Review Article Contemplative understanding of Diabetes and diabetic Neuropathy

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ABSTRACT

Diabetes mellitus has become a major public health concern around the world as a result of the rapid rise in prevalence that has occurred, affecting virtually all regions of the globe and within regions, affecting all age and demographic subgroups, and affecting people from all socioeconomic backgrounds. The global incidence is presently believed to be over 420 million, affecting 9% of males and 8% of women, with the lowest geographical frequency (6%) in Northeastern Europe and the highest prevalence (25%) in Polynesia and Macronesia. Both type 1 and type 2 diabetes have increased in prevalence, with type 2 accounting for 90 to 95 percent of occurrences and the majority of the increase in prevalence. . Diabetes consequences may be diversifying further due to long-term decreases in cardiovascular mortality in many countries, in addition to the effects of diabetes on classically characterized macrovascular and microvascular disorders. Neuropathy is the most common late complication of diabetes and can cause significant disability, including painful foot ulceration, Charcot joints, symptomatic autonomic dysfunction, and depression, anxiety, and sleep disorders. Neuropathy is a broad term that refers to nerve abnormalities. It is frequently and imprecisely used synonymously with polyneuropathy or peripheral neuropathy, the latter two being equivalent. Although substantial progress has been made in the last decade in terms of both customised diagnosis and therapy for T1D, significant challenges and research gaps still exist,between where we are today in terms of knowledge and where we want to go into a common clinical benefit. There is an urgent need for more well-conducted, big head-to-head comparative trials and combination trials of existing treatments. A variety of new therapeutic targets are currently being developed. Future clinical trials, on the other hand, should include procedures for detecting placebo effects to ensure that the genuine treatment benefit is recorded.

Keywords : Diabetes mellitus, type1DM, Type2DM, Pharmacotherapy, Diabetic Neuropathy.

I. INTRODUCTION

Diabetes mellitus has become a major public health concern around the world as a result of the rapid rise in prevalence that has occurred, affecting virtually all regions of the globe and within regions, affecting all age and demographic subgroups, and affecting people from all socioeconomic backgrounds. The global incidence is presently believed to be over 420 million, affecting 9% of males and 8% of women, with the

lowest geographical frequency (6%) in Northeastern Europe and the highest prevalence (25%) in Polynesia and Macronesia. Both type 1 and type 2 diabetes have increased in prevalence, with type 2 accounting for 90 to 95 percent of occurrences and the majority of the increase in prevalence. Even though dozens of individual-level genetic and environmental factors have been linked to type 2 diabetes, the growth in prevalence in most societies is likely due to a smaller set of trends, such as rising obesity rates, declining physical activity levels, poor-quality carbohydrate in our diets, and increasingly diverse socioeconomics. Even within the basic categories of type 2 and type 1 diabetes, there is significant awareness of heterogeneity in diabetes types, which are likely to have varied patterns of risk factors that vary by geography and environment. The rising prevalence of diabetes has grave ramifications for a variety of health and economic reasons. Because of the medication required, the acute and chronic consequences, the demand for health services, the direct impact on quality of life, and the loss of years of life, diabetes ultimately throws a huge burden on individuals, families, health systems, and society. Diabetes consequences may be diversifying further due to long-term decreases in cardiovascular mortality in many countries, in addition to the effects of diabetes on classically characterized macrovascular and microvascular disorders. While the prevalence of diabetes is the most visible indicator of its spread, there are other processes at work in the epidemic, all of which have significant consequences for clinical and public health goals. Primary findings from population studies on the burden and trends in prevalence, incidence, morbidity, and mortality have now been synthesised.[1]

diabetic neuropathy Neuropathy is the most common late complication of diabetes and can cause significant disability, including painful foot ulceration, Charcot joints, symptomatic autonomic dysfunction, and depression, anxiety, and sleep disorders. Neuropathy is a broad term that refers to nerve abnormalities. It is frequently and imprecisely used synonymously with polyneuropathy or peripheral neuropathy, the latter two being equivalent. Polyneuropathy, also known as peripheral neuropathy, is characterised by a predominantly distal, symmetric abnormality of nerves that typically begins in the feet and gradually ascends. A single nerve abnormality is referred to as mononeuropathy. Multiple mononeuropathy, also known as mononeuropathy multiplex, is the presence of an abnormality that affects multiple nerves, usually in a random, asymmetric fashion. It is important to note that these terms imply nothing about the etiopathogenesis.[2]

Biochemistry and molecular cell biology

Large prospective clinical studies show a strong link between glycemia and diabetic microvascular complications in both type 1 and type 2 diabetes (T2DM). There is a continuous, albeit not linear, relationship between glycemia and the risk of developing and progressing these complications. Both hyperglycemia and the consequences of insulin resistance appear to be important in the pathogenesis of macrovascular complications.[3]

Pathophysiological features of microvascular complications_

1. The need for intracellular hyperglycemia.
2. Improper Cell Function
3. Increased Protein Accumulation in the Vessel Wall
4. Loss of Microvascular Cells and Vessel Occlusion
5. Microvascular Complications Develop During Euglycemia after hyperglycemia.
6. Genetic Factors Influencing Susceptibility to Microvascular Complications.[3]

Development and maintenance of the islet β cell¬ _

Pancreas development –

The pancreas is a compound digestive gland that contains both exocrine and endocrine components that secrete digestive enzymes and hormones. The exocrine component, which consists of acinar and duct cells, contributes to approximately 95 percent of pancreas mass. Acinar cells produce and secrete proteases, lipases, amylases, and nucleases, which are required for nutrient digestion. Duct cells form a tubular network throughout the pancreas, secreting mucins and fluids that flush acinar secretions to the intestine.

The mature endocrine component of the pancreas, which is organised into structures known as islets of Langerhans, accounts for 2% of the total organ mass. Adult islets of Langerhans are primarily composed of five distinct hormone-secreting cell types: Cells generate glucagon, insulin, and islet amyloid polypeptide, somatostatin, pancreatic polypeptide, and ghrelin. In vertebrate animals, cells make up the majority (60–80 percent) of the cells that make up the islet.[4]

The progression of pancreas development in vertebrates can be segmented into five major events:
(1) the induction of definitive endoderm,
(2) the formation of the primitive gut tube and the patterning of endoderm into organ-specific progenitor zones,
(3) the induction of dorsal and ventral pancreatic buds
(4) Pancreatic bud outgrowth, branching, and fusion,
(5) The process of cytodifferentiation.

Beta cell

The insulin-producing cell is perhaps the most intensely studied endocrine cell type, owing to its factor in determining the pathogenesis and treatment of diabetes.

Many mouse models have aims to understand the factors required for -cell differentiation, development, and maturation. Neurod1, a basic helix-loop-helix transcription factor, is one such example. Neurod1 is expressed in all endocrine cell types except the somatostatin-producing cell, and in mice, targeted disruption of the Neurod1 gene results in severe reductions in and cells, as well as neonatal diabetes attributable to -cell apoptosis. The Maf transcription factor family is also involved in the - and -cell differentiation pathways. Pancreatic phenotypes can be seen in both MafA- and MafB-deficient mouse models. MafB deficiency causes perinatal lethality, and while total endocrine cell mass is unaffected, the pancreas has fewer and cells. Mice with a targeted deletion of the MafA gene are born viable and with normal islet cell numbers, but develop -cell dysfunction with age, leading to glucose intolerance and diabetes. -cell genes, including those encoding insulin, Neurod1, and Glut2, are effectively diminished in these mice. MafA is regarded as a marker for mature, functional cells due to its importance in -cell function.[4]

Insulin biosynthesis

Pre-proinsulin mRNA is unusually stable in pancreatic cells, and it becomes even more stable as glucose concentrations rise.As a result, there is usually a constant supply of preproinsulin mRNA available for translation in the -cell cytosol. Under normal conditions, the predominant control mechanism for insulin production in the cell is the specific regulation of pre-proinsulin mRNAtranslation. This allows the cell to rapidly replenish insulin stores after they have been depleted by stimulated insulin secretion, and it is more energy efficient for the cell because translational control of insulin production eliminates the need for insulin gene transcription and pre-proinsulin mRNA maturation.[4]

Pathogenesis of type 1 diabetes

T1D is caused by the adaptive immune system destroying insulin-producing cells in the pancreas known as beta cells. This process is aided by an unresolved interaction between a person's genetics

and their environment. Individuals with an overexpression of human leukocyte antigen or HLA class molecules DR4, DQ8, and DQ2 increasing their susceptibility are present in approximately 90% of T1D patients) and one or more environmental factors lead to the recognition of beta cell components as auto antigens that the immune system incorrectly recognises as foreign, resulting in an autoimmune response. Insulin B chain peptide (11-23) and other beta cell secretory granule components such as glutamic acid decarboxylase 65, protein phosphatase-like IA-2, and trans membrane Zn transporter have been recognised as auto antigens. The presence of one known autoantibody connotes a moderate risk of developing T1D, while a presence of each additional autoantibody exponentially increases the risk. These autoantigens are presented to diabetogenic autoreactive T cells by HLA molecules major histocompatibility complexes (MHC) I and II on antigen presenting cells (APCs). APCs, including B cells that produce high-affinity autoantibodies against beta cells, are stimulated by autoreactive CD4 T cells. Autoreactive CD4 T cells also assist diabetogenic CD8+ T cells in acquiring cytolytic activity and attacking beta cells by releasing cytokines (including TNF- and IFN-, Fas/FASL, and perforin/granzyme). Released cytokines also stimulate macrophages and other innate immune cells to further damage beta cells, resulting in a positive feedback loop in which more toxic cytokines are produced to propagate further beta cell destruction.[5]

Diagnosis of T1D :[6]

T1DM is thought to be caused by immune-mediated cellular destruction, which results in insulin deficiency and hyperglycemia. The classic symptoms of hyperglycemia, which include polyuria, polydipsia, weight loss, abdominal symptoms, headaches, and ketoacidosis5, usually appear quickly (days to weeks). The majority (>95 percent) of newly diagnosed patients seek medical care because of symptoms; a minority are diagnosed through routine glucose screening or autoantibody detection as a result of enrollment in longitudinal screening programmes. The American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus in 2016 are based on signs of abnormal glucose metabolism, regardless of diabetes type or age of onset. Unless there are unequivocal symptoms of hyperglycemia, the diagnosis should be confirmed by repeat OGTTs. Insulinopenia, T1DM symptoms, and evidence of cell-targeted autoimmunity are the cornerstones of T1DM diagnosis. If cell-targeting autoantibodies are detected, autoimmune T1DM may be diagnosed. The ADA recognises a category of idiopathic T1DM if patients have a clinical picture consistent with T1DM but no autoantibodies are present. Patients with idiopathic T1DM are older (>20–30 years old) than those with autoimmune T1DM, are more likely to be of African or Asian descent, and have a higher body mass index (BMI) than age-matched individuals with autoimmune T1DM. It is unclear whether patients with idiopathic T1DM have a different underlying pathology, or whether they manifest autoantibodies that are not detectable by standard assays, or autoantibodies that target autoantigens that have yet to be identified. Adult onset diabetes can occur in patients with neonatal diabetes in these cases, it is frequently misdiagnosed as T2DM. . Adults usually present with mild symptoms, and classification based solely on hyperglycemia is not always possible. BMI distribution in children and adults with T1DM is typically similar to that of the general population. As a result, approximately 20–40% of children with T1DM are overweight, though they are rarely as overweight or obese as the majority of youths with T2DM. Indeed, children and young adults with T1DM have lower average BMIs than children and young adults with T2DM. Although family history can help predict whether someone has T1DM, patients with T1DM have a threefold greater incidence of T2DM in their families than the general population139. Although ketoacidosis is more common in T1DM than in T2DM, approximately 30%

of T2DM patients in Africa may have ketosis at disease onset due to hyperglycemia-induced cell toxicity, which results in very low endogenous insulin and C-peptide levels (a marker of insulin production). Thus, Cpeptide levels may be low at the time of T2DM diagnosis, and they may be normal during the honeymoon phase of T1DM, making them ineffective for classifying T1DM at onset. Conversely, affected individuals with a clinical picture suggestive of T2DM may have autoimmunity. In such cases, terms like "type 1.5 diabetes," "double diabetes," "hybrid diabetes," and "mixed diabetes" have been and continue to be used. As a result, there are no standard case definitions for epidemiological research or surveillance of paediatric diabetes.[6]

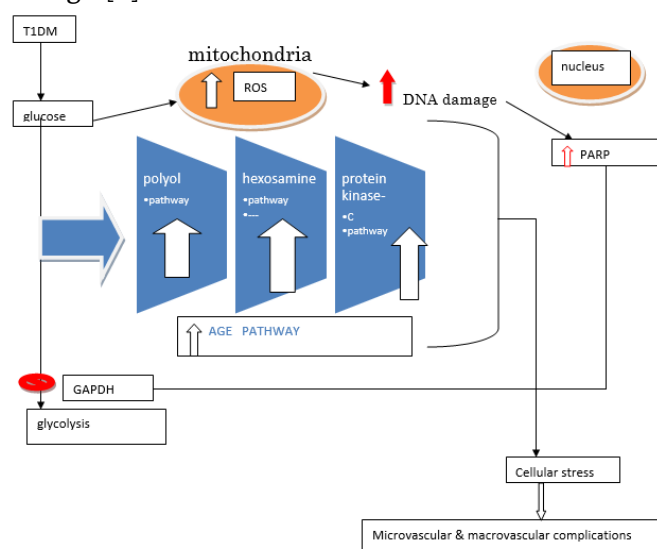## Mechanisms of hyperglycaemia induced cellular damage-[6]

Fig 1

Treatment for T1D:-[7]

- Insulin and combination drug therapies
- Gene therapy
- Stem cell therapies

Insulin therapy in T1D[8]

The treatment focuses on avoiding complications by controlling blood glucose levels with insulin, diet, and changes in lifestyle. Multiple daily injections of short-acting or rapid-acting insulin analogues, given 0–15 minutes before meals, are used in conjunction with

one or more separate daily injections of intermediate or long-acting insulins. Basal insulin (insulin degludec, insulin glargine, insulin detemir, and NPH) and bolus insulin (rapid-acting: insulin aspart, insulin lispro, or insulin glulisine; or short-acting: Regular/Neutral) are part of the basal-bolus regimen. Patients with severe decompensation (e.g., diabetic ketoacidosis, DKA) require intensive treatment, which is typically accomplished with short-acting insulin.

Intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) improved glycemia and resulted in a better long-term outcome in the DCCT study, which used short-acting and intermediate-acting human insulins.[8]

Medications that can be combined with insulin to improve metabolic variables and reduce hyper/hypoglycemia without increasing adverse events Obese/T1D patients who are predisposed to hypoglycemia, as well as those with residual -cell function, may benefit from non-insulin antidiabetic drugs in future clinical trials. Among these are metformin and pramlintide, which play a role in glycemic control in both T1D and T2D & can help T1D patients lose weight by lowering triglyceride levels, lowering haemoglobin A1c (HbA1c), and lowering triglyceride levels. Furthermore, when combined with insulin, glucagon-like peptide-1 receptor agonists (GLP-RAs) can reduce the daily bolus insulin dose required while improving glucose control and weight loss. The incretin glucagon-like peptide 1 (GLP-1) is a gut-derived hormone that is secreted after eating. GLP-1's primary physiological actions are to accelerate nutrient-induced insulin release and inhibit glucagon secretion, thereby helping to regulate postprandial glucose excursion. Furthermore, other functions are represented by inhibition of gastrointestinal motility and thus works as "enterogastrone", a hormone released by the lower gastrointestinal tract in response to lipid intake that constrains the caudal motion of the chyme guts. GLP-RAs, whether used peripherally or centrally, reduce

food intake while increasing glucose-stimulated insulin secretion. The enzyme dipeptidyl peptidase-4 inhibitors (DPP-4) prevents GLP-1 inactivation and acts as an adjunct therapy in a closed loop system to reduce postprandial blood glucose levels and daily insulin dose but not HbA1c or the risk of hypoglycemia.[7][8]

Types of insulin:-[9]

Insulin type(trade name)	Onset	Peak	Duration
Bolus(prandial) insulins analogues (clear)			
Insulin aspart (NovoRapid)	**10-15 min**	**1-1.5 h**	**3-5 h**
Insulin glusine(Apidra)	**10-15 min**	**1-1.5 h**	**3-5 h**
insulin lispro(Humalog)	**10-15 min**	**1-2h**	**3.5-4.75 h**
Short acting insulins(clear) Humulin –R Novolin ge Toronto	**30 min**	**2-3 h**	**65 h**

Basal insulins	Onset	Peak	Duration
Intermediate-acting(cloudy) Humulin – N Novolin ge NPH	1-3 h	5-8 h	Upto18 h
Long acting insulin Analogues(clear) Insulin detemir(Levemir) Insulin - glargine(Lantus)	90 min	NA	Up to 24 h(glargine 24 h detemir 16-24 h)

Premixed insulins Premixed regular insulin – NPH (cloudy) Humulin 30/70 Novolin ge 30/70,40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin)
Premixed insulin analogues (cloudy) Biphasic insulin aspart NovoMix 30 Insulin lispro/lispro protamine (Humalog Mix25 and Mix50)	

Type 2 diabetes mellitus:-
Epidemiology:-
The worldwide rise in obesity, inadequate physical activity, and energy-dense diets has led to a tremendous increase in the number of type 2 diabetes patients. Diabetes was estimated to affect 415 million people in 2015, with type 2 diabetes accounting for more than 90 percent of cases, with a projected increase to 642 million by 2040. The incidence and prevalence of type 2 diabetes vary by geographical region, with more than 80% of patients living in low-to-middle-income countries, but the overall trend since 1980 has been an increase in diabetes prevalence in all countries. An additional 318 million people have impaired glucose regulation in the preclinical stage,15 but intensive lifestyle modification, pharmacotherapy, or both can reverse or delay the development of type 2 diabetes.[10]

Genetic and environmental factors influence the epidemiology of type 2 diabetes. Following exposure to an obesogenic environment characterised by sedentary behaviour and excessive sugar and fat consumption, genetic factors take effect. Common variants of glycaemic genetic traits for type 2 diabetes have been identified through genome-wide association studies, but these only account for 10% of total trait variance, implying that rare variants are important. Transcriptomics, which involves whole-genome analysis of gene expression products (mRNA), has revealed a plethora of gene associations with type 2 diabetes and obesity by trying to equate genotype with phenotype. Increased genetic burden, as measured by additive genetic risk scores, is associated with a higher risk of all-cause mortality, particularly in non-Hispanic white people who are obese and have type 2 diabetes, when compared to other ethnic groups,emphasizing the significance of environmental and lifestyle modification in mortality reduction. Type 1 diabetes genetic risk scores, made up of nine single nucleotide polymorphisms, were created to discriminate between type 1 and type 2 diabetes in persons aged 20–40 years, as diagnosis might be difficult based only on clinical features and autoantibody markers.[10]

Pathophysiology of T2DM:-[11]
Mechanism of beta cell dysfunction:-

Traditionally, -cell impairment has been linked to -cell death. Recent research suggests, however, that -cell dysfunction in T2DM may be caused by a more complicated network of interactions between the environment and many molecular processes implicated in cell biology. Hyperglycemia and hyperlipidemia are common in an excessive dietary state, comparable to that found in obesity, encouraging IR and chronic inflammation. Under these conditions, -cells are exposed to toxic stresses such as inflammation, inflammatory stress, ER stress, metabolic/oxidative stress, amyloid stress, and others due to changes in their genetic vulnerability. It has the potential to lead to the loss of islet integrity in the long run. Excess FFAs and hyperglycemia cause -cell dysfunction by activating the apoptotic unfolded protein response (UPR) pathways, which causes ER stress. In reality, obesity-related lipotoxicity, glucotoxicity, and glucolipotoxicity cause metabolic and oxidative stress, which leads to -cell destruction. Saturated fatty acid stress can activate the UPR pathway through a variety of ways, including inhibition of the sarco/endoplasmic reticulum Ca2+ ATPase (SERCA), which is responsible for ER Ca2+ translocation; activation of IP3 receptors; and direct ER homeostasis impairment. Furthermore, prolonged high glucose levels increase proinsulin biosynthesis and islet amyloid polypeptides (IAAP) in -cells, resulting in the buildup of misfolded insulin and IAAP as well as an increase in the formation of oxidative protein folding-mediated reactive oxygen species (ROS). These changes modify physiological ER Ca2+ mobilisation, favouring proapoptotic signals and the destruction of proinsulin mRNA and cause the release of interleukin (IL)-1, which attracts macrophages and increases local islet inflammation.[11]

Mitochondrial dysfunction:-
T2DM development, age-related IR, and T2DM consequences are all linked to mitochondrial dysfunction, according to a growing body of research.

Indeed, oxidative stress, faulty mitochondrial biogenesis, genetic changes affecting mitochondrial integrity, and ageing all contribute to mitochondrial dysfunction and are linked to the development of T2DM. The primary function of mitochondria is to produce ATP by oxidative phosphorylation in response to metabolic demands. Mitochondria are also involved in the creation of a variety of metabolites that are employed as precursors for a variety of macromolecules (lipids, proteins, and DNA). Furthermore, mitochondria play a crucial role in ion homeostasis, ROS clearance, and other processes, as well as the stress response and the integration of numerous signalling pathways. Mitochondrial dysfunction is defined by a lower ratio of energy generation to respiration due to an imbalance between energy intake and expenditure in the mitochondria. The efficiency of food oxidation is lowered in these conditions, resulting in a lower ratio of ATP synthesis to oxygen consumption, which increases O_2 generation. In fact, one hypothesised mechanism linking mitochondrial dysfunction to IR is the buildup of reactive oxygen species (ROS) in the mitochondria. Obese and insulin-resistant people have lower mitochondrial oxidative capacity in skeletal muscle and have altered lipid metabolism when compared to healthy controls, according to studies. Furthermore, patients with T2DM have been found to have decreased phosphocreatine re-synthesis rate and downregulation of genes involved in oxidative metabolism that are regulated by the peroxisome proliferator-activated receptor co-activator 1 (PGC 1), both of which are indicative of impaired mitochondrial function. Furthermore, some T2DM patients' ancestors were found to have lower mitochondrial respiration, implying that mitochondrial dysfunction may occur prior to T2DM development. T2DM may arise as a result of abnormalities in the oxidative phosphorylation system and the electron transport chain (ETC), rather than a decrease in mitochondrial content, according to some researchers.[11]

Insulin resistance:-

A decrease in the metabolic response of insulin-responsive cells to insulin or, at a systemic level, an impaired/lower response to circulating insulin by blood glucose levels is referred to as insulin resistance (IR). Insulin resistance, often known as insulin deficiency, is divided into three categories:

(1) decreased insulin secretion by –cells.

(2) insulin antagonists in the plasma, either as a result of counter-regulatory hormones or non-hormonal substances impairing insulin receptors or signaling.

(3) impaired insulin response in target tissues.

In the fed state, the interaction of other substances such as growth hormone and IGF-1 influences insulin activity. To prevent insulin-induced hypoglycemia, glucagon, glucocorticoids, and catecholamines suppress the insulin response when fasting. This regulation is influenced by the insulin/glucagon ratio, which regulates the degree of phosphorylation of downstream enzymes in regulatory signalling pathways. Glucocorticoids stimulate muscle catabolism, gluconeogenesis, and lipolysis, while catecholamines enhance lipolysis and glycogenolysis. As a result, it's possible that excessive release of these hormones is what causes IR. In terms of the last category, skeletal muscle, adipose tissue, and the liver are the three main extra-pancreatic insulin-sensitive organs involved in the aforementioned processes. Insulin resistance in these organs frequently precedes the onset of systemic IR, leading to T2DM.[11]

Pathophysiological defect and therapeutic options for T2DM[10]

Pathophysiological defect		Glucose-lowering therapy	
		Existing	Future (phase1-3 clinical trials)
Pancreatic β cell	Loss of cell mass and function; impaired insulin secretion	Sulfonylureas; meglitinides	Imeglimin
Pancreatic α cell	Dysregulated glucagon secretion; increased glucagon concentration	GLP-1 receptor agonist	Glucagon-receptor Antagonists
Incretin	Diminished incretin response	GLP-1 receptor agonist; DPP-IV inhibitors	Oral GLP-1 receptor agonist; once-weekly DPP-IV inhibitors
Infl ammation	Immune dysregulation	GLP-1 receptor agonist; DPP-IV inhibitors	Immune modulators; anti-infl ammatory agents
Liver	Increased hepatic glucose output	Metformin; pioglitazone	Glucagon-receptor Antagonists
Muscle	Reduced peripheral glucose uptake; insulin resistance	Metformin; pioglitazone	Selective PPAR Modulators
Adipose tissue	Reduced peripheral glucose uptake; insulin resistance	Metformin; pioglitazone	Selective PPAR modulators; FGF21 analogues; fatty acid receptor agonists
Kidney	Increased glucose reabsorption caused by upregulation of SGLT-2 receptors	SGLT-2 inhibitors	Combined SGLT-1/-2 Inhibitors
Brain	Increased appetite; lack of	GLP-1 receptor agonist	GLP-1-glucagon-gastric

	satiety			inhibitory peptide dual or triple agonists
Stomach or intestine	Increased rate of glucose absorption	GLP-1 receptor agonist; DPP-IV inhibitors; alpha-glucosidase inhibitors; pramlintide		SGLT-1 inhibitors

Criteria for diagnosis-[3]

Test	Normoglycemia	Increased Risk			
		Impaired fasting glucose	Impaired glucose tolerance	High risk	diabetes
PG, Fasting(mg/dL)	<100	100-125			>126
PG,2h (mg/dL)					>200
HemoglobinA1c (%)	<140		140-199		>6.5
PG casual(mg/dL)				5.7-6.4	>200 plus classical symptoms of diabetes or hyperglycemic crisis

The criteria are based on estimates of the threshold for diabetic complications since plasma glucose concentrations vary on a continuum. Retinopathy is the most common end goal utilised to assess the link between glucose levels and problems. Fasting plasma glucose (FPG), 2-hour plasma glucose (HbA1c), and glycosylated haemoglobin A1c (HbA1c) are all assays that can predict the existence of retinopathy and, by extension, glucose levels that are diagnostic of diabetes. Furthermore, there is a link between high levels of all three markers and cardiovascular disease, however the link is stronger in the case of HbA1c. Previously, HbA1c was not recommended for the diagnosis of diabetes or states of high diabetes risk due to inadequate assay standardisation, but the new HbA1c assay offers numerous technical (preanalytic and analytic) benefits over currently utilised laboratory glucose measures. Furthermore, measurements of fasting and postchallenge glucose concentrations in the same person over time are less consistent than HbA1c measurements. In one study, the intraindividual coefficient of variation for the FPG and 16.7% for the 2-hour PG value was 6.4 percent and 16.7%, respectively, compared to less than 2% for HbA1c. Although the oral glucose tolerance test (OGTT) is a significant research tool. It is not recommended for use in routine diabetes diagnosis. Patients find it inconvenient, and in most situations, the diagnosis can be made based on either an elevated FPG concentration or an elevated random glucose determination in the presence of hyperglycemic symptoms.[3]

Risk factors for type2 DM:-[3]

Genetic Factors

Genetic markers
Family history
"Thrifty genes"
Demographic Characteristics
Sex
Age
Ethnicity
Behavioral and Lifestyle-Related Risk Factors

Obesity (including distribution of obesity and duration)
Physical inactivity
Diet
Stress
Westernization, urbanization, modernization
Metabolic Determinants and Intermediate-Risk Categories of Type 2 Diabetes
Impaired glucose tolerance
Insulin resistance
Pregnancy-related determinants
Parity
Gestational diabetes
Diabetes in offspring of women with diabetes during pregnancy
Intrauterine malnutrition or overnutrition

Major risk factors of T2DM:-[3]

- Overweight (BMI of 25 kg/m2 or 23 kg/m2 for Asian Americans)
- Physical inactivity
- Diabetes in a first-degree relative
- Member of a high-risk ethnic group (e.g., African Americans, Hispanics, etc.)Native American, Asian American, and Pacific Islander)
- a woman who has previously delivered a baby weighing more than 9 pounds GDM is a kind of diabetes.
- Hypertension (140/90 mm Hg or on hypertension medication)

- triglyceride level 35 mg/dL (0.90 mmol/L) or HDL cholesterol level 35 mg/dL (0.90 mmol/L)or both >250 mg/dL (2.82 mmol/L)
- Polycystic ovarian syndrome (PCOS) is a condition in which a woman's ovary produces too 5.7 percent haemoglobin A1c, impaired glucose tolerance, or impaired glucose tolerance.
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease
- Age over 45

Pathogenetic factors implicated in the progressive impairment in insulin secretion in type 2 diabetes mellitus:-[12]
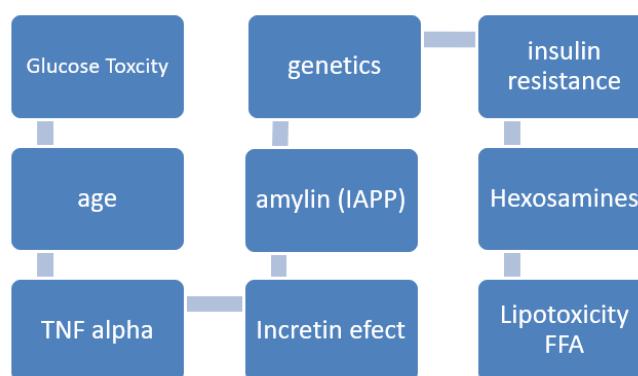

Fig 2

Pharmacotherapy available for type 2 DM:-[13]

Type of agent	Main mode of action	Decrease in HbA1c	Body weight	Problems	Warnings and precautions
Sulphonylureas	Increase insulin secretionc Stimulate pancreatic β-cells by closure of K+ ATP channels	˜1%–2% (11–22 mmol/mol)	Inc.	Hypoglycaemia	Selection restricted by severe liver or renal disease or porphyria
Meglitinides	Increase insulin secretionc,d Usually administered pre-meal: rapid	˜0.5–1.5% (6–17 mmol/mol)	Inc.	Lesser risk of hypoglycaemia (fewer and less severe than sulphonylureas)	Liver or severe renal disease

	onset, short duration of action Stimulate pancreatic β-cells by closure of K+ ATP channels					
Gliptins (DPP-4 inhibitors)	Inhibit DPP-4, allowing increased t½ for incretins, which potentiate nutrient-induced insulin secretion	˜0.5%–1.5% (6–17 mmol/mol)	_		Small risk of hypoglycaemia (seldom severe) when used with other anti-diabetic agents	Dose reduction where necessary in substantial renal or liver disease
Thiazolidinediones (glitazones)	Increase insulin actionb Stimulate PPAR-γ Increase adipogenesis Alter glucose-fatty acid cycle	˜1.0%–1.5% (11–17 mmol/mol)	Inc.		Heart failure, oedema and anaemia, fractures	Cardiac disease, fluid retention and severe liver or renal disease
α-glucosidase inhibitors	Slow carbohydrate digestione	˜0.5%–1.0% (6–11 mmol/mol)	_	_		Intestinal diseases and severe kidney disease
Bromocriptine-QR (quick release)	Not establishedb	˜0.5%–0.8% (6–9 mmol/mol)	_		Fibrotic reactions and hypotension	Psychotic disorders
Colesevelam	Uncertain, may increase GLP-1 secretionc	˜0.5%–0.8% (6–9 mmol/mol)	_		Bile sequestrant	Intestinal diseases
SGLT2 inhibitors	Reduce renal glucose reabsorption Increased glucose elimination in urine Decreased plasma glucose	˜0.5%–1.0% (6–17 mmol/mol)	Dec.		Genitourinary infections (typically transient) and low risk of hypoglycaemia	Moderate-to-severe renal impairment
Parenteral GLP-1 receptor agonistsf	Increase insulin secretionc Decrease glucagon Resistant to	˜0.5%–2.0% (6–22 mmol/mol)	Dec.		Risk of hypoglycaemia when used with other anti-diabetic agents	Not to be used in severe renal or GI disease (e.g. gastroparesis)

	degradation by DPP-4 Potentiate nutrient-induced insulin secretion			and nausea	Discontinue if pancreatitis is suspected
Pramlintidef,g	Decrease gastric emptying Decrease glucagon and satietyf Indicated only as add-on to insulin therapy	~0.3%–0.6% (3–6 mmol/mol)	Dec.	Risk of hypoglycaemia when used with insulin	Contraindicated in gastroparesis or hypoglycaemia unawareness
Insulinsf	Decrease hepatic glucose production Increase peripheral glucose uptake, storage and use Decrease lipolysis	Variable, as required	Inc.	Hypoglycaemia	Substantial lifestyle adjustments and glucose monitoring
Oral Metformin	Decrease insulin resistanceb Reduce hepatic glucose output Increase peripheral glucose use	~1%–2% (11–22 mmol/mol)	Dec./-	Lactic acidosis (rare) and GI intolerance	Renal impairment, acute hypoxemic condition, use of contrast media and severe liver dysfunction

GLP-1 RA(glucagon like peptide-1 receptor agonists)¬:-[14]

Exenatide (twice daily), exenatide extended-release (once weekly), and liraglutide are the most widely available medicines in this class. Because these drugs are peptide hormones, they must be given subcutaneously. As previously stated, GLP-1 analogues stimulate insulin secretion, which is regulated by intracellular glucose levels, and also limit glucagon release from alpha-cells, resulting in a significant HbA1c reduction of 0.8-2.0 percent. However, GLP-1 RA is linked to a number of other positive effects, including a delay in stomach emptying and early satiety, both of which lead to a reduction in oral intake, which could explain the treatment's modest weight loss. GLP-1 RA also has a favourable effect on -cells, as it promotes proliferation and inhibits apoptosis. GLP-1 RA is hypothesised to have favourable effects on the cardiovascular system because to the presence of GLP-1 receptors in the heart, and this occurs independently of glucose management. . In terms of side effects, GLP-1R analogues have been linked to a reduced risk of hypoglycemia when used as monotherapy or in comparison to insulin. When compared to placebo or insulin therapy, there is a higher prevalence of gastrointestinal side effects such as nausea, vomiting, and diarrhoea. One meta-analysis of long-term cardiovascular outcome studies found no evidence of an increase in cardiovascular morbidity when compared to placebo or other medicines. There have

been reports of a short-term risk of acute pancreatitis as well as the possibility of a long-term risk of chronic pancreatitis in patients taking this class of medications; however, patients could have had other causes, and the data available to date does not conclusively prove this risk. Nonetheless, the FDA urges caution when administering these medications to patients and requests that any such incidents be reported. Concerns have also been raised about GLP-1R analogues' proclivity for causing proliferative alterations in rodent thyroid C cells, such as C-cell hyperplasia, adenomas, and Although data in human subjects did not show any elevations in serum calcitonin levels, and there have been no case reports describing medullary thyroid carcinomas in patients receiving GLP-1R agonist treatment, there are no case reports describing medullary thyroid carcinomas in patients receiving GLP-1R agonist treatment. However, more long-term trials on the aforementioned difficulties are needed, as the evidence now available is insufficient. 52 Finally, data on mortality with GLP-1 analogues is scarce, although trials to date imply that there is no increased risk during therapy with such medications.[14]

Dipeptidyl peptidase-4 (DPP-4) Inhibitors:[14]

The incretin system of gut hormones also includes this class of medicines. These function by blocking the breakdown of endogenous GLP-1 and GIP, resulting in higher circulation levels of these hormones, which leads to glucose-dependent insulin secretion and glucagon secretion suppression. The four widely available medicines are sitagliptin, vildagliptin, saxagliptin, and linagliptin, which are all orally active. Because studies have shown that these medications are generally well tolerated, reduce HbA1c by roughly -0.8%, are weight neutral, and are not associated with hypoglycemia on their own, the FDA has approved them for use as monotherapy and in conjunction with other anti-hyperglycemic treatments. DPP-4 inhibitors are appealing for usage in particular groups of persons because of their

pharmacological and pharmacokinetic features. Because they cause glucose-dependent insulin secretion and hence a lower risk of hypoglycemia than SU, as well as the fact that saxagliptin and vildagliptin are metabolised by the liver, they can be taken in elderly patients or those with renal failure. They also have a good general tolerability (when compared to metformin, they have fewer gastrointestinal side effects) and aren't linked to the weight gain seen with SU and TZD use. Furthermore, they are linked to favourable outcomes on surrogate parameters of cardiovascular risk. Triglyceride, HDL-C, and LDL-C levels have showed a good trend in investigations, and emerging results from recent studies and meta-analysis further demonstrate that DPP-4 inhibitors have a positive effect on the cardiovascular system. Patients with coronary artery disease who were given sitagliptin had a higher ejection fraction and better contractile performance in the ischemic areas, according to one study. In addition, DPP-4 inhibitors have been demonstrated to lower blood pressure in a number of trials, and gliptins appear to have a favourable effect on the progression of heart failure in animal experiments that was independent of blood glucose control.[14]

When it comes to the effects of DPP-4 inhibitors on cardiovascular events, two recent meta-analyses have found that they reduce the risk of major adverse cardiovascular events, particularly myocardial infarction, as well as all-cause mortality, and thus are reported as having a safe cardiovascular profile, which is not seen with certain other anti-hyperglycaemic agents. Several further large-scale trials examining the cardiovascular effects of each gliptin are now being planned. The SAVOR-TIMI research, for example, recently published findings indicating that saxagliptin had no effect on the rate of ischemic events. However, individuals who were randomly assigned to the saxagliptin arm had higher incidence of heart failure hospitalisation, which requires more examination. In terms of the link between DPP-4 inhibitors and the

risk of pancreatitis, pancreatic cancer, and C-cell proliferation, data is scarce and inconsistent in human trials, thus further research is needed in this area. According to the research, these innovative medications are proven to be crucial in the treatment Characterised differences between T1DM &T2DM:-[3]

of type 2 diabetes,and that the advantages of DPP-4 inhibitor medication substantially outweigh the dangers, making them important additions to the type 2 diabetes therapeutic arsenal.[14]

Characteristic	Type 1 Diabetes	Type 2 Diabetes
Nature *Very different*	Autoimmune disorder marked by destruction of insulin-producing beta cells and loss of insulin production	A disorder of insulin deficiency involving an interplay between both pancreatic and extrapancreatic contributions to disease
Symptoms *Partial overlap*	Rapid onset; very high to extremely high blood glucose levels; polyphagia; polydipsia, polyurea; ketoacidosis	Mild to moderate onset; modest to high elevations in blood glucose; mild polydipsia/ polyurea; fatigue; visual changes/headache
Onset *Very different* Risk factors *Typically different but overlap*	Sudden (symptoms for days to weeks) Family history of autoimmune disease but in particular, T1D (10-fold increased risk versus general population	Slower onset (symptoms for months to years) Overweight/obese; poor diet; sedentary lifestyle; ethnicity (higher in African Americans, Hispanics); family history of T2D; history of gestational diabetes
Onset age *Typically different but overlap* onset Treatment strategy *Typically different*	Typically early life through adolescence but can occur at any age Absolute requirement for insulin (multiple daily injections or insulin pump); self-management lifestyle modification (monitor food types, exercise, etc.)	Typically adults but trending toward earlier age of Onset Dietary modifications and exercise alongside oral agents (for most); increasingly greater percentage of patients require insulin over time
Can it be prevented? Can it be reversed? *Very different*	Not at present (subject of major research efforts); future cases can be predicted by autoantibodies and genetics Not at present (subject of major research efforts)	Yes, for over half of potential cases, with dietary modifications and exercise No, but for a limited few; patients can see disease managed and risk for complications reduced through diet modifications, exercise; growing evidence for disease improvements through combination therapies
Complications *Mostly similar, but some variation*	Acute emergencies of hypoglycemia and ketoacidosis leading to hypoglycemic unawareness; chronic effects of hyperglycemia can lead to retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.	Acute emergencies of hypoglycemia and ketoacidosis leading to hypoglycemic unawareness; chronic effects of hyperglycemia can lead to retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.

Diabetic neuropathy:-[15]

Diabetic neuropathy is defined as involvement of the cranial, peripheral, and autonomic nerves in people with diabetes; this usually indicates a diffuse, mostly sensory peripheral neuropathy. Nerve function can be affected in a variety of ways, including acute, chronic, transitory, and permanent. The following are the most common clinical implications of neuropathy:

- A different sensation (both pain and I sensitivity to normal sensation).
- Neuropathic ulcers, which most commonly occur on the feet.
- Male erection problems (with autonomic neuropathy).
- Charcot arthropathy(is a type of arthritic condition).

Diabetic neuropathies (DN) are a group of nerve abnormalities caused by diabetes. They are prevalent, with prevalence rates ranging from 5% to 100% depending on the diagnostic criteria. Diabetic peripheral neuropathy (DPN) is linked to a high rate of morbidity, death, and poor quality of life, resulting in a significant financial burden. The duration and severity of hyperglycemia, the existence of dyslipidaemia, hypertension, and smoking are all key risk factors for diabetic polyneuropathy development. Though its many mechanisms underlying various pain sensations are yet unknown, there is ample evidence that aberrant discharges from sick somatosensory neurons are to cause.[16]

Clinical manifestations of diabetic neuropathy:-[17]

Diabetes has a variety of effects on the peripheral nerve system. Because DSP (distal symmetric polyneuropathy) accounts for such a substantial percentage of all diabetic peripheral nerve symptoms, some people confuse the words diabetic DSP with diabetic neuropathy. Numbness, tingling, discomfort, and/or weakness are common symptoms of DSP, which start in the feet and move proximally in a length-dependent pattern (stocking and glove distribution). They even appear to have a dichotomy of numbing and great sensation all at once. Surprisingly, whatever symptom takes precedence varies greatly from patient to patient.[17]

This widespread, debilitating condition has a significant influence on the health-care system. Diabetic neuropathy is predicted to cost between 4.6 and 13.7 billion dollars, with type 2 diabetes accounting for the majority of the costs.[17]

One of the most disabling symptoms of DSP patients is neuropathic pain. It's a difficult condition to cure, therefore it creates a lot of pain for patients and a lot of societal burden10. Diabetic neuropathic pain (DNP) is thought to affect 10% to 20% of the diabetic population overall, and 40% to 60% of those with confirmed neuropathy. However, these figures are likely to be underestimated, as one study found that about 12% of people with DNP never told their doctors about their condition. DNP is characterised by searing, electric, and stabbing sensations with or without numbness, similar to other kinds of neuropathic pain. Allodynia (painful sensations in response to harmless stimuli) and hyperalgesia are common side effects (increased sensitivity to painful stimuli). Despite the availability of numerous effective medicines, less than half of people are treated for pain. Fortunately, there are a variety of neuropathic pain screening tools available to help clinicians identify patients who would benefit from treatment.[17]

Other types of peripheral nerve injury that can occur in patients with diabetes includes:-[16]

- Small fiber predominant neuropathy,
- Autonomic neuropathy,
- Radiculoplexopathy (diabetic amyotrophy),
- Radiculopathy,
- Mononeuritis multiplex,
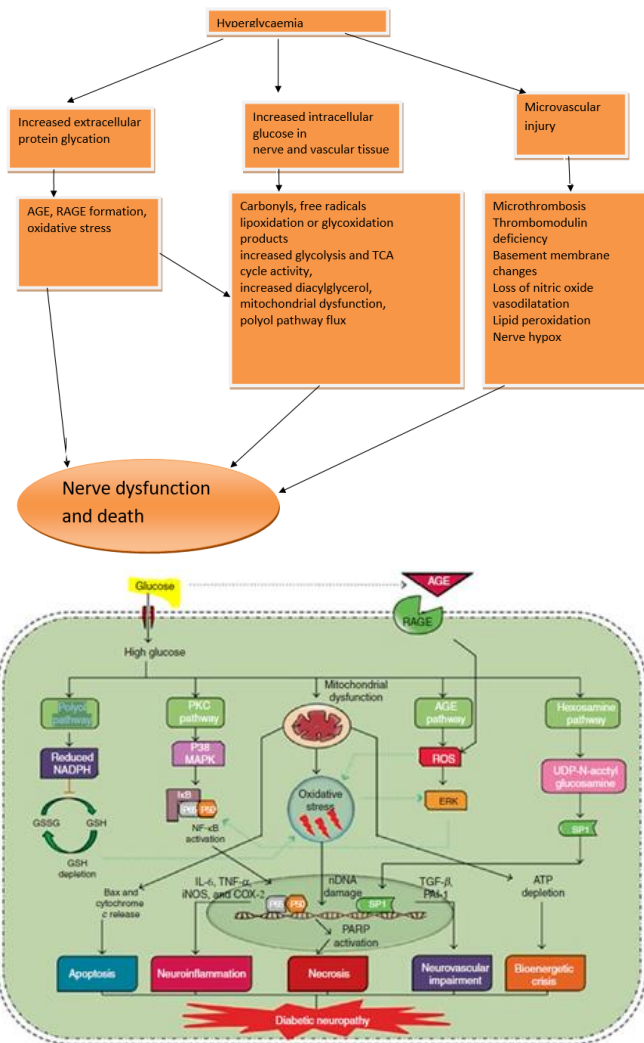- Mononeuropathy,
- Treatment-induced neuropathy.

Fig 3 : Pathophysiology of diabetic Neuropathy[16]

Different types of diabetic neuropathies:-

1. Distal symmetric sensorimotor polyneuropathy

2. Small fiber neuropathy

3. Acute severe distal sensory polyneuropathy

4. Autonomic neuropathy

5. Diabetic neuropathic cachexia

6. Hypoglycemic neuropathy

7. Treatment-induced neuropathy (insulin neuritis)

8. Polyradiculopathy

9. Diabetic radiculoplexopathy

10. Mononeuropathies

11. Cranial neuropathies

Clinical findings and diagnosis :-[18]

A loss of sensation to pinprick, temperature (mainly cold), vibration, and proprioception in a 'stocking and glove' distribution are clinical symptoms of diabetic neuropathy. The delivery of the sensory stimuli to an area where normal responses are expected, such as the forehead, is used to evaluate these sensory modalities first. After then, the stimulus is delivered to the great toe and then advanced proximally up the limb until the sensation returns to normal. Temperature is measured using a cool material, such as a metallic object, whereas pinprick sensation is measured with a sharp object, such as a safety pin, that is discarded after each patient. Vibration is assessed by placing a vibrating tuning fork on the bony prominence on the dorsum of the great toe and noting when it stops vibrating, whereas proprioception is assessed by making little movements of the great toe's distal interphalangeal joint. Small neural fibres are responsible for pinprick and temperature sensations, whereas large nerve fibres are responsible for vibration and proprioception.[18]

Ankle reflex loss occurs early in diabetic neuropathy, so reflex testing should be part of the first assessment. Later, tiny foot muscles and dorsiflexors are found to be weak. Although many patients experience symptomatic weakness, major weakness on examination is only seen in the later stages of advanced diabetic neuropathy. Early neurological dysfunction in the upper limbs should raise the possibility of a mononeuropathy or another diagnosis. [18]

Methods of diagnosis of neuropathy-[19]

Examination name	Examination type	Advantages	Disadvantages
Clinical symptoms & signs	DN4, LANSS, NPQ, MNSI, DNS, TCNS, NDS, UENS	Relevant to the patient, easy to use, inexpensive	Limited sensitivity, high variability
Quantitative sensory testing	CASE IV (WR Medical Electronics), Biothesiometer, Thermoaesthesiometer, TSA Neurosensory Analyser (Medoc Ltd.)	Easy to perform, rapid, noninvasive, evaluates large and small nerve fibers	Variable, subjective, requires special equipment
Sudomotor function	Neuropad (Skyrocket Phytopharma), Sudoscan (Impeto Medical), QSART, sympathetic skin response	Fast, objective, easy to perform, simple, reproducible	Moderate sensitivity, uncertain interpretation
Neurophysiology	NCS of motor and sensory nerves	Objective, widely available	Only assesses large fibers, moderate reproducibility, requires special equipment
Skin punch biopsy	IENFD	Objective, gold standard to assess small fibers	Costly, time-consuming, risk of infections requires specialist equipment and personnel to quantify IENFD
Corneal confocal microscopy	HRT III RCM	Objective, rapid, reproducible, assesses small fibers	Costly, requires specialist equipment

Briefly explained neuropathies:-[20]

· Length-dependent diabetic polyneuropathy
· Autonomic neuropathy in diabetic patients
· CRANIAL NEUROPATHY
· LIMB AND TRUNK NEUROPATHIES
· Proximal diabetic neuropathy of the lower limbs and multifocal diabetic neuropathy length dependent diabetic polyneuropathy

Length-dependent diabetic polyneuropathy (LDDP) typically manifests years after the onset of IDDM, but it frequently reveals NIDDM of mature onset. Numbness, burning feet, pins and needles sensations, and lancinating pains are common early "positive" manifestations of sensory neuropathy, and they are often worse at night and after contact. Sensory neuropathy is completely silent and can only be detected through a thorough neurological examination of the feet. Painless trauma or burns, as well as trophic changes with plantar ulcers or neuroosteoarthropathies, can all reveal neuropathy in these cases. Only in patients with longstanding sensory polyneuropathy, in association with severe sensory loss, can mild distal muscle weakness and wasting due to diabetic neuropathy be observed. Predominantly motor distal polyneuropathy is not a feature of diabetic distal neuropathy. When an associated condition is present, it must be considered. Despite improvements in metabolic markers, established diabetic LDDP is irreversible. At best, sensory deficit remains stable or gradually worsens over time. However, a high proportion of patients witness distressing pains, trophic changes, and autonomic dysfunction. A lower risk of neurological impairment is linked to strict diabetes control.[20]

Autonomic neuropathy

One of the early and sometimes life-threatening signs of diabetic neuropathy is autonomic dysfunction. Resting tachycardia is common in clinical cardiovascular abnormalities; afterwards, the heart rate may revert to normal values, albeit without typical fluctuations. Postural hypotension (a drop in systolic blood pressure of more than 30 mmHg while moving from a lying to a standing posture without an increase in heart rate) can be a very disabling symptom of autonomic neuropathy. Tricyclic antidepressants, which are commonly used to alleviate chronic aches in diabetic neuropathy, might

increase postural hypotension. Because food stagnates in the stomach, gastroparesis can lead to poor diabetes control and hypoglycemia.[20]

Diabetic diarrhoea is watery and happens at night or after meals. It's possible that it'll be accompanied with faecal incontinence. Bladder atony causes a significant residual volume following micturition, which can be made worse by infection. In people with an atonic bladder, retrograde ejaculation is common. Impotence is a prevalent problem in male diabetes patients, which can be assessed with continuous nocturnal penile tumescence and stiffness monitoring. Impotence can be caused by vascular and psychogenic causes, as well as ageing.[20]

Cranial neuropathy

Diabetes ophthalmoplegia, like focal neuropathy in other parts of the body, is uncommon in diabetic patients. Gray reported two cases of ophthalmoplegia out of 500 diabetic patients investigated in 1933, while Waite and Beetham estimated the incidence of oculomotor palsy in diabetics to be 0.8 percent. Oculomotor palsy was found in 0.8 percent of individuals under 45 years old, but 2.1 percent of those over 45 years old. Diabetic ophthalmoplegia affects diabetic people beyond the age of 50 in almost all cases, both insulin-dependent and non-insulin-dependent diabetic patients. The onset is quick, taking only a day or two. Often, the patient would endure pain for a few hours or days before experiencing diplopia. Pain therefore preceded the development of diplopia in 14 of the 25 cases reported by and in 18 of the 22 occurrences of oculomotor palsy recorded by. The pain is usually painful, and it occurs behind or above the eye. It can also be more diffuse, but it always occurs on the same side as the oculomotor palsy. The involvement of the first and second divisions of the trigeminal nerve within the cavernous sinus is frequently blamed for pain. Others propose that activation of pain-sensitive terminals within the third nerve's sheath as it passes through

the cavernous sinus plays a function. After the commencement of diplopia, the pains do not last.[20]

Limb and trunk neuropathies

Trunk neuropathy is either unilateral or principally unilateral. The onset is sudden or quick, and the major symptoms are aches or dysesthesias. The discomfort may be radicular in nature and is exacerbated by contact and at night. Abdominal muscular weakness arises. With the exception of nerve entrapment, isolated peripheral nerve involvement of the limbs is extremely unusual. Sensorimotor deficits in the territory of one or more nerve trunks, radicular, or plexus regions are highly uncommon in diabetic individuals, and necessitate the elimination of alternative causes of neuropathy, including nerve biopsy if necessary.[20]

Proximal diabetic neuropathy of the lower limbs and multifocal diabetic neuropathy

Diabetic people between the ages of 50 may develop proximal neuropathy of the lower limbs, which is characterised by varying degrees of discomfort and sensory loss, as well as unilateral or bilateral proximal muscle weakness and atrophy. This syndrome has been referred to as diabetic myelopath, diabetic amyotrophy femoral neuropathy, PDN femoral-sciatic neuropathy, the Bruns–Garland syndrome, and diabetic lumbosacral radiculoplexus neuropathy since Bruns first described it in 1890. The neurological picture is frequently lopsided and limited to the lower limbs. Acute or subacute onset is possible. The patient reports numbness or pain in the anterior area of the thigh, which is usually burning and worsens at night. Walking and ascending stairs become difficult due to quadriceps and iliopsoas muscular weakness. Quadriceps muscle wasting is a common early symptom. The patellar reflex is no longer active. In most cases, the illness advances over weeks or months before stabilising and spontaneous pain diminishing, sometimes fast. There is a distinct sensory loss over

the anterior portion of the thigh in about one-third of the patients, and a painful contact dysesthesia in the distribution of the cutaneous branches of the femoral nerve in the other two-thirds.Without any discernible sensory loss Most of the characteristics identified by Bruns (1890) and Garland (1955) were later validated, including the generally satisfactory long-term prognosis, regardless of diabetes management quality. Relapses on the other side happened within a few months in one-fifth of the patients we tested for this illness. As a result, PDN has clinical characteristics such as frequent motor involvement, asymmetry of the deficiency, and slow but often incomplete restoration. The symptoms of LDDP, in which motor indications appear only in the most severe instances and never improve, are substantially different.[20]

A multifocal neuropathy (MDN) is seen in a small proportion of diabetic people, with sequential or simultaneous involvement of roots and nerves of the lower limbs, trunk, and upper extremities over weeks or months, occasionally with a relapsing course In most patients, the distal lower limbs are implicated unilaterally or bilaterally, along with a proximal impairment. Nerves in the thoracic and upper limbs are less usually impacted. The protein content in the cerebrospinal fluid is elevated in the majority of individuals. An axonal pattern is visible on electrophysiological testing. Multifocal neuropathy is not limited to diabetic patients, highlighting the importance of ruling out a secondary cause of neuropathy in this situation.[20]

Neuropathic pain caused by damage of peripheral nerve:-[21]

Etiology	Typical syndromes (examples)	Experimental models
Mechanical (compressive/traumatic)	Carpal tunnel syndrome Postsurgical pain Painful radiculopathy Cancer pain Phantom limb pain	Complete or partial nerve transection, chronic constriction or compression of peripheral nerves
Metabolic/ischemic	Diabetic polyneuropathy Vitamin B12 deficiency	dPNP: hyperglycemic condition or streptozotocin induced; genetic models
Inflammatory (infectious/autoimmune)	Post-herpetic neuralgia HIV neuropathy Leprosy Guillain–Barré Syndrome Critical illness polyneuropathy	Injection of viral proteins or cells systemically or specifically to e.g., sciatic nerve Rat sepsis model
Toxic	Chemotherapy-induced peripheral neuropathy Alcoholic neuropathy	Injection of drugs or ethanol, systemically or specifically to, e.g., sciatic nerve
Radiation	Post-radiation neuropathy	X-radiation on peripheral nerves of the mouse
Hereditary	Charcot–Marie–Tooth disease Fabry disease	Genetic model (e.g., α-GAL-deficient mice for Fabry disease)

Diabetic painful neuropathy & autonomic dysfunction:-[22]

In the same patient, DPN and autonomic neuropathy coexist. Using Autonomic Functions Tests (AFT), our research discovered that there is no difference in autonomic dysfunction between painless and painful diabetic neuropathy. Painful DPN is associated with much more autonomic dysfunction than painless DPN, according to a recent study. However, differences were discovered utilising spectrum analysis of HRV (a basic test based on a 5-minute ECG recording) rather than traditional AFTs. The

increased autonomic dysfunction reported in painful DPN could be due to a higher prevalence of small fibre involvement, adding to the accumulating body of evidence that small fibre involvement plays a role in the pathophysiology of painful DPN. This could be explained by the fact that tiny fibres (which modulate pain sensation and autonomic function) are either weakly myelinated or unmyelinated, making them more prone to diabetic neuropathy's pathologic processes.[22]

Diabetic peripheral neuropathy & Skeletal muscles functions :-[23]

In this patient population, prolonged DPN is known to cause substantial skeletal muscular impairments, including neurogenic muscle atrophy, loss of muscle strength, power, and endurance. These elements work together to cause altered gait and balance, Pharmacotherapy for Diabetic neuropathy:-

Treatment protocol for neuropathic pain:-[24]

which is especially relevant for individuals with DPN because falls frequently result in bone fractures and persistent infections, which may need amputation. The current level of information about the effects of DPN in skeletal muscle impairment was addressed. The rapid loss of motor axons is a prominent effect of DPN on skeletal muscle. The intrinsic foot muscles and leg dorsiflexors, as well as the intrinsic hand muscles, have all been observed to lose motor units. When compared to age-matched healthy control subjects, the loss can be as high as 50%. When compared to individuals with DM who do not have neuropathy, people with DPN had more motor unit losses. The conventional pattern of reinnervation after denervation increases the size of existing motor units as indicated by the motor unit potential.[23]
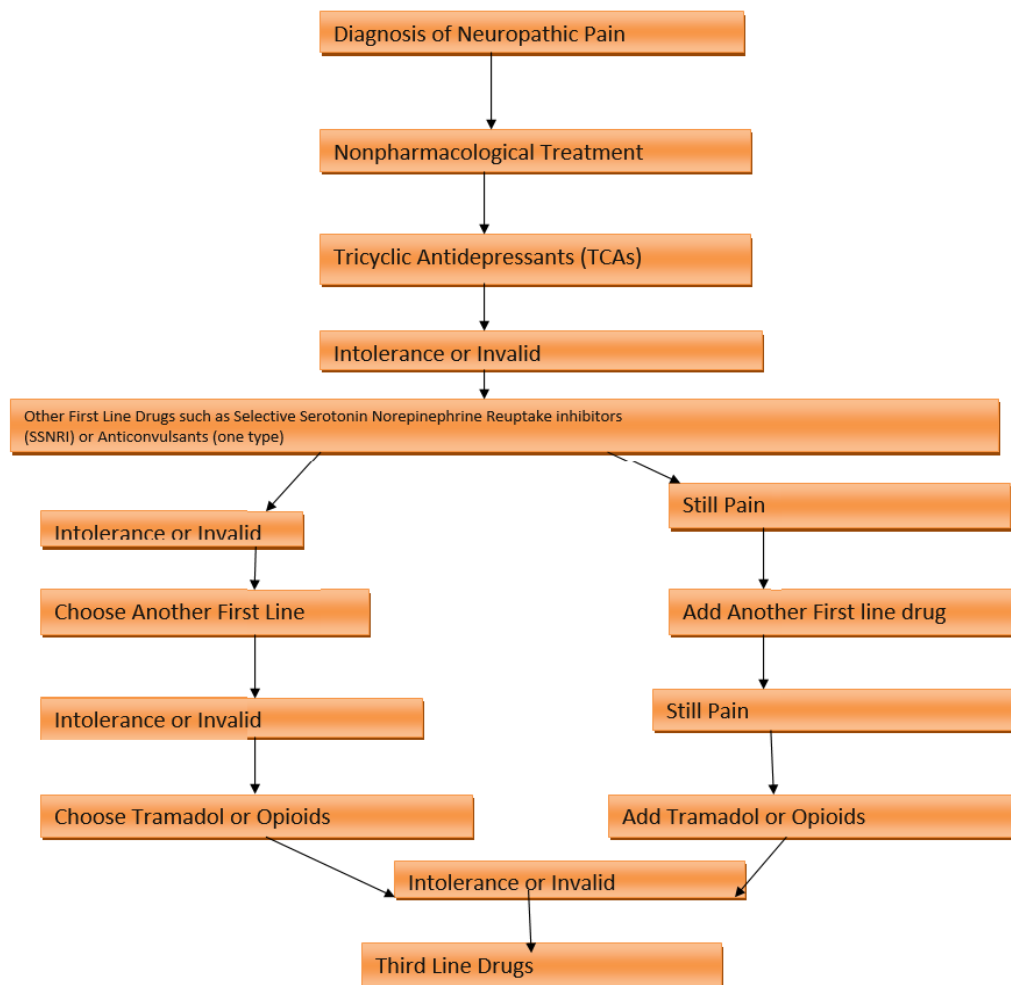
Pharmacotherapy for painful diabetic neuropathy:-[25]

Drug	Dose range	Starting dose	Dose escalation	Mechanism
Pregabalin	150-600 mg	75 mg bid	Escalate to 150 mg bid within 1 week of initiation based on tolerability; *Max Dose*: 300 mg bid	Inhibition of voltage gated calcium channel and ATP gated potassium channel
Gabapentin	300-3600 mg	300 mg daily (Day 1)	Day 2: 300 mg bid; Day 3: 300 mg tid; *Max Dose*: 1800-3600 mg/day in 3 divided doses.	Inhibition of voltage gated calcium channel
Duloxetine	60-120 mg	30 mg bid	Lower dose based on tolerability. *Max Dose*: 60 mg/day.	SNRI
Venlafaxine	37.5-225 mg	37.5 mg bid	Escalate to 150 mg daily: *Max Dose*: 225 mg daily	SNRI or SSRI at low doses
Amitriptyline	10-150 mg	10 mg daily at bedtime	*Max Dose*: 150 mg daily at bedtime	Inhibition of voltagegated sodium channels, NDMA receptors, and reuptake of serotonin and norepinephrine
Tapentadol	100-250 mg	50 mg bid	Escalate to 100-250 mg bid as tolerated; *Max Dose*: 250 mg bid	μ-opioid receptor agonist and norepinephrine reuptake inhibitor Addiction, paradoxical hyperalgesia, respiratory depression
Topical Capsaicin	0.075-8%	Apply 4 times daily	Not applicable	Vanilloid receptor agonist
Topical Lidocaine	5%	1 patch every 12 hours	12-hour patch free interval. *Max Dose*: 3 patches daily	Inhibition of voltage gated sodium channels.
α-Lipoic acid Actovegin	100-1800 mg 600- 2000 mg	600 mg 600 mg tid	Not applicable Not applicable	Antioxidant Anti-hypoxic agent

Management of diabetic foot complication:-[26]
All patients with peripheral neuropathy should consider early detection and education. The most significant measure that doctors can take to lessen the risk of ulceration and amputation in diabetic patients is to check their patients' feet without shoes and socks at every appointment. Patients with known risk factors, podiatric treatment, and general preventative foot self-care education can completely avoid neuropathic foot disorders. Diabetic individuals at high risk, such as those with severe neuropathy or

amputation history, should wear specialised therapeutic footwear.[26]

Conclusion

DPN is a complicated and complex condition in which a variety of variables, including hyperglycemia, play a role. Bedside diagnostics and electrophysiological tests are used to diagnose DPN. It is treated using a combination of symptomatic, pharmacological, and non-pharmacological therapies,

as well as pathogenic, such as ALA, benfotiamine, and antioxidant therapy.

CAN, diabetic foot, neuromuscular impairment, anxiety, and its negative effects on QoL are the most common consequences of DPN. Complication management and patient education are crucial aspects of DPN management.

Agents from the TCA, SNRI, and Gabapentanoid medication families are currently indicated therapy with the most considerable clinical evidence. Even these medicines, however, have only a limited efficacy, which is frequently countered by unacceptable adverse effects. Furthermore, the evidence for mixing drugs is poor, despite the fact that this is a typical occurrence in clinical practice. . There is an urgent need for more well-conducted, big head-to-head comparative trials and combination trials of existing treatments. A variety of new therapeutic targets are currently being developed. Future clinical trials, on the other hand, should include procedures for detecting placebo effects to ensure that the genuine treatment benefit is recorded. Although substantial progress has been made in the last decade in terms of both customised diagnosis and therapy for T1D, significant challenges and research gaps still exist,between where we are today in terms of knowledge and where we want to go into a common clinical benefit. As in many other cases,Precision medicine for T1D is a new and

promising treatment option, a burgeoning field Boosts ethical, social, and legal concerns as well as the need to identify exact measures to preserve subjects' privacy personal health data's privacy and confidentiality. Furthermore,Patients must be aware of and comprehend the risks. Diabetes is one of the most frequent health conditions, especially among the elderly. Although drug-induced diabetes is unlikely to be eradicated, we expect that multiple-drug regimens will enhance glucose management in the affected population. Better glycemic management, we think, will result in a significant reduction in the number of diabetic complications in the general population.

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