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REVIEW ARTICLE

An Extensive Analysis of Diseases Associated with Diabetes

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Abstract: Diabetes mellitus (DM) is a chronic disease marked by hyperglycemia and a range of clinical neuropathies, as well as microvascular disease of the kidney and eye. Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases characterized by persistently elevated blood sugar levels. In both developed and developing nations, the prevalence of the disorder is rapidly spiraling out of control. A major metabolic illness that currently affects over 350 million people worldwide is diabetes mellitus (DM). These metabolic abnormalities are caused by inadequate insulin secretion, resulting in insufficient response and/or insulin resistance of target tissues, primarily the liver, adipose tissue, and skeletal muscles, at the level of insulin receptors, signal transduction systems, and/or effector enzymes or genes. Modern lifestyle choices like a diet rich in fat, physical inactivity, and heredity are particularly associated with T2DM. Numerous complications can arise from untreated diabetes. The fundamental role of insulin as an anabolic hormone leads to disturbances in protein, lipid, and carbohydrate metabolism. Our goal in this review is to highlight several issues, cellular, subcellular, and molecular mechanisms, as well as cascades or pathways (polyol, hexosamine, advanced glycation-end product etc.) of events linked to DM-induced hyperglycemia.

Keywords: Diabetes mellitus; Insulin; Retinopathy; Cataract; Nephropathy; Neuropathy

1. Introduction

Diabetes mellitus (DM) is a chronic, multifaceted group of metabolic disorders characterized by elevated blood glucose levels (hyperglycemia) resulting from the body's inability to produce or effectively utilize the hormone insulin. This persistent hyperglycemic state has far-reaching implications, leading to a myriad of complications that can affect nearly every organ system in the body. The escalating prevalence of diabetes has evolved into a global health crisis, with the number of diagnosed cases continuing to surge at an alarming rate. [1-3] The primary forms of diabetes are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). In T1DM, an autoimmune process destroys the insulin-producing beta cells of the pancreas, leading to an absolute deficiency of insulin. This form typically manifests in childhood or adolescence and accounts for approximately 5-10% of all diagnosed cases. [4, 5] On the other hand, T2DM, which constitutes the vast majority (90-95%) of cases, is primarily characterized by insulin resistance, wherein the body's cells become less responsive to the actions of insulin. This resistance is often exacerbated by a relative insulin deficiency as the pancreatic beta cells struggle to compensate for the increased insulin demand. [6,7]

The pathogenesis of diabetes is multifactorial, influenced by a complex interplay of genetic predisposition and environmental factors. While the exact mechanisms are not fully elucidated, several contributing factors have been identified. These include obesity, sedentary lifestyle, unhealthy dietary patterns, advancing age, and a positive family history of the disease. [8,9] Additionally, certain ethnic groups and populations demonstrate a heightened susceptibility to developing diabetes, suggesting a genetic component. The persistent hyperglycemia associated with uncontrolled diabetes can lead to a range of complications, affecting various organ systems. These complications can be broadly classified into macrovascular and microvascular categories. Macrovascular complications, such as cardiovascular disease, peripheral arterial disease, and stroke, arise from the damaging effects of hyperglycemia on the larger blood vessels. [10, 11] Conversely, microvascular complications involve damage to the smaller blood vessels, leading to conditions like diabetic retinopathy (affecting the eyes), diabetic nephropathy (affecting the kidneys), and diabetic neuropathy (affecting the nerves).

Diabetic retinopathy is a leading cause of vision loss and blindness among working-age adults in developed nations. It is characterized by progressive damage to the retinal blood vessels, leading to various manifestations, including microaneurysms,

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hemorrhages, and the formation of new, abnormal blood vessels (neovascularization). If left untreated, diabetic retinopathy can result in severe vision impairment or complete vision loss. [12-14] Our goal in this review is to highlight several issues, cellular, subcellular, and molecular mechanisms, as well as cascades or pathways (polyol, hexosamine, advanced glycation-end product etc.) of events linked to DM-induced hyperglycemia.

2. Diabetic cataract

Diabetic retinopathy (DR) is a sight-threatening retinal complication associated with diabetes mellitus. In developed countries, DR remains one of the leading causes of vision impairment and blindness. [15, 16] Diabetes retinopathy (DR) continues to be the primary cause of vision loss in working-age individuals (20–65 years) in industrialized nations, significantly impacting the quality of life of diabetes patients. Currently, around 90 million diabetics suffer from DR worldwide, with 17 million having proliferative diabetic retinopathy (PDR), 21 million having diabetic macular edema (DME), and 28 million having vision-threatening DR. It is projected that by 2025, the prevalence of DR will have doubled if more effective preventive therapy strategies are not developed. [17, 18] The two primary causes of vision loss are diabetic maculopathy and complications of PDR, including vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. Up to 50% of type 1 diabetes patients and 30% of type 2 diabetic patients progressively experience potentially sight-threatening retinal modifications, but early retinal changes are often asymptomatic and unnoticed by patients.

Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). [19, 20] In the early stage of DR, NPDR, the retinal vasculature exhibits increased vascular permeability and capillary occlusion. Retinal abnormalities such as microaneurysms, hemorrhages, and hard exudates can be detected through fundus photography, even in asymptomatic patients. [21-24] PDR, a more advanced stage of DR, is characterized by neovascularization. Patients in this stage may experience significant visual impairment if tractional retinal detachment occurs or if new abnormal vessels bleed into the vitreous (vitreous hemorrhage).

2.1. Pathophysiology of DR

2.1.1. Polyol Pathway

In addition to its well-known role in glucose metabolism, aldose reductase, a rate-limiting enzyme of the polyol pathway (Figure 1) that converts glucose to sorbitol, has been implicated in the loss of retinal capillary cells. [25-28] Aldose reductase inhibitors have been shown to prevent the death of retinal capillary cells induced by high glucose levels. In response to hyperglycemia, sorbitol, a common organic osmolyte in many cells, accumulates in retinal capillary cells, causing cellular hyperosmolality. Consequently, intracellular water and lactate production increase, while oxygen uptake decreases due to hyperosmolality. [29, 30] In the second step of the polyol pathway, glutathione reductase converts NADPH to NAD+, and aldose reductase competes with NADPH for this reduction.

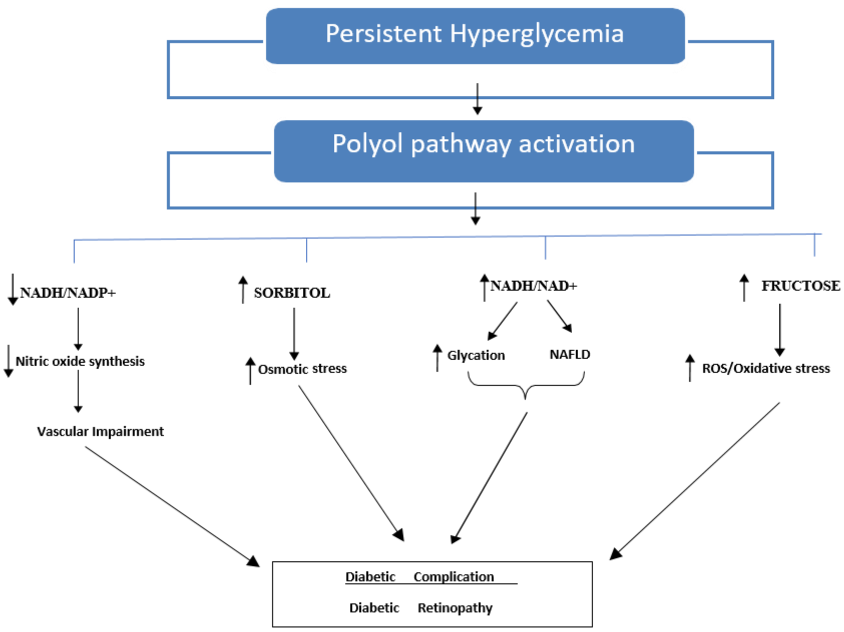

Figure 1. Polyol Pathway

2.1.2. Glycation Pathway

Elevated blood and tissue glucose levels cause proteins, lipids, and nucleic acids to be modified and converted into advanced glycation end-products (AGEs) upon contact with aldose sugars. The formation of AGEs under hyperglycemia involves a non-enzymatic glycation mechanism known as the "Maillard reaction," in which reversible, unstable Schiff base adducts are initially formed, followed by their transformation into relatively stable, covalently bound Amadori rearrangement products. [31-33] Additional oxidative and dehydrating processes in Amadori products lead to the formation of irreversibly bound protein-AGEs.

AGEs accumulated over time have been demonstrated to be detrimental to tissues and cells through various mechanisms. Abnormal cross-links between AGEs and essential extracellular matrix molecules cause vessels to become less elastic and more rigid, increasing vessel wall thickness and rigidity. [34-36] Furthermore, AGE binding to multiple cellular receptors may activate various cell signaling pathways. RAGE (receptor for advanced glycation end-products) is the first AGE receptor discovered and remains an active area of research. When AGEs bind to RAGE, multiple downstream pathways are activated, leading to the disruption of cell functions. These pathways include the p21ras and mitogen-activated protein kinases (MAPKs) pathways, nuclear factor-kB (NF-kB) translocation, and increased production of growth factors, proinflammatory cytokines, and adhesion molecules.

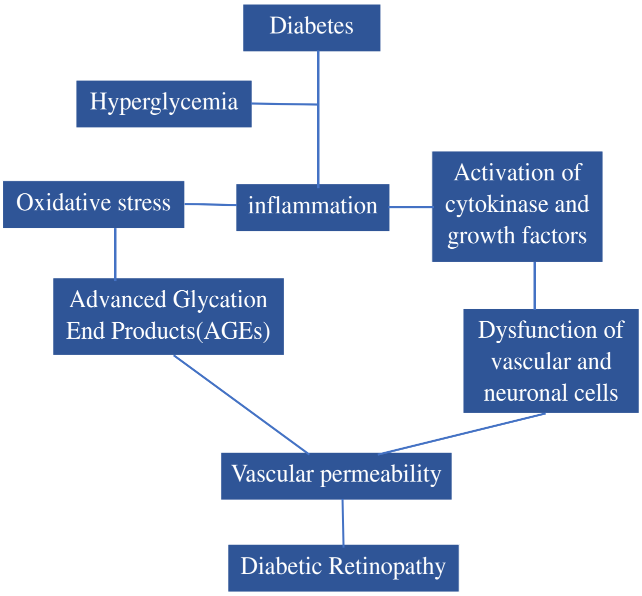

Figure 2. Glycation pathway

2.1.3. Oxidative stress

Oxidative stress is a crucial contributor linked to the pathophysiology of diabetes-related DR, induced by alterations in hormones and metabolites. An excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS) accelerates various pathological processes, including increased retinal vascular permeability, neurovascular injury, and retinal inflammation. These free radicals cause retinal degeneration in diabetic retinas by oxidizing lipids, proteins, and DNA, and altering their antioxidant status. [37] Diabetes mellitus is a metabolic disease characterized by abnormal levels of growth factors, lipids, amino acids, and blood glucose. These abnormalities trigger multiple metabolic processes that exacerbate oxidative stress in DR. The activation of enzymes such as xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and nitric oxide synthase further contributes to increased oxidative stress in diabetes. [38, 39] Moreover, declining tissue concentrations of endogenous antioxidants like glutathione and decreased activity of antioxidant defense enzymes like superoxide dismutase (SOD) and catalase aggravate the imbalance between oxidants and antioxidants

3. Diabetic cataract

Diabetes mellitus (DM) is a chronic and systemic metabolic disorder that is becoming increasingly prevalent worldwide. One of the most common ocular complications of DM is cataract formation, which can affect any structure within the eye. Cataracts are a leading cause of blindness globally. Cataract formation occurs more frequently in the diabetic population due to various underlying reasons. With technological advancements, cataract surgery has become a common and safe treatment option.

However, diabetic patients remain at risk for potential postoperative complications that could impair their vision, including posterior capsular opacification, progression of diabetic retinopathy, diabetic macular edema (ME), and diabetic retinopathy development after surgery. [40, 41] The prevalence of DM is projected to rise above 33% by 2050 due to an aging population and increased life expectancy. DM, being both a microangiopathic and a systemic chronic metabolic illness, can cause pathologies in various tissues across the ocular structure. Cataract is one of the most common reasons for visual impairment in diabetic patients. Patients with DM have been observed to have up to a five-fold increased risk of cataract development, especially in younger individuals.

3.1. Mechanism for cataract formation

Several mechanisms have been proposed for the pathogenesis of cataract in diabetic patients, including:

3.1.1. Polyol Pathway

The polyol metabolic pathway, involving the enzyme aldose reductase (AR) that reduces glucose to sorbitol, which is then converted to fructose, is considered a central part of cataract development. [42, 43] It is one of the most compelling candidate mechanisms to explain, at least in part, the cellular toxicity of diabetic hyperglycemia because:

i. It is activated when intracellular glucose concentrations are elevated.

ii. The two enzymes (AR and sorbitol dehydrogenase) are found in human tissues and organs that are the sites of diabetic complications.

iii. The by-products of the pathway and the altered balance of cofactors produce the kinds of cellular stress that occur at the sites of diabetic complications.

3.1.2. Osmotic and Oxidative Stress

Osmotic stress and oxidative stress play significant roles in cataract formation in diabetic patients. Accumulation of sorbitol within lens fibers leads to osmotic stress, causing lens fiber swelling and rupture. Additionally, increased oxidative stress due to hyperglycemia and impaired antioxidant defense mechanisms contributes to the oxidation of lens proteins and lipids, leading to cataract formation. [44, 45]

3.1.3. Autoimmunity

Autoimmune mechanisms have been implicated in the development of diabetic cataracts. Diabetes can trigger an autoimmune response, leading to the production of autoantibodies against lens proteins. These autoantibodies can cross-react with lens proteins, causing protein denaturation and subsequent cataract formation. [46, 47]

3.1.4. Blood Vessel Damage

Diabetes can cause damage to the blood vessels supplying the lens, leading to impaired nutrient and oxygen delivery. This ischemic state can contribute to the development of diabetic cataracts by altering lens metabolism and promoting lens fiber degeneration. [48, 49

3.1.5. Aqueous Humor Swelling

Hyperglycemia can lead to an increase in the osmotic pressure of the aqueous humor, causing it to swell. This swelling can disrupt the lens capsule and alter the metabolic balance within the lens, contributing to cataract formation.

3.2. Risk factors

Several factors increase the risk of developing cataracts in diabetic patients, including:

3.2.1. Duration of diabetes

The longer a person has been living with diabetes, the higher the risk of developing cataracts.

3.2.2. Poor glycemic control

Uncontrolled blood sugar levels contribute significantly to the development of diabetic complications, including cataracts.

3.2.3. Age

Older individuals with diabetes are at a higher risk of developing cataracts compared to younger individuals.

3.2.4. Presence of other diabetic complications

Individuals with other diabetic complications, such as retinopathy and nephropathy, are more prone to developing cataracts.

3.2.5. Lifestyle factors

Factors like smoking, excessive alcohol consumption, and exposure to ultraviolet radiation can increase the risk of cataract formation in diabetic patients.

3.3. Signs and symptoms

The signs and symptoms of diabetic cataracts can vary depending on the stage and severity of the condition. Some common signs and symptoms include: [50]

- Blurred or cloudy vision
- Sensitivity to light and glare
- Double vision in one eye
- Frequent changes in eyeglass or contact lens prescription
- Fading or yellowing of colors
- Difficulty seeing at night or in low-light conditions

3.4. Prevention

While cataracts cannot be completely prevented, there are several measures that can be taken to reduce the risk or delay the onset of diabetic cataracts:

3.4.1. Maintaining good glycemic control

Keeping blood sugar levels within the target range can significantly reduce the risk of developing diabetic complications, including cataracts.

3.4.2. Regular eye exams

Regular eye examinations by an ophthalmologist or optometrist can help detect early signs of cataract formation and allow for timely intervention.

3.4.3. Lifestyle modifications

Adopting a healthy lifestyle, including a balanced diet, regular exercise, and smoking cessation, can help manage diabetes and reduce the risk of complications.

3.4.4. Antioxidant supplementation

Some studies have suggested that supplementation with antioxidants like vitamins C and E may help prevent or slow the progression of cataracts in diabetic patients.

3.5. Cataract surgery

If cataracts progress to the point where they significantly impair vision and interfere with daily activities, cataract surgery may be recommended. This involves removing the clouded natural lens and replacing it with an artificial intraocular lens (IOL).

3.5.1. Preoperative considerations

Before undergoing cataract surgery, diabetic patients [51] should be evaluated for the following:

- Glycemic control: Ensuring optimal blood sugar control before surgery can reduce the risk of postoperative complications.
- Diabetic retinopathy: The presence and severity of diabetic retinopathy should be assessed, as it can influence the surgical approach and timing.

- Other ocular complications: Conditions like diabetic macular edema or neovascular glaucoma should be addressed before or during cataract surgery.
- Systemic complications: Evaluation of other diabetic complications, such as nephropathy and neuropathy, is essential to ensure appropriate perioperative management.

3.5.2. Postoperative considerations

After cataract surgery, diabetic patients should be closely monitored for potential postoperative complications, including:

- Progression of diabetic retinopathy: The stress of surgery can exacerbate existing diabetic retinopathy or trigger the development of new retinopathy lesions.
- Diabetic macular edema: Cataract surgery can increase the risk of developing or worsening diabetic macular edema, which can affect visual outcomes.
- Posterior capsular opacification: Diabetic patients are at a higher risk of developing posterior capsular opacification, which can obscure vision after cataract surgery.
- Delayed wound healing: Poor glycemic control and other diabetic complications can impair wound healing after cataract surgery.

4. Diabetic nephropathy

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) and a major microvascular complication of both type 1 and type 2 diabetes mellitus (DM). It is characterized by progressive kidney damage, initially manifesting as microalbuminuria and progressing to macroalbuminuria, declining glomerular filtration rate (GFR), and eventually, ESRD. DN is a significant contributor to the overall morbidity and mortality associated with diabetes, and its prevalence is increasing globally, paralleling the rising rates of diabetes. [52, 53]

4.1. Pathophysiology

The pathogenesis of DN is multifactorial, involving a complex interplay of metabolic, hemodynamic, inflammatory, and genetic factors. Several pathways and mechanisms have been implicated in the development and progression of DN.

4.1.1. Metabolic Pathways

Polyol Pathway: The polyol pathway is a metabolic pathway that is activated in hyperglycemic conditions. In this pathway, glucose is reduced to sorbitol by the enzyme aldose reductase, and sorbitol is then converted to fructose by sorbitol dehydrogenase. The accumulation of sorbitol and fructose in renal cells can lead to osmotic stress, oxidative stress, and cellular injury, contributing to the development of DN. [12-14]

Hexosamine Pathway: The hexosamine pathway is another metabolic pathway that is upregulated in hyperglycemic conditions. In this pathway, fructose-6-phosphate is diverted from glycolysis and converted to glucosamine-6-phosphate, which is ultimately used for the synthesis of proteoglycans and glycoproteins. The increased flux through the hexosamine pathway can lead to abnormal protein glycosylation, which can alter the function and structure of various proteins, contributing to the development of DN.

Protein Kinase C Activation: Hyperglycemia can also lead to the activation of protein kinase C (PKC), a family of enzymes involved in various cellular processes. PKC activation can contribute to the development of DN through several mechanisms, including increased production of vasoconstrictors, increased expression of profibrotic and inflammatory mediators, and altered permeability of the glomerular filtration barrier. [15-19]

Advanced Glycation End-products (AGEs): AGEs are formed through non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids. The accumulation of AGEs in the kidneys can lead to cross-linking of proteins, oxidative stress, and inflammation, all of which can contribute to the development and progression of DN.

Hemodynamic Factors: Hemodynamic factors play a crucial role in the pathogenesis of DN. Hyperglycemia can lead to increased glomerular capillary pressure and hyperfiltration, which can contribute to glomerular injury and proteinuria. Additionally, the activation of the renin-angiotensin-aldosterone system (RAAS) can lead to increased intraglomerular pressure, glomerular hypertrophy, and progressive kidney damage. [5,9]

4.1.2. Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress are key contributors to the development and progression of DN. Hyperglycemia can induce the production of inflammatory mediators, such as cytokines and chemokines, which can promote the infiltration of inflammatory cells into the kidneys and contribute to renal injury. Additionally, increased oxidative stress can lead to cellular damage, apoptosis, and the activation of various signaling pathways that contribute to the development of DN. [11,18]

4.1.3. Genetics and Epigenetics

Genetic and epigenetic factors also play a role in the susceptibility and progression of DN. Certain genetic variants have been associated with an increased risk of developing DN, while epigenetic modifications, such as DNA methylation and histone modifications, can influence gene expression and contribute to the development of DN. [2, 19]

4.2. Stages of Diabetic Nephropathy

DN progresses through several stages (Table 1), each characterized by distinct clinical and pathological features.

4.2.1. Hyperfiltration Stage

In the early stages of diabetes, hyperglycemia can lead to increased glomerular filtration rate (GFR) and hyperfiltration. This stage is often asymptomatic and may precede the development of microalbuminuria.

4.2.2. Microalbuminuria Stage

Microalbuminuria, defined as an albumin excretion rate of 30-300 mg/day, is the earliest clinical manifestation of DN. At this stage, there may be no significant decline in GFR, but the presence of microalbuminuria indicates glomerular injury and an increased risk of progression to overt nephropathy. [4, 19]

4.2.3. Macroalbuminuria/Proteinuria Stage

As DN progresses, microalbuminuria can progress to macroalbuminuria (albumin excretion rate >300 mg/day) or overt proteinuria. At this stage, there is a significant decline in GFR, and patients may experience symptoms of kidney dysfunction, such as edema, hypertension, and anemia. [5, 20]

4.2.4. End-Stage Renal Disease (ESRD)

In the advanced stages of DN, the kidneys progressively lose their ability to filter waste products, leading to ESRD. At this stage, patients require renal replacement therapy, such as dialysis or kidney transplantation, to sustain life.

Table 1. Stages of kidney failure

Stages	Description
1	Kidney damage but can be functioned normally, GFR 90% or above
2	Kidney damage with some loss of function, GFR 60-89%
3	Kidney damage with mild to severe loss of function, GFR 30-59%
4	Kidney damage with severe loss of function, GFR 15-29%
5	Kidney failure and GFR of under 15%

4.3. Risk Factors

Several factors can increase the risk of developing DN, including:

4.3.1. Poor glycemic control

Chronic hyperglycemia is a major risk factor for the development and progression of DN.

4.3.2. Hypertension

Uncontrolled hypertension can exacerbate glomerular injury and accelerate the progression of DN.

4.3.3. Genetic factors

Certain genetic variants have been associated with an increased risk of DN.

4.3.4. Smoking

Smoking can contribute to the development of DN through various mechanisms, including oxidative stress and endothelial dysfunction.

4.3.5. Dyslipidemia

Abnormal lipid levels, particularly elevated triglycerides and low HDL cholesterol, can increase the risk of DN.

4.3.6. Obesity and insulin resistance

These conditions can contribute to the development of DN through various metabolic pathways.

4.4. Diagnosis and Screening

The diagnosis (Table 2) of DN is based on the detection of persistent microalbuminuria or proteinuria in the presence of diabetes. Screening for DN typically involves: [9, 21, 22]

4.4.1. Urine albumin excretion

Microalbuminuria can be detected through a spot urine albumin-to-creatinine ratio or a 24-hour urine collection for albumin excretion.

4.4.2. Estimated glomerular filtration rate (eGFR)

eGFR is calculated based on serum creatinine levels and other factors to assess kidney function.

4.4.3. Renal biopsy

In some cases, a renal biopsy may be performed to confirm the diagnosis and assess the extent of kidney damage.

Table 2. Diagnosis tests

Test	Description
Urinary Albumin test	Urine can be used to test for albumin, a blood protein. Albumin is typically not removed from the blood by the kidneys. A high level of albumin in the urine may indicate renal disease.
Albumin/creatinine ratio	Healthy kidneys remove waste products from the blood, such as creatinine. A urine sample's albumin/creatinine ratio indicates the relative amounts of the two substances. It illustrates how well the kidneys are functioning
Glomerular Filtration Rate (GFR)	Blood can be tested to determine how rapidly the kidneys filter blood using the creatinine level in the sample. The glomerular filtration rate is what is meant by this term. Kidney function is compromised by a low rate.
Imaging tests	Ultrasonography and X-rays can reveal the structure and dimensions of the kidneys. Blood flow within the kidneys can be visualized with CT and MRI imaging. Other imaging tests might also be necessary for you.
Renal Biopsy	Sample of kidney tissue is studied in laboratory

4.5. Management and Treatment

The management of DN involves a multifaceted approach, including glycemic control, blood pressure control, and the use of specific pharmacological interventions.

4.5.1. Glycemic Control

Achieving optimal glycemic control is the cornerstone of DN management. Strict blood glucose control can slow the progression of DN and reduce the risk of complications. This can be achieved through lifestyle modifications, such as dietary changes and regular exercise, as well as the use of antihyperglycemic medications, including insulin therapy.

4.5.2. Blood Pressure Control

Tight blood pressure control is crucial in the management of DN. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are recommended as first-line antihypertensive agents due to their ability to reduce intraglomerular pressure and provide renoprotective effectss

4.5.3. Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

RAAS inhibitors, such as ACEIs and ARBs, play a pivotal role in the management of DN. These agents not only help control blood pressure but also have direct renoprotective effects by reducing intraglomerular pressure, decreasing proteinuria, and slowing the progression of kidney disease. RAAS inhibitors are recommended for patients with DN, even in the absence of hypertension.

4.5.4. Other Pharmacological Interventions

Several other pharmacological agents may be used in the management of DN, depending on the individual patient's needs and comorbidities:

Diuretics: Diuretics can help manage fluid overload and hypertension in patients with DN.

Lipid-lowering agents: Statins and other lipid-lowering drugs may be used to manage dyslipidemia and reduce cardiovascular risk in patients with DN.

Erythropoiesis-stimulating agents: These agents may be used to treat anemia associated with DN, particularly in later stages of the disease.

Vitamin D and calcium supplements: These supplements may be prescribed to manage mineral and bone disorders that can occur in advanced stages of DN.

4.5.5. Renal Replacement Therapy

In the end-stage of DN, when the kidneys can no longer adequately filter waste products, renal replacement therapy becomes necessary. This can involve either dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation. The choice of therapy depends on various factors, including the patient's age, comorbidities, and overall health status

5. Diabetic neuropathy

Diabetic neuropathy is a debilitating and potentially disabling complication of diabetes mellitus (DM) that affects the peripheral nerves. It is one of the most common chronic complications of both type 1 and type 2 diabetes, with a high prevalence and significant impact on patients' quality of life. Diabetic neuropathy can involve various components of the peripheral nervous system, including sensory, motor, and autonomic nerves. [12, 18, 20]

The development and progression of diabetic neuropathy are closely linked to the duration of diabetes and the degree of glycemic control. However, other factors, such as age, metabolic derangements, and vascular abnormalities, also play a role in the pathogenesis of this complication. Early recognition and appropriate management of diabetic neuropathy are crucial to prevent irreversible nerve damage and associated complications.

5.1. Classification of Diabetic Neuropathy

Diabetic neuropathy can be classified into several types based on the distribution and characteristics of nerve involvement:

5.1.1. Peripheral Neuropathy

Peripheral neuropathy is the most common form of diabetic neuropathy and can be further subdivided into sensory, motor, and autonomic neuropathies.

- Sensory Neuropathy: Sensory neuropathy is characterized by impaired sensation, often starting in the toes and gradually progressing proximally. Patients may experience numbness, tingling, or burning sensations in their extremities, which can lead to loss of protective sensation and an increased risk of foot ulcers and amputations.
- Motor Neuropathy: Motor neuropathy involves the impairment of motor nerves, leading to weakness and muscle wasting, particularly in the distal muscles of the lower extremities. This can result in foot deformities, such as foot drop or claw toes, and impaired mobility.

- Autonomic Neuropathy: Autonomic neuropathy affects the autonomic nervous system, which controls involuntary bodily functions such as heart rate, blood pressure, digestive processes, and bladder control. Symptoms may include postural hypotension, gastroparesis, bladder dysfunction, and impaired sweating or temperature regulation.

5.1.2. Focal Neuropathies

Focal neuropathies involve damage to specific nerves or nerve groups, resulting in localized symptoms. Examples include:

- Mononeuropathy: Involvement of a single nerve, such as carpal tunnel syndrome or cranial nerve palsies.
- Radiculopathy: Compression or inflammation of nerve roots, often causing radiating pain or weakness in specific regions.
- Truncal neuropathy: Affecting the thoracic or abdominal wall nerves, leading to pain or weakness in the trunk area.

5.1.3. Proximal Neuropathy

Proximal neuropathy, also known as diabetic amyotrophy or lumbosacral radiculoplexus neuropathy, is a rare but distinct form of diabetic neuropathy. It is characterized by sudden onset of severe pain in the thighs, hips, or buttocks, followed by profound muscle weakness and atrophy in the proximal lower extremities.

5.2. Pathophysiology

The pathogenesis of diabetic neuropathy is multifactorial and involves various metabolic, vascular, and immunological mechanisms:

5.2.1. Metabolic Factors

Hyperglycemia plays a central role in the development of diabetic neuropathy through several metabolic pathways:

- Polyol pathway: Increased flux through the polyol pathway leads to the accumulation of sorbitol and fructose, which can induce osmotic stress and oxidative damage to nerves.
- Advanced glycation end-products (AGEs): AGEs can cross-link with proteins and alter their structure and function, contributing to nerve damage.
- Hexosamine pathway: Increased flux through the hexosamine pathway can lead to abnormal protein glycosylation and impaired nerve function.

5.2.2. Vascular Factors

Diabetes can cause microvascular and macrovascular complications, leading to ischemia and impaired nerve perfusion. Endothelial dysfunction, thickening of the basement membrane, and decreased endoneurial blood flow can contribute to nerve ischemia and subsequent nerve damage.

5.2.3. Oxidative Stress

Increased oxidative stress, resulting from hyperglycemia and impaired antioxidant defense mechanisms, can lead to the production of reactive oxygen species (ROS) and subsequent nerve damage. ROS can cause lipid peroxidation, protein oxidation, and DNA damage in nerve cells.

5.2.4. Inflammation

Chronic inflammation is implicated in the pathogenesis of diabetic neuropathy. Elevated levels of inflammatory mediators, such as cytokines and chemokines, can contribute to nerve damage through various mechanisms, including the activation of immune cells and the promotion of oxidative stress.

5.2.5. Neuronal Injury and Repair

Diabetic neuropathy involves both neuronal injury and impaired nerve repair mechanisms. Hyperglycemia can disrupt neuronal signaling, axonal transport, and mitochondrial function, leading to neuronal degeneration. Additionally, diabetes can impair the ability of Schwann cells to support nerve regeneration and remyelination.

5.3. Risk Factors

Several factors increase the risk of developing diabetic neuropathy, including:

- Poor glycemic control: Chronic hyperglycemia is a major risk factor for the development and progression of diabetic neuropathy.
- Duration of diabetes: The risk of developing neuropathy increases with the duration of diabetes.
- Age: Older age is associated with a higher risk of diabetic neuropathy.
- Obesity and dyslipidemia: These metabolic factors can exacerbate nerve damage and contribute to the development of neuropathy.
- Smoking: Smoking can further impair nerve function and increase the risk of neuropathy.
- Alcohol consumption: Excessive alcohol intake can exacerbate nerve damage and contribute to the development of neuropathy.
- Genetic factors: Certain genetic variants may increase an individual's susceptibility to developing diabetic neuropathy.

5.4. Diagnosis and Screening

Regular screening for diabetic neuropathy is recommended for all individuals with diabetes, as early detection and intervention can prevent or delay the progression of the condition. [17, 21] The diagnosis of diabetic neuropathy is based on a combination of clinical evaluation, neurological examination, and diagnostic tests:

- Symptom assessment: Patients should be evaluated for symptoms such as numbness, tingling, pain, weakness, or autonomic dysfunction.
- Physical examination: A comprehensive neurological examination, including assessment of sensation, muscle strength, and reflexes, can help identify the presence and distribution of neuropathy.
- Electrophysiological studies: Nerve conduction studies and electromyography can provide objective evidence of nerve dysfunction and help differentiate between different types of neuropathy.
- Quantitative sensory testing: This test can assess the perception of vibration, temperature, and pain sensations, which can help detect early signs of neuropathy.
- Autonomic function testing: Tests such as heart rate variability, sweat production, and gastric emptying studies can evaluate autonomic nerve function.

5.5. Management and Treatment

The management of diabetic neuropathy involves a multifaceted approach that addresses glycemic control, pain management, and the prevention of complications:

5.5.1. Glycemic Control

Achieving optimal glycemic control is the cornerstone of managing diabetic neuropathy. Strict blood glucose control can slow the progression of neuropathy and may even partially reverse some of the nerve damage in the early stages. This can be achieved through lifestyle modifications, such as dietary changes and regular exercise, as well as the use of antihyperglycemic medications, including insulin therapy.

5.5.2. Pain Management

Pain management is an essential aspect of diabetic neuropathy treatment, as neuropathic pain can significantly impact quality of life. Various pharmacological and non-pharmacological approaches may be employed:

- Medications: Antidepressants (e.g., duloxetine, amitriptyline), anticonvulsants (e.g., pregabalin, gabapentin), and topical agents (e.g., lidocaine patches) can be used to manage neuropathic pain.
- Non-pharmacological therapies: Interventions such as transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, and cognitive-behavioral therapy may be beneficial for some patients.

5.6. Nutritional Supplementation

- Alpha-lipoic acid: An antioxidant that has been shown to improve neuropathic symptoms and nerve conduction in some studies.
- Vitamin B complex: Deficiencies in vitamins B1, B6, and B12 have been associated with an increased risk of neuropathy, and supplementation may provide benefits.
- Gamma-linolenic acid (GLA): An omega-6 fatty acid found in evening primrose oil that may have neuroprotective effects.

5.7. Physical Therapy and Rehabilitation

Physical therapy and rehabilitation programs can help manage the functional impairments associated with diabetic neuropathy:

- Exercise and strengthening programs: Tailored exercise regimens can improve muscle strength, balance, and mobility, reducing the risk of falls and injuries.
- Gait training and assistive devices: Proper gait training and the use of assistive devices, such as canes or braces, can improve mobility and prevent complications like foot ulcers.
- Foot care and footwear modifications: Regular foot inspections, proper footwear, and customized insoles or orthotics can help prevent foot complications in patients with neuropathy.
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5.8. Surgical Interventions

In some cases, surgical interventions may be necessary to manage the complications of diabetic neuropathy: [31, 33]

- Decompression surgery: For focal neuropathies, such as carpal tunnel syndrome or ulnar neuropathy, surgical decompression of the affected nerve may provide relief.
- Amputation: In severe cases of foot ulceration or gangrene, amputation of the affected limb or digit may be necessary to prevent further complications.
- Implantable devices: Spinal cord stimulators or intrathecal drug delivery systems may be considered for patients with refractory neuropathic pain

6. Conclusion

Diabetic neuropathy is a prevalent and debilitating complication of diabetes that can significantly impact a patient's quality of life. With its diverse clinical manifestations and multifactorial pathogenesis, the management of diabetic neuropathy requires a comprehensive and multidisciplinary approach. Early recognition, strict glycemic control, and targeted interventions for pain management, nutritional support, physical rehabilitation, and prevention of complications are crucial elements in the care of these patients. Despite ongoing research efforts, there is still a need for more effective therapeutic strategies and personalized treatment approaches. Continued advancements in our understanding of the pathophysiology, identification of novel therapeutic targets, and the development of regenerative therapies hold promise for improving the outcomes of individuals affected by this challenging complication of diabetes.

References

[1] Curtis T, Gardiner T, Stitt A. Microvascular lesions of diabetic retinopathy: Clues towards understanding pathogenesis? Eye. 2009;23(7):1496.

[2] Fong DS, Aiello AP, Ferris FL, Klein R. Diabetic retinopathy. Diabetes Care. 2004;27(10):2540-53.

[3] Candrilli SD, Davis KL, Kan HJ, Lucero MA, Rousculp MD. Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. J Diabetes Complications. 2007;21(5):306-14.

[4] Safi SZ, Qvist R, Kumar S, Batumalaie K, Ismail IS. Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. Biomed Res Int. 2014;2014:801269.

[5] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556-64.

[6] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4-14.

[7] Stefánsson E, Bek T, Porta M, Larsen N, Kristinsson JK, Agardh E. Screening and prevention of diabetic blindness. Acta Ophthalmol Scand. 2000;78(4):374-85.

[8] Shah CA. Diabetic retinopathy: A comprehensive review. Indian J Med Sci. 2008;62(12):500-19.

[9] Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB. Inflammation and diabetic retinal microvascular complications. J Cardiovasc Dis Res. 2011;2(2):96-103.

[10] Frank RN. Diabetic retinopathy and systemic factors. Middle East Afr J Ophthalmol. 2015;22(2):151-6.

[11] Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, Lopez-Galvez M, Navarro-Gil R, Verges R. Diabetic macular edema pathophysiology: vasogenic versus inflammatory. J Diabetes Res. 2016;2016:2156273.

[12] Segawa M, Hirata Y, Fujimori S, Okada K. The development of electroretinogram abnormalities and the possible role of polyol pathway activity in diabetic hyperglycemia and galactosemia. Metabolism. 1988;37(5):454-60.

[13] Robinson WG, McCaleb ML, Feld LG, Michaelis OE, And NL, Mercandetti M. Degenerated intramural pericytes ('ghost cells') in the retinal capillaries of diabetic rats. Curr Eye Res. 1991;10(4):339-50.

[14] Goldfarb S, Ziyadeh FN, Kern EFO, Simmons DA. Effects of polyol-pathway inhibition and dietary myo-inositol on glomerular hemodynamic function in experimental diabetes mellitus in rats. Diabetes. 1991;40(4):465-71.

[15] Narayanan S. Aldose reductase and its inhibition in the control of diabetic complications. Ann Clin Lab Sci. 1993;23(2):148-58.

[16] Stevens MJ, Henry DN, Thomas TP, Killen PD, Greene DA. Aldose reductase gene expression and osmotic dysregulation in cultured human retinal pigment epithelial cells. Am J Physiol. 1993;265(3 Pt 1):E428-38.

[17] Lim SS, Jung SH, Ji J, Shin KH, Keum SR. Synthesis of flavonoids and their effects on aldose reductase and sorbitol accumulation in streptozotocin-induced diabetic rat tissues. J Pharm Pharmacol. 2001;53(5):653-68.

[18] Sato S, Secchi EF, Lizak MJ, Fukase S, Ohta N, Murata M, et al. Polyol formation and NADPH-dependent reductases in dog retinal capillary pericytes and endothelial cells. Invest Ophthalmol Vis Sci. 1999;40(3):697-704.

[19] Bravi MC, Pietrangeli P, Laurenti O, Basili S, Cassone-Faldetta M, Ferri C, et al. Polyol pathway activation and glutathione redox status in non—insulin-dependent diabetic patients. Metabolism. 1997;46(10):1194-8.

[20] Prasad K, Mishra M. AGE-RAGE Stress, Stressors, and Antistressors in Health and Disease. Int J Angiol. 2018;27(1):1-12.

[21] Takeuchi M, Yamagishi S. Involvement of toxic AGEs (TAGE) in the pathogenesis of diabetic vascular complications and Alzheimer's disease. J Alzheimers Dis. 2009;16(4):845-58.

[22] Kandarakis SA, Piperi C, Topouzis F, Papavassiliou AG. Emerging role of advanced glycation-end products (AGEs) in the pathobiology of eye diseases. Prog Retin Eye Res. 2014;42:85-102.

[23] McNulty M, Mahmud A, Feely J. Advanced glycation end-products and arterial stiffness in hypertension. Am J Hypertens. 2007;20(3):242-7.

[24] Zhang WJ, Li PX, Guo XH, Huang QB. Role of moesin, Src, and ROS in advanced glycation end product-induced vascular endothelial dysfunction. Microcirculation. 2017;24(4).

[25] McCance DR, Dyer DG, Dunn JA, Bailie KE, Thorpe SR, Baynes JW, et al. Maillard reaction products and their relation to complications in insulin-dependent diabetes mellitus. J Clin Invest. 1993;91(6):2470-8.

[26] Milne R, Brownstein S. Advanced glycation end products and diabetic retinopathy. Amino Acids. 2013;44(6):1397-407.

[27] Kern TS. Interrelationships between the Retinal Neuroglia and Vasculature in Diabetes. Diabetes Metab J. 2014;38(3):163-70.

[28] Stem MS, Gardner TW. Neurodegeneration in the pathogenesis of diabetic retinopathy: molecular mechanisms and therapeutic implications. Curr Med Chem. 2013;20(26):3241-50.

[29] Payne AJ, Kaja S, Naumchuk Y, Kunjukunju N, Koulen P. Antioxidant drug therapy approaches for neuroprotection in chronic diseases of the retina. Int J Mol Sci. 2014;15(2):1865-86.

[30] Ola MS, Ahmed MM, Ahmad R, Abuohashish HM, Al-Rejaie SS, Alhomida AS. Neuroprotective Effects of Rutin in Streptozotocin- Induced Diabetic Rat Retina. J Mol Neurosci. 2015;56(2):440-8.

[31] Nawaz MI, Abouammoh M, Khan HA, Alhomida AS, Alfaran MF, Ola MS. Novel drugs and their targets in the potential treatment of diabetic retinopathy. Med Sci Monit. 2013;19:300-8.

[32] Al-Shabrawey M, Smith S. Prediction of diabetic retinopathy: role of oxidative stress and relevance of apoptotic biomarkers. EPMA J. 2010;1(1):56-72.

[33] Ola MS, Nawaz MI, Siddiquei MM, Al-Amro S, Abu El-Asrar AM. Recent advances in understanding the biochemical and molecular mechanism of diabetic retinopathy. J Diabetes Complications. 2012;26(1):56-64.

[34] Bekar IB. Growth Factors in the Pathogenesis of Retinal Neurodegeneration in Diabetes Mellitus. Curr Neuropharmacol. 2016;14(7):792-804.

[35] Reiter CE, Wu X, Sandirasegarane L, et al. Diabetes reduces basal retinal insulin receptor signaling: reversal with systemic and local insulin. Diabetes. 2006;55(4):1148-56.

[36] Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res. 2007;2007:43603.

[37] Ola MS, Berkich DA, Xu Y, et al. Analysis of glucose metabolism in diabetic rat retinas. Am J Physiol Endocrinol Metab. 2006;290(6):E1057-67.

[38] Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord. 2008;9(4):315-27.

[39] Sonta T, Inoguchi T, Tsubouchi H, et al. Evidence for contribution of vascular NAD(P)H oxidase to increased oxidative stress in animal models of diabetes and obesity. Free Radic Biol Med. 2004;37(1):115-23.

[40] Kiziltoprak H, Tekin K, Inanc M, Goker YS. Cataract in diabetes mellitus. World J Diabetes. 2019;10(3):140-53.

[41] Asogwa PO, Sarella PN. Observational Studies of Prescription Pattern and Use of Antibiotics in Selected Rural Areas. Int J Pharm Sci and Medicine. 2023;8:21-30.

[42] Bixler JE. Cataracts and Their Treatment in People with Diabetes. In: Prevention and Management of Diabetes- Related Eye Disease. Arlington (VA): American Diabetes Association; 2019 May.

[43] Javadi MA, Zarei-Ghanvanti S. Cataracts in diabetic patients: a review article. J Ophthalmic Vis Res. 2008;3(1):52-65.

[44] Sarella PN, Mangam VT. AI-Driven Natural Language Processing in Healthcare: Transforming Patient-Provider Communication. Indian Journal of Pharmacy Practice. 2024;17(1)

[45] Lim AK. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis. 2014;7:361-81.

[46] Sarella PN, Vipparthi AK, Valluri S, Vegi S, Vendi VK. Nanorobotics: Pioneering Drug Delivery and Development in Pharmaceuticals. Research Journal of Pharmaceutical Dosage Forms and Technology. 2024 Feb 22;16(1):81-90.

[47] Karmakar S, Bhowmik M, Laha B, Manna S. Recent advancements on novel approaches of insulin delivery. Medicine in Novel Technology and Devices. 2023 Jul 14:100253

[48] Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int. 2021;2021:1497449.

[49] Gorrepati N, Tummala SR. A Case Report on Antiphospholipid Antibody Syndrome with Chronic Pulmonary Embolism Secondary to Deep Vein Thrombosis and Thrombocytopenia: Case report. Journal of Pharma Insights and Research. 2024 Apr 30;2(2):272-4

[50] Sarella PN, Vegi S, Vendi VK, Vipparthi AK, Valluri S. Exploring Aquasomes: A Promising Frontier in Nanotechnology-based Drug Delivery. Asian Journal of Pharmaceutical Research. 2024 May 28;14(2):153-61

[51] Mallu UR, Nair AK, Sankar J, Bapatu HR, Kumar MP, Narla S, Bhanap TA, Thamma NK, Raman NV. Impact of API (active pharmaceutical ingredient) source selection on generic drug products. Pharmaceut Reg Affairs. 2015 Mar 13;4(2):11

[52] Kumar AV, Joseph AK, Gokul GU, Alex MP, Naveena G. Clinical outcome of calcium, Vitamin D3 and physiotherapy in osteoporotic population in the Nilgiris district. Int J Pharm Pharm Sci. 2016;8:157-60.