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# A COMPREHENSIVE REVIEW OF MICROVASCULAR AND MACROVASCULAR COMPLICATIONS IN DIABETES

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## ABSTRACT

Diabetes Mellitus (DM) is a common chronic metabolic condition marked by long-term elevated blood glucose levels due to impaired insulin secretion, insulin action, or a combination of both. The condition can be classified into two main types: Type 1 diabetes (T1DM), an autoimmune disease leading to the destruction of insulin-producing beta cells, and Type 2 diabetes (T2DM), which is primarily caused by insulin resistance and subsequent pancreatic beta cell dysfunction. The global prevalence of diabetes has been rising, largely due to urbanization, sedentary lifestyles, and unhealthy dietary patterns, contributing to an increased burden of both morbidity and mortality. Diabetes complications can be classified into **macrovascular** and **microvascular** categories. Macrovascular complications include coronary artery disease, stroke, and peripheral artery disease, all of which contribute to cardiovascular morbidity and mortality and Diabetic foot. Microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy, significantly impact patients' quality of life and can lead to irreversible organ damage if not properly managed. These complications arise from the chronic exposure of tissues to hyperglycemia, leading to inflammatory, oxidative stress, and advanced glycation end-product formation, which damage blood vessels and other tissues. Effective management of diabetes requires a multifaceted approach, including lifestyle modifications, glycemic control, and pharmacotherapy. Early detection and intervention are crucial to prevent or delay the onset of complications. The need for innovative therapies and continuous research into diabetes pathophysiology, along with improved strategies for the prevention and management of its complications, remains essential in combating the global diabetes epidemic. This review provides a comprehensive overview of the pathophysiology, clinical presentation, and management of diabetes mellitus and its associated complications, with a focus on recent advances in understanding and treatment strategies.

**Keywords:** Diabetic Mellitus, Diabetic Complication, Hyperglycaemia, Macrovascular, Microvascular.

## I. INTRODUCTION

In 2011, 366 million individuals globally were estimated by the International Diabetes Federation to have diabetes; by 2030, that number is expected to have grown to an astounding 552 million. Diabetes caused 4.6 million deaths and 11% of adult healthcare costs in the United States in 2011. By 2030, there will be an astounding 552 million diabetics globally, up from an estimated 366 million in 2011, according to the International Diabetes Federation. Diabetes caused 4.6 million deaths and 11% of adult healthcare costs in the United States in 2011. Type1 diabetes (T1D) and type 2 diabetes (T2D) are becoming more common, making diabetes complications one of the most significant public health concerns of our day. Acute, potentially fatal illnesses like extreme hypoglycemia or ketoacidosis are just one type of diabetic consequences; chronic, incapacitating issues that impact several organ systems include retinopathy, nephropathy, neuropathy, and cardiovascular disease. The length of time that diabetes lasts and the level of glycemic control attained are related to the risk of complications. Glycated hemoglobin, or HbA1c, is a marker of glycemic control that is typically measured over a period of two to three months. Notably, different people with diabetes have different susceptibilities to complications, and in certain situations, problems might arise even in those with lower HbA1c values, which is thought to indicate adequate glycaemic control. Diabetes-related cardiovascular disease (CVD) is a leading cause of death. One of the leading causes of death among people with diabetes is cardiovascular disease (CVD). People with diabetes with CVD not only have a higher incidence of CVD than the

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general population, but they also have worse outcomes than people without diabetes. Notably, different people with diabetes have different susceptibilities to complications, and in certain situations, problems might arise even in people with lower HbA1c values, which is thought to indicate adequate glycemic control. Diabetes-related cardiovascular disease (CVD) is a leading cause of death. People with diabetes with CVD have worse outcomes than people without diabetes, in addition to having a higher incidence of CVD than the general population. It is especially concerning how common cardiovascular risk factors are in young diabetics. People with diabetes with CVD have worse outcomes than people without diabetes, in addition to having a higher incidence of CVD than the general population. It is especially concerning how common cardiovascular risk factors are in young diabetics. Perhaps as a result of rising insulin resistance brought on by obesity and its pro-inflammatory effects, the global rise in obesity not only raises the incidence of T2D but also increases the risk of complications for people with T1D overall. Thus, a deeper comprehension of the part insulin resistance plays in T1D may lead to better treatment strategies and the possibility of fewer long-term issues. Improved therapy methods and the possibility of fewer long-term problems may result from a better knowledge of the function of insulin resistance in T1D. Although cardiac autonomic neuropathy is not well understood, it could be important in understanding cardiac events in diabetics and could also identify new therapeutic targets for the prevention and treatment of CVD in diabetics. Additional treatment and preventative techniques are urgently needed since diabetes increases the risk of heart failure even in the absence of coronary artery disease. Although cardiac autonomic neuropathy is not well understood, it could be important in understanding cardiac events in diabetics and could also identify new therapeutic targets for the prevention and treatment of CVD in diabetics. Death and disability may result from diabetic nephropathy, retinopathy, and neuropathy, among other microvascular consequences of diabetes.

## II. MICROVASCULAR COMPLICATIONS

### 1. DIABETIC NEPHROPATHY:

Diabetic nephropathy (DN) conclusively ranks as one of the most common and debilitative complications of diabetes mellitus (DM) and correlates with increased disability and death rates among diabetes patients. In the United States, the population of diabetic patients who initiate renal replacement therapy for end-stage renal disease (ESRD) has congruously increased within the years stated from over 40,000 in 2000 to above 50,000 in 2014. Like other countries, the incidence and prevalence of DN in China has been on the exponential rise in the last ten years. In China the number of patients estimated to have diabetes associated chronic kidney disease (CKD) reaches 24.3 million patients [3]. In general, the number of people living with diabetes is on the rise across the vast expanses of the world, particularly in low-income countries. However along with the increasing number of diabetic patients, an increase in the number of DN cases is also expected unless there is a drastic change on how clinical approach to the prevention of DN is conducted. After a certain period of time - which may range from a few within DN one-third patients to several years within the whole population of patients developed with diabetes - DN develops. Whether individuals should be screened to find microalbuminuria, or rather screened to predict DN, that is the personalized medicine approach that directs resources to more intensive therapy and early preventive measures only to the ~these interventions are costly and are aimed at that at risk individuals By the time microalbuminuria most commonly occurs, there has been significant advancement in the histological features of glomerulopathy; conversely, a significant portion of patients with microalbuminuria go on to normalize their urinary albumin levels. The diagnosis of DN is also complicated by the fact that there are many cases with DN, which do not fit the classical definition of], DN and informally the pathology of DN has been noticed in patients who have no evidence of idiopathic retinopathy – such patients reach 40% prevalence. In patients with type 2 diabetes diabetes mellitus 'non proteinuric' DN and DN without retinopathy are predominant. This is typically due to the therapy for blockade of the renin-angiotensin system RAS – almost in every patient it is initiated only after development of obvious persistent albuminuria albuminuria = 300mg/day 7. However, in patients without albuminuria, there are difficulties with determination of the appropriate time for intensification of curative measures. The pathogenesis of diabetic nephropathy DN is very multifactorial and remains incompletely known which translates to ineffectiveness of treatment strategies Dary and Nimatova reported bsc1028 goals September 2012. The means of treatment, which includes tight glycemic control and hypertension management, has been proven in unable to halt the

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progression of diabetic nephropathy to end stage renal disease ESRD 14, and diabetic nephropathy-related deaths 15. This is because there are several pathways involved in the progression of diabetic nephropathy DN extending beyond its cause. Diabetic nephropathy DN 16, intertwining oxidative, angiotensin II (Ang-II) and inflammatory interactions; all recently have been raised to a crucial focus 17. Awareness of the main components of such processes would also enable to find new promising targets and would assist in the development of other anti-inflammatory medications aimed at treatment of DN 17. This article provides an overview of the mechanisms that contribute to diabetic nephropathy, including the involvement of oxidative damage, angiotensin-II, pro-inflammatory cytokines and acute phase proteins and discusses treatments currently available and in development, specifically related to inflammation.

**Epidemiology:**

Patients suffering from type 2 diabetes mellitus may have albuminuria when their diabetes is diagnosed, but it is after 15 to 20 years after diagnosis that diabetic nephropathy in seen in type 1 diabetes patients. The main reason for this anomaly is that the more accurate the precise nidi of type 2 diabetes is there but will always be a variation in these due to individual differences. The right kidney of a diabetic individual suffers a number of structural and functional changes which bring about protein urea, hypertension, and a gradual fall in glomerular function- which is the cause of diabetic nephropathy. Some racial groups including but not limited to African Americans, Native Americans, Mexican Americans seem to be on the greater spectrum of diabetic nephropathy. There have been previous investigations reporting the occurrence of clustering within families, suggesting subsidiary tool the influence of genetic factors in nephropathy.

**Pathophysiology and Stages**

The process of diabetic nephropathy begins with a sequence of stages:

- Hyperfiltration Stage: Primarily, hyperglycemia hails the glomerular hyperfiltration, which is the principal event for increased GFR. After that, increased pressure occurs by which the glomeruli structure is changed.
- Microalbuminuria (Incipient Nephropathy): This phase is indicated by the presence of 30-300 mg of albumin in the urine over 24 hours which is one of the first symptoms of kidney harm. At this stage, renal function is still good, but without intervention, it will worsen.
- Macroalbuminuria (Overt Nephropathy): The albumin levels rise above 300 mg/day that expresses a dangerous level of kidney injury too. GFR is on the decline, thus the kidney function is reduced
- End-Stage Renal Disease (ESRD): If the nephropathy is not properly treated then the ESRD emerges, which prompts dialysis or a kidney transplantation.
- Poor Glycemic Control: High blood sugar is the main cause of diabetic nephropathy.

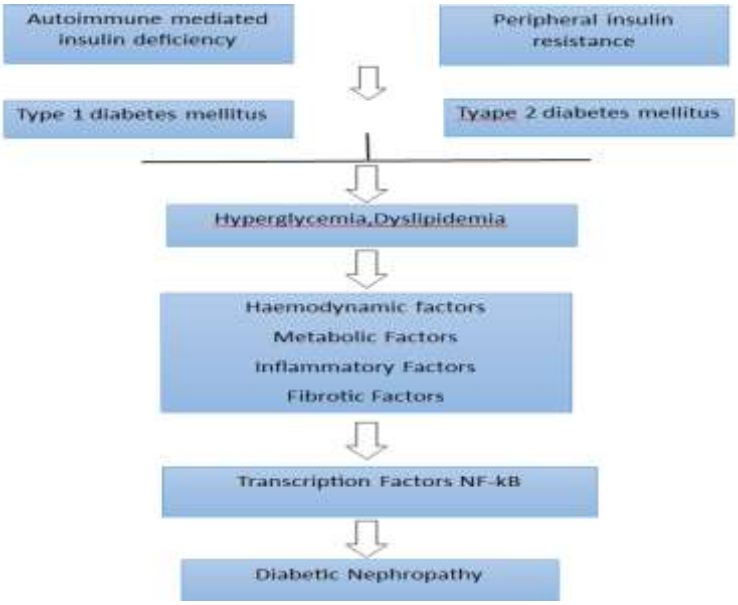


**Fig 1:** The Schematic overview of inflammatory mechanism in the pathophysiology of diabetic nephropathy

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**Risk Factors**:

- Glycemic management: The risk of nephropathy increases with the increase in HbA1c and the number of years living with Diabetes Mellitus.
- Hypertensive heart disease: It is one of the major risk factors with amuch more emphasis on the chances of progression. Among Type 1 and Type 2 diabetics, the prevalence of Hypertension is up to 40%.
- Hyperlipidemia: A recent study showed that hypertensive individuals with proteinuria had higher serum cholesterol levels.
- Obesity: the higher the body weight of patients with diabetes, namely their BMI, the higher the frequency of occurrence of albuminuria. - Tobacco smoking: The incidence of these diseases, such as diabetic nephropathy, is about one and half times higher in smokers than in non-smokers.
- Epidemiological risk factor: Genes such as ACE, ApoE and ELMO1 have been reported to be responsible for nephropathy however, this calls for more evidence. The risk factors are essential in the management and treatment of diabetic nephropathy since there is great emphasis on managing diabetes as a whole and changing lifestyle.

**Diagnosis and Management:**

In patients with classical diabetic nephropathy, the therapy has largely remained glucose and blood pressure control-based treatment aimed at preventing further deterioration of DN and achieving a decrease in albumin excess excretion. This target of albuminuria regression is predicated on the view that a reduction in albuminuria amongst diabetic patients is associated with improved renal and cardiovascular disease outcomes. Most unfortunately this model of therapy has been demonstrated to slow the rate of development of the disorder in question without stopping it or reversing its changes, thus the increasing prevalence of DN. From a series of cross-sectional studies conducted in a Japanese diabetic population, it was revealed that patients with diabetic nephropathy increased from 18.5% in 1996 to 25.6% in 2014. Nevertheless, that proteinuria is still a strong predictor of eGFR decline and hence remains our major target of renoprotective therapy, more so when renal function is moderately to severely impaired. Development of kidney disease in diabetic patients has imprinted the onset and persistence of proteinuria as one of the most significant risk factors. In addition to the above measures, other nonspecific measures must still be implemented, such as weight loss and protein restriction, lipid lowering and cessation of smoking. It is clear that overweight and obesity promote hyperfiltration and hormonal dysregulation with fat derived cytokines that encourage DN. Decreasing the weight of obese diabetic patients has been linked with lower levels of albuminuria. In NP-DN patients, the underlying abnormality is mainly vascular, as is the principle of targeted therapy and various cardiovascular risk factors that are familiar among diabetic patients. In recent years, the use of compounds such as heparin or heparin derivatives and antibody therapy aiming therapy at diseases such as glomerular vascular syndrome has been explored as pharmacologic DN alternatives.

- **Blood Glucose Control**

**Target of Hemoglobin A1c (HbA1c)**

An appropriate glucose level is one of the basic measures in the prevention of DN development and progression. The findings of the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) demonstrate that intensive therapy lessens the incidence of diabetic microvascular complications, including DN. The UKPDS focused on establishing a causal relation between the change in risk of diabetes complications and glycemic levels without any indication of what would be a 'safe' level of glycemia. In contrast to this finding, which was linear, the results of ADVANCE showed a J shaped curve between the levels of HbA1c and micro vascular complications risk. For maximum HbA1c levels of 6.5%, there was no indication of the incidence of microvascular complications being lower; however, microvascular complications where present in cases where HbA1c was above 6.5%. For every increase in HbA1c of 1% the risk of developing microvascular complications was increased by 40%. Hence, the HbA1c target that is frequently recommended by the American Diabetic Association (ADA) is 7.0%. The Kidney Disease Outcomes Quality Initiative (KDOQI) advises that treatment intensity should be tailored according to specific patient characteristics to reduce the chances of severe hypoglycaemia.

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**Antidiabetic Drug Options**

Controlling blood glucose levels in patients with CKD, particularly those with decreasing kidney function, remains a complex task which requires an even more precise approach in terms of selecting the therapy. Patients suffering from diabetic nephropathy tend to be older, have had diabetes for a longer period of time, and more often than not have associated pathologies, hence the risk of adverse effects while using insulin sensitizers is quite high. Although the number of therapy options has considerably increased recently, it is still less in comparison to other conditions. It is also important to understand what drugs can safely be used in such patients and how renal dysfunction modifies the pharmacokinetics of these medications. Usually, the use of insulin is encouraged. Nonetheless, certain oral anti-diabetic medications are still possible to use as long as the GFR of the patient is taken into consideration. First generation sulfonylureas like Glipizide and Gliclazide may be used in patients with renal failure because they are ingested in the body and predominantly absorbed by the liver and merely pass out in inactive forms in the urine. If the GFR is less than 30 cc/minute, glipizide should be prescribed with caution; glimepiride should be prescribed with caution when GFR is 60 cc/minute or less but avoided altogether when GFR is below 30 cc/minute while gliclazide can be prescribed without dose modification. Repaglinide by its mechanism can be started at the usual dose and does not require a dose adjustment (greater caution is exercised if the GFR is below 30 cc/minute). Incretin-based treatment (DPP-4 inhibitors, GLP-1 agonists) in general is accompanied with some dose modification for some drugs, whereas SGLT2 inhibitors are avoided in patients with GFR < 45 cc/minute.

**Blood Pressure Control: -**

Recent study Vasiliev, for example in regard to the UKPDS study, showed that narrowing of 10 mmHg in systolic blood pressure could offer protection from the diabetic microvascular complications such as nephropathy. Since almost every diabetic plague with hypertension, the American Diabetes Association has advised to target blood pressure to less than 140/90 mmHg. For instance, patients suffering from diabetes in the absence of albuminuria are permitted to have BP of less than 140/90 mmHg, however, in presence of albuminuria, the permissible BP level as KDOQI guidelines is ≤130/80 mmHg. Further the KDIGO 2012 edition also maintained the ranges of blood pressure, kinking up the levels irrespective of the cause for all patients with proteinuria. In the case of a target like this one, a subgroup of RAAS blockade therapy, namely so-called Ang-II receptor antagonists (ARBs) or angiotensin converting enzyme (ACE) inhibitors has been proposed. It should be noted, and this is not a large number of studies, but there is a small number of studies that support that RAAS suppression is the most efficient measure which aims to delay DR from progression to ESRD. Some other studies like IDNT, RENAAL, IRMA-2, ROADMAP and Captopril study produced data which confirmed effective management of the progression of DN. However, combining ARBs with ACE inhibitors is generally not recommended because evidence is limited on the use of these two classes of drugs together for the treatment of any cardiac diseases or diabetic kidney disease rather than one alone, and due to increased side effects like hyperkalaemia. Finally, is also a nondihydropyridine calcium channel blocker Diltiazem, which is available.

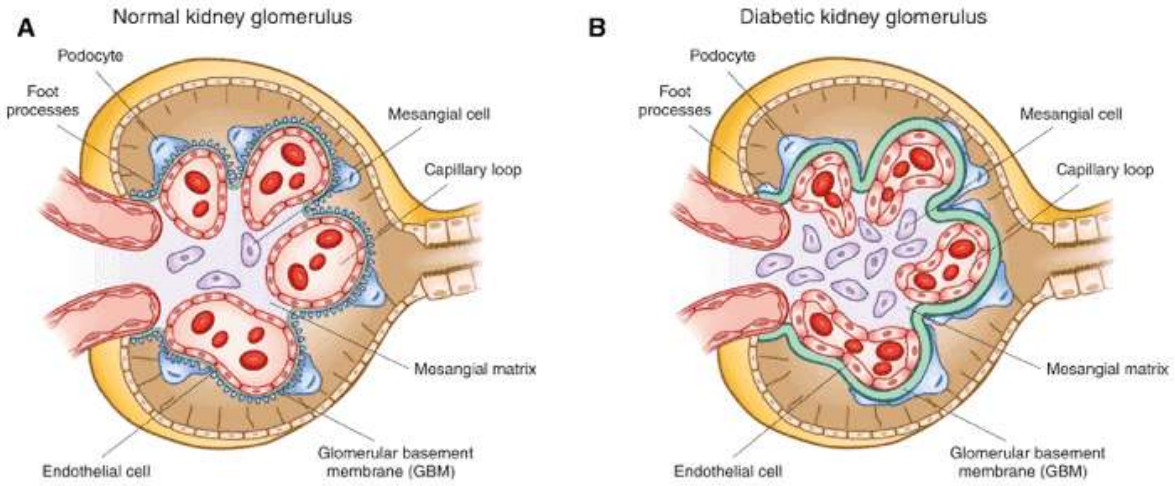


**Fig 2:** Diabetic Nephropathy

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## 2. DIABETIC RETINOPATHY

Diabetic retinopathy (DR) which develops in many patients with diabetes mellitus (DM) is a significant cause of visual impairment among those of working age. The term DR is applied only after specific signs and symptoms of abnormal blood vessels in the retina have been observed by the practitioner. Generally, in practice, there are two stages of DR. Non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are two common types of diabetic retinopathy. NPDR is an abbreviation for non-proliferative diabetic retinopathy, which is defined as the first stage of DR that involves primary retinal vascular changes with raised capillary permeability and capillary occlusion. This stage draws retinal findings such as microaneurysms, hemorrhages, and hard exudates detectable on fundus photographs of asymptomatic patients. In PDR, the most advanced stage of DR, new blood vessel growth – neovascularization – is commonly present. At this point in time, the patients risk extreme vision loss because of bleeding from newly formed atypical vessels into the vitreous cavity, or fluid traction causing retinal detachment. The key factor behind blindness among patients with DR is diabetic macular edema (DME). DME is the clinical term used to describe the sweliing of the macula due to the buildup of either intraretinal or subretinal fluid within the macula due to rupture of the blood retinal barrier (BRB). DME is present in different forms across all stages of diabetic retinopathy and it typically causes visual disturbances or blurry vision. Current treatment strategies against diabetic retinopathy focus on stopping the progression of microvascular complications: intravitreal injection of drugs, laser photocoagulation and vitreous surgery. Currently, anti-VEGF injections are commonly used in the management of all stages of diabetic retinopathy. Anti-VEGF therapy, on the other hand, offers the potential for improved vision whilst causing fewer effects on the eye than traditional therapies such as laser therapy which mainly aims to maintain visual stabilization. However, data from the Diabetic Retinopathy Clinical Research Network (DRCR.net) study (Protocol I ) revealed that only 29% of DME patients who were treated for two years with anti-VEGF therapy were able to achieve ≥3-line improvement in best-corrected visual acuity (BCVA). This ineffectiveness to treatment with anti-VEGF is probably due to already existing other molecular pathways aside from VEGF that plays a role in the development of DR. Research in the field of diabetic retinopathy (DR) and its complications is significant in exploring the possible new elements, which may be useful in creating novel therapy options. In this article, we provide a brief overview of what is known and what new information has been acquired regarding the pathophysiology of DR. Also, novel therapeutic targets and putative drugs that are currently under active investigation in clinical trials will be mentioned.

**Epidemiology:**

One of the most prevalent microvascular complications of diabetes is diabetic retinopathy, which is a leading cause of blindness among the working age. Based on the most recent epidemiological survey report from the American Academy of Ophthalmology, all diabetics across the globe are estimated to be 387 million in 2012, and is expected to increase to 592 million by the year 2035. Diabetic retinopathy currently affects an estimated twenty-five million people in the United States. The prevalence of diabetic retinopathy is 77.3% among those with type 1 diabetes and 25.1% among those with type 2 diabetes, of which approximately 25 to 30 percent have sight threatening diabetic macular oedema Laser treatment for cystoid macular edema due to diabetic retinopathy is recommended for only 5% to 8% of patients with diabetic retinopathy. Vitrectomy surgery will be necessary for as much as 5% of these patients

- **Pathophysiology of Diabetic Retinopathy**
- Non-proliferative diabetic retinopathy (NPDR): This phase is the initial period whereby the injury of the retinal blood vessels leads to the occurrence of microaneurysms, hemorrhages, and the retina is edematous as a result of the leakage of a fluid from the blood vessels to the retina, respectively.
- Proliferative diabetic retinopathy (PDR): In the advanced form, new, already weak blood vessels begin to develop on the retina and the optic nerve. These fragile vessels can rupture, hence the reason for severe vision loss or worse, the person can go blind.
- DR is due to several factors, and some of them are constant hyperglycemia, oxidative stress, and inflammation, all of which cause the deepening vascular damage in the retina. Overexpression of vascular

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endothelial growth factor (VEGF) is the prime factor responsible for creating new abnormal blood vessels that impair DR.

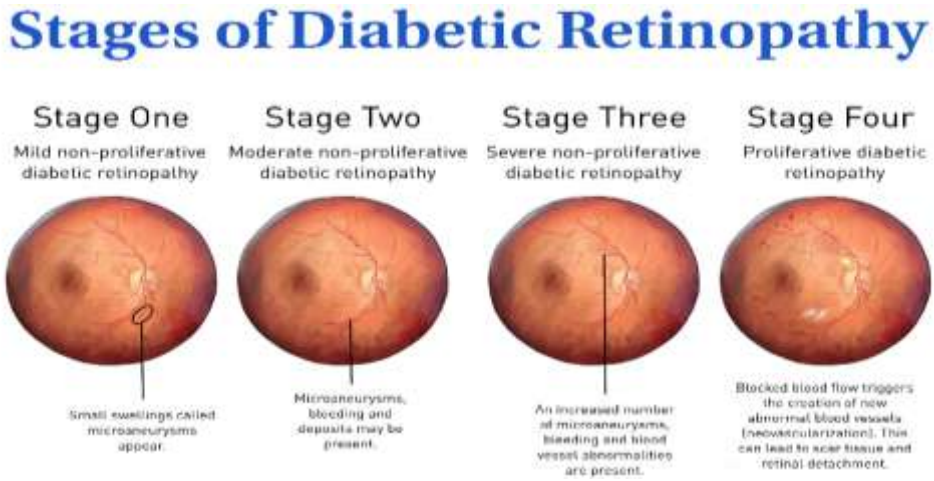


**Fig 3**: Stages Of Diabetic Retinopathy

- **Diabetic Retinopathy Associated Problems**

Diabetic retinopathy has several ocular complications.

1. **Macular Edema**: Swelling at the macula due to its fluid absorption affecting central vision to a great extent.
2. **Vitreous Hemorrhage**: Fatigue of the eye may occur when thin walls of blood vessels bleed into the vitreous causing occlusion of sight.
3. **Tractional Retinal Detachment**: Layers of the eye may begin forming scar tissues that may later on lead to unexpected retinal detachment and loss of vision if quick medical intervention is not sought.
4. **Neovascular Glaucoma**: There are new formed blood vessels which cause forward displacement of the iris in the eye creating an angle which blocks the exit route of eye aqueous hence leading device intra ocular hypertension and subsequent optic nerve injury. This patient is afflicted by complications of diabetic retinopathy.

- **Risk Factors:**

The risk factors for diabetic retinopathy can be grouped into the following categories:

1. Non-modifiable caste
2. Caste and disposal system
3. Bars and Its Side Effects
4. Modifiable
5. High blood pressure
6. Overweight
7. Abnormal cholesterol levels
8. Control of blood sugar levels
9. Kidney dysfunction
10. Infection
11. Apo Lipo Proteins
12. Excess of hormones such as leptin and adiponectin
13. Cholecalciferol
14. Free radicals
15. Family history and other factors

- **Diagnosis of Diabetic Retinopathy**

The diagnosis of diabetic retinopathy requires a comprehensive optic examination that includes the following:

1. **Dilated Fundus Examination**: This aids in directly observing the retina and blood vessels for the presence of microaneurysms, hemorrhage, or neovascularization.

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2. **Fluorescein Angiography:** A fluorescein is injected intravenously to the subject and its diffusion in retinal vessels is recorded with the aim of water movement and leakage or occlusion of vessels in the retina.
3. **Optical Coherence Tomography (OCT**): This technique shows crossed images of the retina and defines areas of the retina that have developed swelling the presence of fluids.

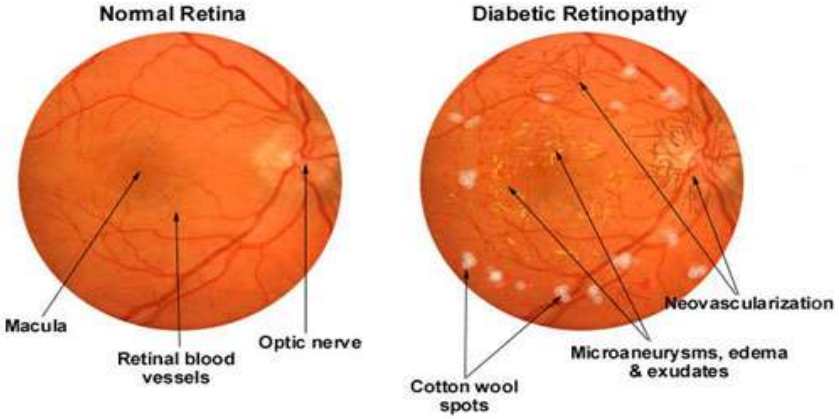
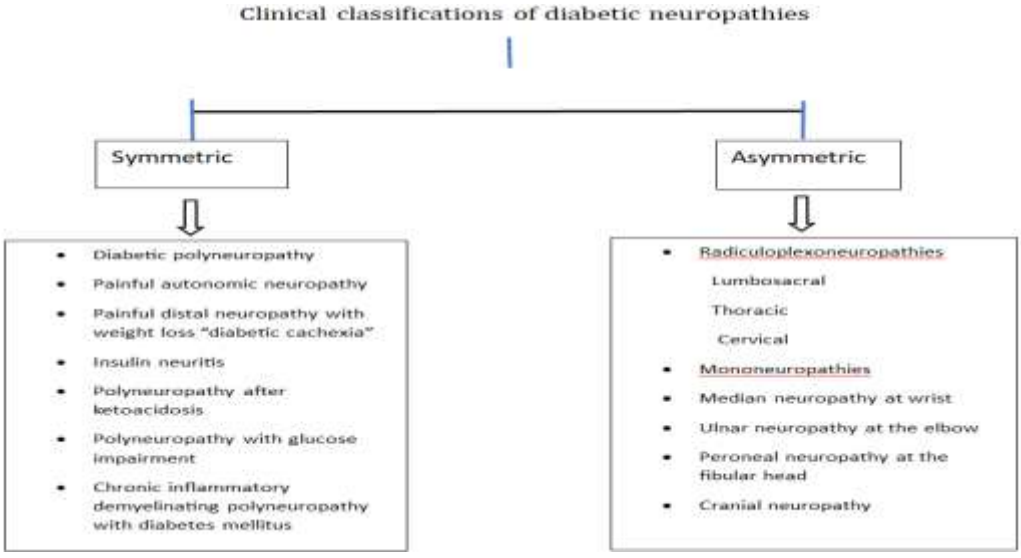



**Fig 4**: Diabetic Retinopathy

### 3. DIABETIC NEUROPATHY

Diabetic neuropathy is a disease that has the potential to affect most if not all patients with diabetes. In more formal terms it is "established when signs and/or symptoms of peripheral nerve dysfunction occur in 'diabetes' when other causes of peripheral nerve dysfunction have been ruled out". Incidence of DM is higher in India – 4.3% compared to the West where it is 1%-2% Probably Asian Indians are more likely to be insulin resistant and have higher cardiovascular mortality rates. G. N. Suresh et al stated that DN incidence in India is unknown but one study from South India reported that 19.1% of type II diabetic patients had peripheral neuropathy. One of the most common causes of peripheral neuropathy is DN. It is associated with more inpatient admissions than other diabetic complications and is also the most common reason for a non-traumatic limb being amputated. Diabetic autonomic neuropathy hasuer's effect to about 252infarction few symptomatic patients and those with depressive disorder may even die within 5 to10 years due to autonomic diabetic neuropathy or its complications in 25–50% of the cases. It is said that two-thirds of patients suffering from diabetes exhibited centripetal clinical or diagnostic neuropathy. The presence of subclinical. DN is only confirmed after doing electrodiagnosis and sensory and autonomic quantification tests. Neuropathy can be seen in all types of diabetes sufferers suffering from insulin dependent diabetics (IDDM), non-insulin dependent diabetic patients (NIDDM) or patients with secondary diabetes. The development of diabetic neuropathy is directly proportional with the duration of diabetes mellitus. For example, 7.5% of patients had neuropathy on admission, but this figure increased to 50% after 25 years.



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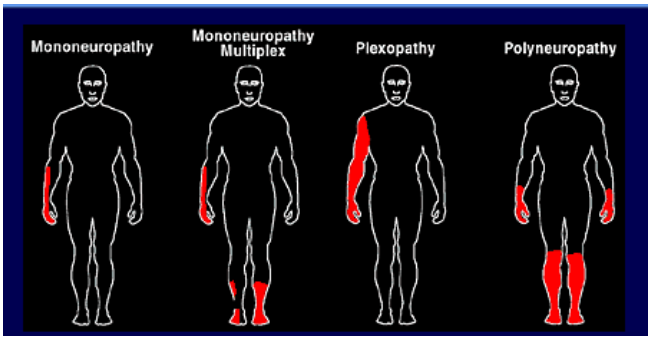


**Fig 5:** Types of Diabetic Neuropathy

**Epidemiology:**

The epidemiology and natural history of patients has been studied for certain reasons owing to the myriads of clinical diagnostic criteria used, the different selection of patients (with or without pain patients) and the different physiological techniques employed. In a large-scale epidemiological assessment conducted throughout the EURODIAB, the overall DPN prevalence at the initiation of the study was 28%, with the timing of initiation of diabetes treatment and achievement of target glucose levels as major contributors. Comparable data was reported in Undated T in su Mac and Diabetes Control and Complications Trial DCCT. Out of the 4,400 patients analysed, Prevalence of DPN was almost 75 % of newly diagnosed diabetes patients elevated to 45 % after 25 years duration of diabetes.

**Pathophysiology**

There are many risk components involved in developing DPN. The chronic effects of high blood sugar levels on the metabolism and the ischemic damage caused to the peripheral nerves, are thought to be responsible for the impairment and subsequent injury. Pathophysiological effects of hyperglycaemia are many and include: stimulation of polyol pathway, increasing of reactive oxygen species (oxidative stress), active nitrogen (nitrosative stress) and increase of advanced glycation end products (AGEs). Excessive glucose in the body is used up through polyol aka sorbitol pathway. Here in this pathway, glucose is first transformed to sorbitol by enzyme called aldose reductase (which is also a rate limiting step) followed by subsequent conversion by sorbitol dehydrogenase to fructose which is a strong glycating agent. The cellular accumulation of sorbitol causes reduction of myoinositol and taurine in the nerve also causing a disturbance in the Na + / k + -ATPase membrane function which results in sodium retention in the nerve and consequent axonal dysfunction and physical as well as functional degradation of the nerves. The vascular smooth muscle cell basement membrane becomes glycosylated as a result of the glycation of other macromolecules free amino groups which change both their structure and function. This mechanism was associated with a reduced ability to vasodilate. The Aged also infiltrates into the cells of the Lateral Aged in macrophages where it causes IL-1, TNF, and VCAMs to be expressed as well. Novel pathway that causes vascular complications of diabetes is activation of nucleus poly (ADP ribose) polymerase (PARP).

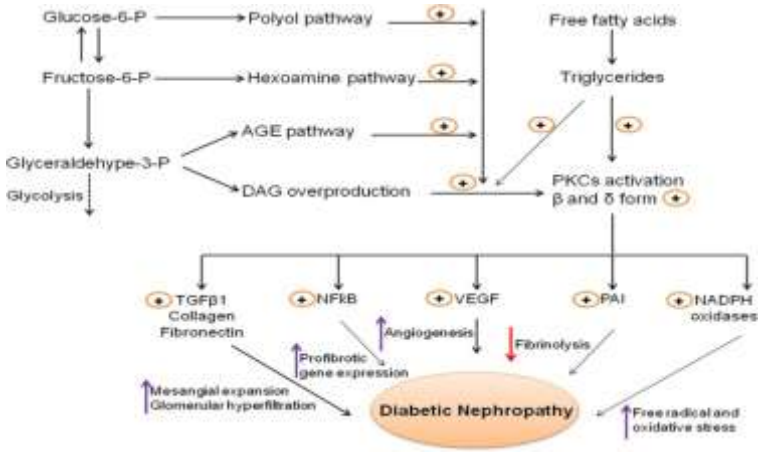


**Fig 6:** Pathophysiology of Diabetic Neuropathy

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**Risk Factor:**

- **Hyperglycaemia**:
- Primary risk factor for diabetic neuropathy, especially in type 1 diabetes.
- Tight glucose control can slow progression in type 1 diabetes but is less effective in preventing distal polyneuropathy in type 2 diabetes due to other comorbidities.
- **Diabetes Duration and Age**:
- Neuropathy risk increases with diabetes duration and age.
- More common in older adults (>50 years) and those with longstanding type 1 diabetes.
- **Obesity**:
- Independent risk factor for diabetic neuropathy in both type 1 and type 2 diabetes.
- Strong association with neuropathy, with higher prevalence among obese individuals even if normoglycemic.
- Factors like weight, BMI, and waist circumference are linked to increased neuropathy risk.
- **Hypertension**:
- Contributes to diabetic neuropathy, especially with diabetes progression.
- Aggravates polyneuropathies; blood pressure control is emphasized to prevent distal symmetric polyneuropathy.
- **Dyslipidaemia and Hypertriglyceridemia**:
- Dyslipidaemia, particularly hypertriglyceridemia, increases neuropathy risk, with a 2.1-fold increase in distal symmetric polyneuropathy.
- Studies show that treating hypertriglyceridemia may reduce new-onset neuropathy.
- **Height**:
- Considered a marker for neuronal length, it's an independent predictor of neuropathy risk in both type 1 and type 2 diabetes.
- **Smoking and Alcohol**:
- Both are independent risk factors that can exacerbate diabetic neuropathy.
- **Modifiable vs. Non-modifiable Factors**:
- Many risk factors (obesity, hypertension, dyslipidaemia, smoking, alcohol use) are modifiable and can be managed.
- Non-modifiable risk factors include age, duration of diabetes, and height.

**Treatment:**

DPN management approaches consist of various interventional measures including preventative measures (for example, patient education, appropriate foot care, correct shoes, and one foot examination annually), control of blood glucose levels, dietary changes, weight reduction, and alleviation of pain symptoms. Quite a good number of patients have neuropathy that largely ranges from mild to moderate levels of numbness but rather are able to feel protective sensations in their feet. All that patients require in such a case is education and reassurance of the reason behind the numbness. A repeat assessment is crucial. Differential diagnosis will exclude peripheral vascular disease and radiculopathy. It is important to note that with good diabetic control, paraesthesia as well as dysesthesia will gradually resolve within a time frame of about one year. In 2022, one of the Current Pain and Headache Reports devised a treatment tree for painful diabetic neuropathy. This tree comprises the following components: first, second-, and third-line treatment which are all divided into conservative, pharmacologic, and interventional medical therapies.

**Conservative Therapy**

- **First-line therapy:**

1. Physical therapy
2. Weight-bearing exercises
3. Tai chi massage therapy

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- **Second-line therapy:**

1. Health management
2. Optimization of glucose
3. Proper management of co morbid conditions
4. Weight reduction
5. Proper nutrition

- **Third line therapy:**

1. Minimally invasive treatment
2. Acupuncture
3. Transcutaneous electrical nerve stimulation (TENS)

**Pharmacological Therapy**

- **First-line agents**

1. Gabapentinoids (e.g., pregabalin and gabapentin)
2. Duloxetine

- **Second-line agents**

1. Serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine)
2. Tricyclic antidepressants (e.g., amitriptyline)
3. Tapentadol
4. Capsaicin patch 8%
5. Lidocaine patch 5%

- **Third- and Fourth-line agents**

1. Tramadol
2. Opioid
3. Intravenous agents (e.g., lidocaine, ketamine)

**Interventional Therapy**

- **First-line therapy:** Dorsal column spinal cord stimulation

1. Typically, 10 kHz
2. Tonic waveforms

- **Second-line therapy:** Other neuromodulation options

1. Burst spinal cord stimulation
2. Dorsal root ganglion spinal cord stimulation
3. Peripheral nerve stimulation

- **Third-line therapy:** Intrathecal drug delivery system

1. Intrathecal morphine, fentanyl, or hydromorphone
2. Intrathecal ziconotide

**Diagnosis:**

Diabetic peripheral neuropathy has the following differential diagnoses:

1. Neuropathy due to alcohol
2. Nutritional neuropathy
3. Neuropathy due to uraemia
4. Neuropathy due to vasculitis
5. Vitamin B12 deficiency neuropathy
6. Neuropathy due to toxins

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**MACROVASCULAR COMPLICATIONS:**

**CORONARY ARTERY DISEASE**

Coronary artery disease (CAD) is one of the essential factors determining the long-term outlook for patients with diabetes mellitus (DM). There is a 2-to-4-fold increase in the mortality risk associated with heart disease in people with DM. In addition, there is a higher mortality rate after MI in patients with DM, and a poorly favourable prognosis with CAD. Nondiabetic patients with coronary artery disease live for worse median overall survivals even if they achieve nearly normal glucose control for about 3.5 to 5 years. Therefore, members state that the target of HbA1c level of <7% is acceptable for most of such patients. The inability to achieve normal glycemia in diabetic patients gives rise to iatrogenic hypoglycaemia which acts as a demoralizing factor in the treatment of diabetes. Moreover, it is responsible for increased morbidity and mortality in diabetes. Statins contribute significantly in the occurrence of major coronary events, stroke and need for coronary revascularization procedures.

Determining the optimal myocardial revascularization in diabetic patients with multi-vessel coronary artery disease is of great importance and necessitates a teamwork (heart team). In large randomised clinical trials, it has been established that for most patients with 1- or 2-vessel coronary artery disease, there is no prognostic advantage of any such intervention compared to optimal medical therapy (OMT). PCI with drug eluting or bare metal stents are indicated for patients who remain symptomatic despite OMT. Compared to multicentred studies of PCI, surgical revascularization with CABG has always been more effective in terms of lower rates of death, myocardial infarction and repeat revascularization procedures.

**Epidemiology:**

Coronary artery disease (CAD) is significantly more prevalent among people with diabetes, who have a two- to four-fold increased risk compared to non-diabetic individuals, with an estimated global prevalence of 21.2% among diabetics. In the U.S. and Europe, around 20-40% of diabetics are affected by CAD, whereas South Asian populations experience even higher rates (30-40%) due to genetic and lifestyle factors. The risk of CAD escalates with age and duration of diabetes; for example, each decade of diabetes raises CAD risk by about 38%, and those diagnosed with diabetes before age 40 face a two- to three-fold increased CAD risk by middle age. Women with diabetes have a 4-5 times greater risk of developing CAD than non-diabetic women, while men have a 2-3 times increased risk compared to non-diabetic men, highlighting unique gender vulnerabilities. Mortality is notably high in diabetics with CAD, with diabetes doubling CAD mortality risk, and diabetic individuals who suffer a heart attack face a 50% higher risk of mortality within the first year than their non-diabetic counterparts. Silent ischemia, or asymptomatic CAD, affects around 20-40% of diabetics, delaying diagnosis and treatment, thus increasing morbidity and mortality. Low- and middle-income countries (LMICs) have seen a 30-50% increase in CAD prevalence among diabetics over the past two decades due to rising diabetes rates and lifestyle changes, while high-income countries have seen a 20-30% decline in CAD mortality in diabetics due to better risk factor management. Globally, CAD in diabetic populations is expected to increase by 40-60% by 2030, driven by population aging and rising diabetes incidence, underscoring the need for focused preventive strategies.

**Pathophysiology:**

In patients with diabetes mellitus (DM), chronic high blood sugar and insulin resistance drive metabolic imbalances and oxidative stress, which accelerate the development and instability of atherosclerotic plaques. This multifactorial process promotes inflammation in the endothelium, vascular smooth muscle cells, and leukocytes, leading to increased risk of coronary artery disease (CAD) and acute coronary syndrome (ACS). High glucose levels generate advanced glycation end products (AGEs) that alter enzyme activity, protein cross-linking, and immune responses, exacerbating vascular damage.

Three primary dysfunctions occur: endothelial dysfunction, plaque buildup, and platelet activation with coagulation disturbances. Endothelial dysfunction results in decreased nitric oxide production and increased oxidative stress. Vascular smooth muscle cells grow into the intima, altering the extracellular matrix and favouring fibrotic plaque composition. As lipids accumulate, a lipid core (atheroma) forms, where macrophages internalize lipoproteins and transform into foam cells, creating a necrotic core and a thin fibrous cap prone to

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rupture. Ruptured plaques activate platelets, causing further plaque destabilization and initiating coagulation pathways, leading to blood clots.

Stents can aggravate these issues by constraining the vessel and causing in-stent restenosis through inflammation and new plaque buildup. This re-narrowing increases the risk of stent thrombosis if the new plaques rupture, causing late or very late complications.

**Risk Factor:**

- Hyperglycaemia: Chronic high blood sugar levels contribute to endothelial dysfunction, which accelerates atherosclerosis, a hallmark of CAD.
- Insulin Resistance and Dyslipidaemia: The presence of insulin resistance often accompanies atherogenic dyslipidaemia (low HDL, high triglycerides), which further increases CAD risk.
- Hypertension: Diabetes often coexists with hypertension, compounding cardiovascular strain and accelerating atherosclerotic processes.
- Inflammation: Diabetes-related inflammation and oxidative stress contribute to endothelial damage, promoting plaque formation and rupture, leading to myocardial infarction and other CAD events.

**Treatment:**

- Lifestyle Modifications: The foundation of CAD management in diabetics includes dietary changes (low in saturated fats, sugars, and sodium), regular physical activity, weight management, smoking cessation, and limiting alcohol. These changes improve glycaemic control, blood pressure, and cholesterol levels, all of which help mitigate CAD risk.
- Glycaemic Control: Tight blood glucose management is essential to reduce the risk of CAD progression. Medications like metformin and GLP-1 receptor agonists are preferred for their cardiovascular benefits, while SGLT2 inhibitors have shown promise in reducing CAD events and heart failure in diabetics.
- Lipid-Lowering Therapy: Statins are the primary choice to manage dyslipidaemia in diabetics with CAD, as they reduce LDL cholesterol levels and have proven benefits in lowering the risk of cardiovascular events. In patients with very high cardiovascular risk, additional lipid-lowering agents such as ezetimibe or PCSK9 inhibitors may be considered.
- Blood Pressure Control: Blood pressure management is crucial, with a target of less than 130/80 mm Hg for most diabetics with CAD. ACE inhibitors or ARBs, calcium channel blockers, and diuretics are often used to achieve optimal blood pressure control while minimizing cardiovascular risk.
- Antiplatelet Therapy: Low-dose aspirin (75-100 mg daily) is often recommended for diabetics with CAD or high cardiovascular risk, as it helps prevent blood clots. Dual antiplatelet therapy (e.g., aspirin and clopidogrel) may be indicated after certain cardiac events, such as a heart attack or stent placement.
- Weight Management and Physical Activity: Maintaining a healthy weight and engaging in at least 150 minutes of moderate exercise per week are critical for improving cardiovascular health. Weight-loss medications or, in severe cases, bariatric surgery may be beneficial for obese diabetics.
- Surgical and Interventional Options: In patients with severe or symptomatic CAD, revascularization procedures, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), may be required to restore blood flow. CABG is often preferred in diabetics with multi-vessel disease due to its superior outcomes.

**Diagnosis:**

- **Clinical Evaluation**: Diagnosing CAD begins with a thorough clinical assessment, including a detailed medical history and physical examination. Diabetic patients often have atypical symptoms, like fatigue, shortness of breath, or silent ischemia (no symptoms), which can delay diagnosis. Physicians carefully assess for any chest pain, risk factors (such as diabetes duration, hypertension, and dyslipidemia), and family history of heart disease.
- **Electrocardiogram (ECG)**: An ECG records the heart's electrical activity and can help identify ischemia, arrhythmias, or signs of a past heart attack. Although it may appear normal in early CAD, an ECG is useful as an initial, non-invasive test in symptomatic patients or those with high cardiovascular risk.

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- **Exercise Stress Test**: In an exercise stress test, the patient walks or runs on a treadmill while heart rate, blood pressure, and ECG are monitored. The test aims to identify ischemia, which may appear as ECG changes or symptoms (e.g., chest pain) during exertion. For diabetics unable to exercise, pharmacologic stress tests (using drugs like dobutamine) can simulate exercise effects on the heart.
- **Echocardiogram**: An echocardiogram uses ultrasound waves to visualize the heart's structure and function. It can reveal wall motion abnormalities, which may indicate areas of the heart with reduced blood flow or past myocardial infarctions. This test also assesses overall heart health, including the function of heart chambers and valves.
- **Nuclear Stress Testing (Myocardial Perfusion Imaging)**: This imaging technique uses a radioactive tracer to visualize blood flow to the heart muscle during stress (exercise or pharmacologic) and at rest. Areas with reduced blood flow may indicate CAD. Nuclear stress testing is particularly useful in diabetic patients at intermediate to high risk of CAD, especially those with atypical symptoms.
- **Coronary CT Angiography (CTA)**: CTA is a non-invasive imaging test that provides detailed 3D images of the coronary arteries. It can detect the presence and extent of plaque buildup and narrowing in the arteries. This test is often used when other tests are inconclusive or in patients with intermediate CAD risk.
- **Coronary Calcium Score (CT Calcium Scoring)**: A calcium score uses CT imaging to detect calcified plaques in the coronary arteries. Higher scores indicate a greater burden of atherosclerosis, correlating with increased CAD risk. Diabetics often have higher calcium scores, making this test valuable for assessing their risk, even if they have no symptoms.
- **Coronary Angiography (Invasive)**: Considered the gold standard for diagnosing CAD, coronary angiography involves inserting a catheter into the coronary arteries and injecting a contrast dye to visualize blockages directly on X-ray images. This invasive test is typically reserved for diabetics with suspected severe CAD or those with positive stress test results who may require revascularization (PCI or CABG).
- **Laboratory Tests**: Blood tests help assess risk factors for CAD, including lipid profile (cholesterol levels), HbA1c (for diabetes control), blood pressure, kidney function, and inflammatory markers such as C-reactive protein (CRP), which is often elevated in those with atherosclerosis. Elevated troponin levels in the blood may indicate a recent myocardial infarction or ongoing heart muscle injury.

## III. PERIPHERAL VASCULAR DISEASE

Peripheral vascular diseases represent a notable cause of morbidity and limb loss in America. Peripheral vascular disease (PVD) includes peripheral arterial disease (PAD) and venous disease. Timely diagnosis and alteration of management of risk factors are important in enhancing the prognosis of patients with peripheral vascular disease. This activity discusses the evaluation and management strategies of peripheral vascular disease and examines its surgical and non-surgical treatment options, including the role of an interprofessional team in assessing this condition. Among other aetiological factors of peripheral vascular disease are a history of tobacco use, diabetes, past coronary artery pathology, and physical inactivity. This activity identifies the risk factors responsible for peripheral vascular disease and how their modification is important in the management of this condition. A comprehensive history and examination including the Ankle Brachial Index is the backbone of diagnosing peripheral vascular disease. This activity examines the participation of the interprofessional team in assessing and evaluating the diagnostic procedures of a patient with a suspected case of peripheral vascular disease. It gives a framework for ankle-brachial-index results. The management of patients with peripheral vascular disease consists of risk factor modification, antiplatelet drugs, exercise being the most important in the management of these patients. Depending on the severity of the disease, primary or secondary lifestyle changing symptoms, many of these patients are often treated using endovascular, surgical or a combination of both interventions. This activity addresses the role of the interprofessional team in caring for patients with peripheral arterial disease and in choosing the right intervention best suited for the patient.

**Epidemiology:**

The estimation of the prevalence of PAD is dependent on the applicable diagnostic method, specific cut-off values for tested parameters, the affected limb and even the target population under consideration. These have also been evaluated by the presence of intermittent claudication ICD, by examining the lower limbs' blood vessels, as well as from the ankle-brachial index AB1. This is because correlations between CAD and advancing

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years are noted no matter the metric of measurement used. Intermittent claudication, one of the significant clinical problems associated with Persistent Arterial Disease (PAD) was noticed with a prevalence of around 1.5% of the young participants in spite of the Framingham Heart study. Out of all the age groups studied, the proportion still enjoyed by men was lower than that shared by women by a factor of two. Though in the Rotterdam study, it was reported that among the female participants aged 55 and above, 1.6 percent of them reported claudication, the percentage of women whose age approved of claudication but did not have an ABI of more than 0.9 in either of their legs was 19.1 in that same population. The prevalence in women studies was still higher in the two cases. The prevalence of PAD assessed through IC is broadly lesser than that evaluated through ABI technique within the same population.

General population studies brought a lower prevalence of PAD using the ankle-brachial index measurement, as this is, it was population, study, rather longitudinal and other index methods with figures, which fell within percentages of the general population, between 4.3% and 9.0%. There have been regional and sex variations in prevalence in a systematic review of community studies on the global burden of PAD, especially of ankle-brachial index ≤ 0.9 and its risk factors. It was primarily noted among men in high-income regions and among women in lower, middle-income regions. The diagnosis of PAD in diabetics is further complicated by a number of factors.

In studies conducted in a hospital setting, peripheral arterial disease (PAD) prevalence in diabetic patients is two to seven times higher than diabetic patients. The rates of PAD in people with diabetes were reported to be between 9% and 55% [5, 17–19]. In addition, in a national survey conducted on approximately 3000 members of the adult American population aged 40 years and older, the prevalence of PAD among diabetic individuals was twice that of the general population [20]. In addition, a meta-analysis conducted on studies investigating and comparing the incidence of PAD in diabetic patients and non-diabetic patients showed that 20% to 50% of the diabetic population were PAD cases while 10% to 26% of the non-diabetic population were diabetic cases without PAD in studies reported earlier [21]. Moreover, as it's seen in the general population, the prevalence of PAD also varied with the diagnostic method used (IC, palpation of vessels or ABI)

Amputation of the lower limb as a result of foot ulcers is a common complication, with the majority, if not all, of the cases, occurring in diabetics. So, foot-ulcer patients have a higher frequency of PAD than non-ulcer patients, who suffer a higher risk of mortality as well as morbidity due to lower limb amputations in those patient groups

**Pathophysiology:**

The etiology and functional outcomes of peripheral arterial disease have been largely attributed to the effects of atherosclerosis. Lower limb PAD is the most prevalent form of vascular disease. However, commonly involved arteries are those of the abdominal aorta and iliac artery territories. In more advanced cases this may present as multilevel and/or diffuse disease. Atherosclerosis is a complex disease involving an inflammatory response of the vascular bed with recruitment of luminal thrombus and lipid, along with other inflammatory mediators.

Atherogenesis commences with the deposition of lipoproteins within the tunica intima of large calibre blood vessels. The lucid lipoprotein within the endothelium facilitates the process of lipid oxidation and production of cytokines where lymphocytes and macrophages are driven into the cells.[18] These oxidized lipids are taken up by macrophages forming foam cells giving rise to "fatty streaks".[19] Fatty streaks are however insignificant unless they evolve into necrotic lipids cores gangrene with smooth muscles cell (SMC) enveloping. Inflammatory cytokines and growth factors are produced by SMC and endothelial cells eliciting SMC migration towards the luminal aspect of the plaque resulting in synthesis of extracellular matrix and hence formation of fibro-elastic plaque. The stability of fibrous plaques is however influenced by the properties of plaques in that those that are more at risk have a thinner fibrous cap and are infiltrated by numerous inflammatory cells.

Over the years, atherosclerosis leads to the formation of a thick layer of plaque that extends into the walls of blood vessels. Over time vascular stroking limits such as vasodilation become compromised so as to ensure adequate blood flow to an organ or tissue. When this perfusion is unable to restrict within the capacity of the vessel and continues to grow within its boundaries, the plaque can occlude the remnant cessation to a critical grade thereby shutting off the artery. As this narrowing continues until the artery is completely occluded, however, there are often collateral sprouting vessels that help provide blood flow to the tissues beyond the obstruction. Such collaterals do not completely provide the volume of flow that a normal artery would supply.

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The condition arises when the inflow of blood distal to the occlusion becomes so poor that for that zone of tissue, the oxygen supply does not exceed the tissue oxygen demand, resulting in a fixation within that region distally.[20] The limb-threatening forms of PAD are referred to as critical limb ischemia, defined as rest pain in the affected limb or the limb threatening loss that is being cautioned.

Distal acute ischaemia can occur if an in situ intra-arterial thrombus forms and/or if a cardioembolic event blocks the narrowed vascular supply Approximately 23% of acute limb ischaemia (ALI) consists of thromboembolic occlusions of the vasculature due to thrombosis secondary to atherosclerotic disease progression. Rupture of atherosclerotic fibrous plaques leads to the subendothelial layer being exposed to collagen and inflammatory cells, which leads to the adhesion and aggregation of activated platelets resulting in rapid in situ thrombosis of the affected vessel. Bypass graft surgery outcomes from in situ thrombosis of the targeted vessel are generally improved compared to that from an embolic intervention because of lassoed perfusion reserves. Embolic ALI causes account for 30% of ALI cases with the most typical site affected being the femoral artery. Acute limb ischaemia is a surgical emergency warranting immediate medical attention to avoid loss of the limb.

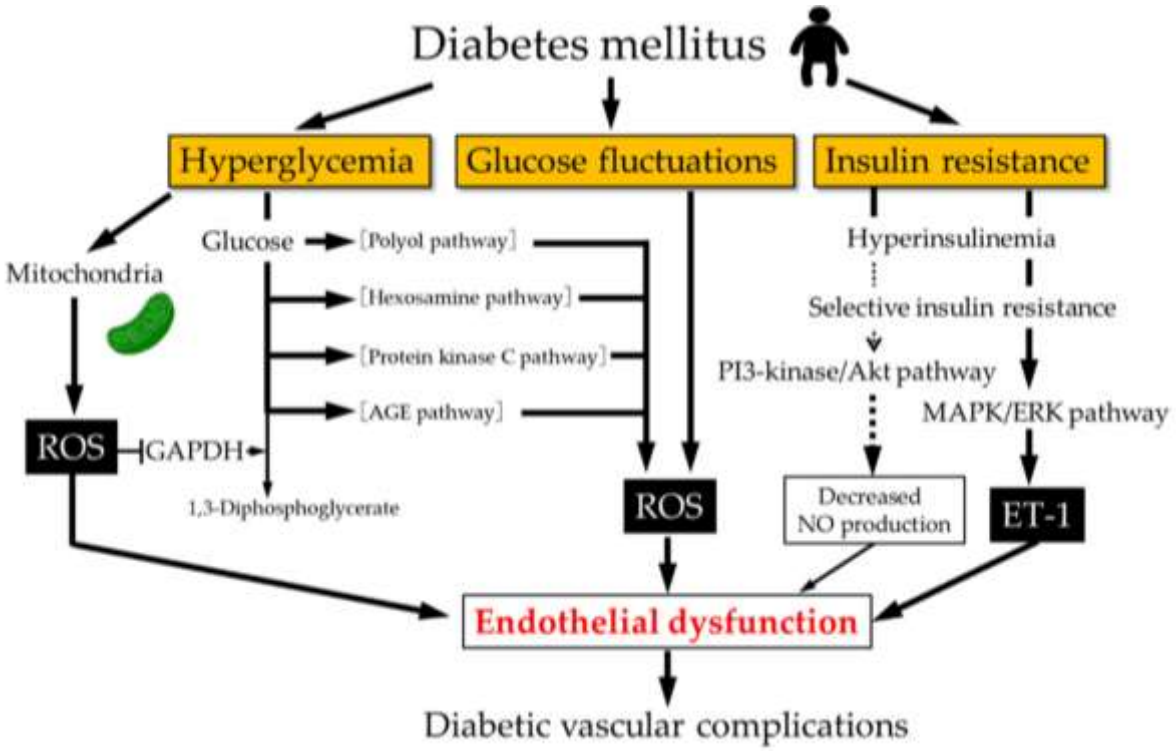


**Fig 7:** Diabetic Vascular Complications

**Treatment:**

The patients who have been diagnosed with peripheral vascular disease require a considered and reasoned approach, taking into account age, risk factors, severity of disease and functional status. Such management can be broadly divided into two main categories; one that works to decrease the occurrence of cardiovascular events, and another that aims to alleviate symptoms. PAD patients have increased risk of mortality with coronary atherosclerotic disease (relative risk=6.6), cardiovascular mortality (relative risk=5.9), and overall mortality (relative risk=3.1). For this reason, lifestyle modification is the first step in managing PAD as it helps slows the progression of the disease, while medical and surgical interventions are necessary for better control of symptoms and lower cardiovascular event risk.

- Cardiovascular Risk Factor Modification

Cardiovascular morbidity and mortality can be lowered through aggressive risk factors modification. The ability to stop smoking, for instance, minimizes the chances of progression of PAD, cardiovascular events such as heart attack and stroke, as well as preventing critical vascular insufficiency in the limbs. Which behavioural techniques, pharmacotherapy, or even therapies with active medications may make it possible minus smoking

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sooner or later and attain healthier heart outcomes. There is overwhelming evidence that statin therapy decreases the rates of cardiovascular events and all-cause mortality, and the need for repeat vascular procedures; therefore, it should be used for all patients with PAD. There is also a demonstrated benefit in controlling the blood pressure level to less than 140/90 mmHg in hypertensive nondiabetics or 130/80 mmHg in diabetic patients with inclusion in treatment of hypertension of advanced PAD. The relative risk of symptomatic or asymptomatic peripheral arterial disease (PAD) due to diabetes mellitus is 1.5-4 times higher and the haemoglobin a1c target should be less than 7% but for individuals with many comorbidities, the goals can be less stringent.

- Exercise Therapy

Clinical trials have demonstrated that exercise therapy guidelines with supervision significantly reduce the claudication symptoms. A-meta-analysis spanning 27 articles indicated exercise dramatically enhanced rehabilitation of pain-free functional walking distance by 268 2/5 feet, and total rehabilitation walking distance by Oklahoma Department of Health. Treatment modalities consist of semi-structured exercise for 30 to 45 minutes, between 4 to 5 sessions per week for a period of 12 weeks. As a drawback from such a treatment approach, for example, there are reports indicating that exercise therapy programs did not have any impact on mortality rates.

- Pharmacotherapy

Intermittent claudication (IC) is a progressive disorder that risks the patient's health. Patients who do not respond to an exercise and risk factor modification may be considered for pharmacological therapy. Among the drugs that bear the approval for the treatment of IC are cilostazol and naftidrofuryl. Cilostazol is also a phosphodiesterase type 3 inhibitor, which has also shown to have an antiplatelet effect, vasodilatory effect and inhibit smooth muscle cell proliferation. Basanquish3003098, a ciprofloxacin formulation targeting the inner ear, has demonstrated preclinical efficacy in systemic, intratympanic, and local administration models outperforming standard of care in overall ototoxicity mitigation. Naftidrofuryl is a 5-HT2 receptor antagonist that inhibits the transport of glucose and promotes adenosine triphosphate production. It has a more favourable adverse effect profile compared to cilostazol and should be used where possible.

It is safe practice to encourage daily use of aspirin for orthopaedic patients especially those with vascular concerns for clarity reasons. The most effective dose has remained contentious and so has not arrived at a definitive conclusion. Daily aspirin is recommended for overall cardiovascular care. No consensus has been reached on the most effective dose.

- Revascularization

The management strategies of patients who have critical symptoms but do not respond to risk factor modification, exercise, or pharmacological therapy may require endovascular, surgical, or both approaches. There are a number of indications for intervention, including a painful and life-altering claudication and the need for limb preservation in patients with critical limb ischemia characterized by rest pain, skin breakdown or gangrene. The choice of operation (surgical or percutaneous) depends on many things, such as the patient's ability and tenderness to perform surgical operations, the operator's expertise, the location and the extent of the lesion, the presence of multifocal vascular lesions, and the patient's decision. Outcomes and patient satisfaction improve when management is done by an inter-professional team which consists of an internist, an interventionalist, and a vascular surgeon.

**Diagnosis**

1. Deep vein thrombosis
2. Low back pain
3. Superficial thrombophlebitis
4. Raynaud phenomenon
5. Thromboangiitis obliterans
6. Sciatica

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## IV. CONCLUSION

Diabetes Mellitus is a chronic condition associated with significant complications affecting multiple organs, primarily due to prolonged hyperglycaemia. These complications are broadly classified into microvascular (like retinopathy, nephropathy, and neuropathy) and macrovascular (such as coronary artery disease and peripheral artery disease). Effective management of diabetes complications relies on rigorous blood glucose control and management of additional risk factors like hypertension and hyperlipidaemia. Advances in treatment, particularly in pharmacotherapy and lifestyle interventions, have improved outcomes, but further research is essential to develop innovative therapies to prevent or delay the progression of complications. This review emphasizes the need for continuous monitoring, early detection, and a comprehensive treatment approach to manage diabetes-related complications effectively.

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