues. It is also the organ system with the highest level of GLUT 5 in the lumen. On the luminal side of tiny intestinal epithelial cells, the protein resembles an apical brush border protein. The sodium-dependent glucose transporter is the primary transporter of glucose from the lumen to the epithelial cells. GLUT 5 is expressed in a variety of tissues, including muscles, the brain, and adipose tissue. This transporter cannot go through insulin-stimulated translocation in adipocytes, and there is an apparent absence of insulin-stimulated fructose transport in human adipocytes.

1.15.7 GLUT 7

Based on sequence similarities, it has been placed in class II of the GLUT 2 family, and the closest family membrane is GLUT 5, an intestinal fructose transporter. It has been shown to be expressed in the gut and colon, but investigations also reveal that it is present in the testis. GLUT-7 has a high affinity for glucose and fructose transport. GLUT 7 is a protein that is closely related to GLUT 5 and shares 53% of its identity. GLUT 7 is only found in the distal portion of the small intestine, the ileum, and it does not contain a large concentration of glucose or fructose.

According to this study, GLUT 7 does not play a significant role in the uptake of glucose and fructose from the food, although it may be important at the final stage of the meal when luminal concentrations of hexoses in the ileum are low. Sequence alignments and mutation studies on GLUT 7 revealed a particular hydrophobic residue in transmembrane domain 7 that affects fructose sensitivity (Chris Cheeseman 2008).

1.15.8 GLUT 8

The expression of GLUT-8 mRNA is found in most other tissues, including the brain, spleen, liver, and insulin-sensitive tissues such as skeletal muscles, heart, and adipose tissues, but in lesser numbers. GLUT 8 transports NH4-terminal dileucine, which determines the protein's intracellular location. The transporter is directed to the plasma membrane by changing the leucine residues to alanine (Schmidt S et al., 2009).

1.15. 9 GLUT 9

It is a new facilitative isoform with different splice variants expressing two proteins with NH2 terminal sequence differences (GLUT9a and GLUT9b). The GLUT-9 protein and mRNA are both expressed in the epithelia of diverse organs. However, the splice variants are distributed differently inside polarized cells, with GLUT9a mostly expressed on the basolateral surfaces and GLUT9b prevalent on the apical surfaces. Under malnutrition conditions, the concentration of GLUT-9 protein expression decreases. However, it rises when the body's level of glucose rises. Other than transporting hexose carbohydrates, GLUT 9 also transports high-capacity uric acid. The amino acid sequence of GLUT 9 is 44% identical to that of another class II transporter, GLUT 7. GLUT 9a RNA is mostly expressed in the liver, kidney, and placenta, whereas GLUT 9b RNA is primarily expressed in the kidney and placenta. The location of GLUT 9 has also been examined in murine early embryos, sperm, and testis. Because glucose is a key substrate for early embryonic development, only GLUT-9 expression has been found at the single-cell zygote stage. However, at this early stage of development, this transporter is not localized at the plasma membrane, and hence GLUT 9 may operate as the only GLUT responsible for glucose delivery. Human articular cartilage has been shown to express GLUT 9. The Km of glucose is 0.61 mM, while the Km of fructose is 0.42 Mm (Manuel Doblado and Kelle H. Moley 2009)

1.15.10 GLUT 10

Human GLUT 10 cDNA encodes 541 amino acid proteins with 31% to 35% amino

acid similarity to human GLUT 1–8. The human facilitative glucose transporter GLUT 10 is found on human chromosomes 20 sq 12–13.1 in the type II diabetes-related region. The amino acid sequence of GLUT 10 is substantially identical to that of GLUT 9, although it is longer than that of any other GLUT family. GLUT-10 transcription is present in the human heart, lungs, brain, liver, skeletal muscles, pancreas, and kidney (Dawson et al., 2001). GLUT 10 is a glucose transporter that transfers the simple sugar glucose across the cell membrane and helps maintain the right amount of glucose within cells. The level of GLUT 10 appears to be employed in the transforming signaling pathway regulatory process. According to research, GLUT 10 may potentially be linked to the functioning of mitochondria, the energy-producing organelles within cells.

It is a member of the GLUT family II. GLUT 10 was found in both cell types and was involved in the 24-hour transfer of L-dehydroascorbic acid (DHA), the oxidized form of vitamin C, into mitochondria. DHA transport into mitochondria through GLUT 10 enhanced vitamin C production in both mitochondria and cells, as well as protecting cells from oxidative damage by decreasing the generation of 46 reactive oxygen species (ROS) (Lee et al., 2010).

1.15.11 GLUT 11

Human GLUT11 (encoded by the solute carrier 2A11 gene, SLC2A11) s a novel sugar transporter 23 with significant sequence similarities to existing GLUT family members. The fructose transporter GLUT 5 is the closest relative of GLUT 11 (sharing 41.7% amino acid similarity with GLUT 11) (Doege et al., 2001). GLUT11 is a sugar transport facilitator in class II. Exons 1 (exon 1A, exon 1B, and exon 1C) have separated three GLUT-11 mRNA variants. Exons 1 (exon 1A, exon 1B, and exon 1C) have separated three GLUT-11 mRNA variants. GLUT 11 variations (GLUT11-A, GLUT11-B, and GLUT11-C) vary in amino acid sequence N termini. Northern blotting investigation using specific probes for exon 1A, 1B, and 1C showed that GLUT11-A is expressed in the heart, skeletal muscle, and kidney, GLUT11-B in the kidney, adipose tissue, and placenta, and GLUT11-C in the adipose tissue, heart, skeletal muscle, and pancreas. (Scheepers et al.,2005).

1.15.12 GLUT 12

The GLUT-12 cDNA encodes 617 amino acids and has sugar-related properties. GLUT 12 shares 29% of its amino acid sequence with GLUT 4 and 40% with GLUT 10. GLUT 12's genomic organization sequence is substantially conserved with GLUT 10 but unique to GLUT 1–5. The expression of GLUT 12 appears

highly selective in skeletal muscles, adipose tissues, and the small intestine, as demonstrated by immunoblotting. GLUT 12 is a member of the GLUT transporter family's class III. GLUT 12 transports two deoxyglucose molecules, as well as fructose and glactose (Rogers et al., 2002

1.15.13 GLUT 13

Human GLUT-13 is made up of 629 amino acids. Glut 13 is present mostly in the brain, specifically in the ganglia and some neurons. GLUT 13 has myinositol-specific electrogenic activity.

HMIT is restricted to intracellular space. Instead of sugar transport function, HMIT has been found as H^+-pair myo-inositol simporters with a K_m of around 100 μM. It has been discovered that HMIT transports inositol-3-phosphate. The standard GLUT inhibitors, phloretin, phlorizin, and cytochalasin B, although only at high doses, inhibit HMIT. Myoinositol is a precursor for phosphatidylinositol, a key regulator of several signalling pathways in the brain (Robert Augustin 2010).

1.15.14 GLUT 14

It maps to chromosomes 12 and 13.3, approximately 10 Mb upstream of GLUT 3, with which it exhibits remarkable identity. It consists of 11 axons with genomic construction identical to GLUT 3 and is most likely the outcome of a GLUT 3 duplication. GLUT 14 has two alternatively spliced forms; the shorter type (GLUT14s) has 10 axons and generates 497 amino acids, which is 94% similar to GLUT 3. The long version, GLUT 14 l, contains an extra axon and codes for a protein with 520 amino acids that varies only at the ends of GLUT 14 s. Both GLUT -14 isoforms are seen in highly exposed testis ().

1.16 Alloxan

Justus Von Liebig and Friedrich Wohler were the first German scientists responsible for the synthesis of alloxan which is a pyrimidine derivative. Dum and MC Letchie induction of alloxan in an animal model is responsible for the induction of diabetes which is occurring due to necrosis of pancreatic β cells. This phenomenon has been postulated in the year 1943. The resulting insulinopenia was called alloxan diabetes. The reduction product of alloxan is dialuric acid which is also a diabetogenic in animals.

1.16.1 Mechanism of action of alloxan

i. The pathogenic effects of alloxan are distinct in two ways.

ii. By glucokinase inhibition, glucose-induced secretion is inhibited.

iii. Inhibiting glucose sensors in cells induces the formation of insulin-dependent diabetes due to its ability to enhance the synthesis of ROS, which causes the necrosis of pancreatic cells.

1.16.2 β cells selectivity of alloxan

Alloxan is an extremely unstable chemical molecule that has a molecular structure similar to glucose. Because of their hydrophilic nature, none of them can penetrate the plasma membrane's lipid bilayer. Because alloxan and glucose are similar, the glucose transporter GLUT II present in cell plasma membranes accepts this mixture and transfers it to the cytosol. Alloxan is not responsible for the suppression of transporter production and hence can enter cells without limitation. Alloxan has a limited half-life and is not harmful to insulin-producing cells. Because alloxan degrades into non-diabetic alloxanic acid in aqueous conditions in a few minutes, it must be immediately taken up and collected in the cells. If there is no disturbance in blood flow to the pancreas within the first few minutes after injection, it may be useless.

1.16.2 Glucokinase Inhibition

Alloxan thiol group reactivity has the primary pathophysiological effect of inhibiting glucose-induced insulin release. Five carbonyl groups of alloxan react quickly with thiol groups. The most sensitive thiol enzyme in β cells, glucokinase has an inhibitory concentration that ranges from 1 to 10 m mol/L. Alloxan has the ability to inhibit a wide range of functionally significant enzymes, as well as many proteins and cellular proteins, at higher concentrations. When glucokinase is inhibited, there is a reduction in the amount of glucose that is oxidized during ATP synthesis and a suppression of the ATP signals that cause insulin production. Within 1 minute of being exposed to alloxan, glucokinase was inhibited. The biosynthesis of insulin is also inhibited by alloxan.

1.17 Objectives of the study

The research gap indicated the necessity of such work which can minimise the knowledge gap and boost the utility of candidate plants. Hence the present study is anticipated with the following objectives:

i. To design a herbal formulation for antihyperglycemic activity.

ii. To amalgate herbs to developed an antihyperglycemic formulation.

iii. To screen the phytochemical constituent of the polyherbal formulation.

iv. To evaluate the in vitro antioxidant activity of standardized polyherbal formulation.