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DIABETIC NEPHROPATHY: RISK FACTORS AND MANAGEMENT

Abstract

Diabetic nephropathy is a clinical condition characterized by severe albuminuria, decreased glomerular filtration rate (GFR), and increased arterial blood pressure. The first sign of diabetic nephropathy is albuminuria, followed by accessory edema. Fluid retention occurs early during the kidney disorder, even before a significant decrease in serum albumin. A 24-hour urinalysis is useful in quantifying protein losses and estimating GFR. Systemic hypertension accelerates the progression of diabetic nephropathy, and there is a correlation between blood pressure and the rate of GFR decline. Histological changes in the glomeruli include mesangial expansion, thickening of the glomerular basement membrane, and glomerular sclerosis. These changes have prognostic significance. The pathophysiology of diabetic nephropathy begins with poorly regulated blood glucose levels, leading to abnormalities in the nephrons. Diabetic nephropathy is associated with significant morbidity and mortality, with proteinuria being a predictor of both. The frequency of albuminuria in both types of diabetes is approximately 30-35%.

Keywords: Diabetic nephropathy, albuminuria, glomerular filtration, peripheral edema, creatinine, mesangial expansion, hyperglycemia, proteinuria

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I. INTRODUCTION

Diabetes mellitus (DM) is a condition that can lead to a significant concern known as diabetic retinopathy (DR), which remains the primary cause of vision loss in the working-age population. The diagnosis of DR is based on the clinical manifestations of vascular abnormalities in the retina. DR is clinically categorized into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the early phase of DR, where the main observations in the retinal vasculature are increased vascular permeability and capillary occlusion. Even though patients may not exhibit symptoms, fundus images can reveal retinal pathologies such as microaneurysms, hemorrhages, and hard exudates. On the other hand, PDR is a more advanced stage of DR characterized by neovascularization. During this phase, patients may experience severe visual impairment due to vitreous hemorrhage or tractional retinal detachment caused by the bleeding of abnormal vessels into the vitreous.

Diabetic macular edema (DME) is the primary cause of vision loss in patients with diabetic retinopathy (DR). DME occurs when the macula, which is responsible for central vision, becomes swollen or thickened due to fluid accumulation within the macula. This fluid buildup is a result of the breakdown of the hematoretinal barrier (BRB), leading to sub- and intraretinal fluid accumulation [1]. DME can occur at any stage of DR and can cause visual distortion and a decrease in visual acuity. Current treatment strategies for DR primarily focus on managing the microvascular complications associated with the disease. These approaches include the use of intravitreal pharmacological agents, laser photocoagulation, and vitreous surgery. Among these treatment options, the intravitreal administration of anti-VEGF agents has emerged as the cornerstone of therapy for both early and advanced stages of DR. Unlike traditional laser therapy, which only stabilizes visual acuity, anti-VEGF treatment has shown the potential to improve vision while minimizing ocular adverse effects. However, despite the effectiveness of anti-VEGF therapy [2], studies have revealed that a significant proportion of DME patients do not respond adequately to this treatment. The Diabetic Retinopathy Medical Studies Community (DRCR.net) conducted a study known as Protocol-I, which demonstrated that only 29% of DME patients experienced a significant improvement in visual acuity after receiving several years of anti-VEGF therapy. This lack of response to anti-VEGF treatment suggests that there may be other molecular pathways involved in the development of DR, beyond just VEGF. Therefore, it is crucial to conduct further research to gain a deeper understanding of the underlying mechanisms of DR. By identifying these mechanisms, researchers can potentially discover new therapeutic targets that can be utilized to develop alternative treatments for DR. The discovery of new therapeutic approaches is essential to effectively address the complexities of DR and improve outcomes for patients. By unraveling the underlying mechanisms of the disease, researchers can pave the way for the development of innovative treatments that target these specific pathways. Ultimately, this research has the potential to revolutionize the management of DR and provide better visual outcomes for patients suffering from this debilitating condition. Researchers have the opportunity to discover new routes and potential focal points that could lead to the creation of groundbreaking treatments that may enhance or exceed the effectiveness of anti-VEGF therapy in the treatment of Diabetic Macular Edema (DME) and various types of Diabetic Retinopathy (DR). By delving into different avenues and considering various targets, scientists can potentially uncover novel approaches that can enhance or even outperform the efficacy of anti-VEGF therapy when it comes to addressing Diabetic Macular Edema (DME)

and other manifestations of Diabetic Retinopathy (DR).

II. DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders that lead to high levels of blood glucose, also referred to as blood sugar. This medical condition can be caused by insufficient insulin production, ineffective response of the body's cells to insulin, or a combination of both factors. The term "Diabetes Mellitus" is utilized to define a metabolic disorder with diverse origins, marked by continual elevation of blood sugar levels and disturbances in the metabolism of carbohydrates, fats (dyslipidemia), and proteins. These disturbances happen due to abnormalities in insulin secretion, its function, or both. The primary varieties of diabetes are:

1. Type 1 Diabetes

Type 1 diabetes is a medical condition where the body is unable to produce insulin, requiring the individual to administer insulin injections. Formerly referred to as "Insulin-dependent Diabetes Mellitus" (IDDM) or "Juvenile Diabetes", this autoimmune disease involves the immune system targeting and eliminating the beta cells responsible for insulin production in the pancreas, leading to insufficient insulin levels in the body. Consequently, the affected person must regularly inject insulin to manage their blood sugar levels effectively.

2. Type 2 diabetes

Insulin resistance is the leading factor behind the development of type 2 diabetes, a condition characterized by cells failing to effectively utilize insulin, sometimes accompanied by a complete absence of insulin. Previously known as Noninsulin-dependent Diabetes Mellitus (NIDDM) or "adult-onset diabetes," this type of diabetes is distinguished by a range of symptoms, including frequent urination (polyuria), increased thirst (polydipsia), and heightened hunger (polyphagia). The kidneys play a vital role in filtering the blood and eliminating excess fluid and waste products through urine. However, elevated levels of sugar in the bloodstream can cause damage to the small blood vessels and tiny filters within the kidneys. Consequently, these filters may become permeable and less efficient. As a result, abnormal amounts of protein from the blood can be excreted in the urine, often serving as an early indication of kidney disease.

Diabetic nephropathy (DN) stands as the primary cause of chronic kidney disease (CKD) on a global scale and represents one of the most severe complications of diabetes. It is a significant, yet often overlooked, contributor to the overall burden of chronic diseases. Despite the numerous advancements in diabetes management witnessed in recent decades, DN still affects approximately 30% of individuals with type 1 diabetes and nearly 50% of those with type 2 diabetes. Although the incidence of end-stage renal disease (ESRD) has shown signs of stabilization in the past ten years, the rising prevalence of diabetes due to factors such as obesity, aging, and a decrease in deaths related to cardiovascular diseases has led to a substantial increase in the number of individuals living with diabetes. In 2015, the estimated number of diabetes cases worldwide was 415 million, with projections indicating a rise to 642 million cases by 2040, with 90% to 95% of these cases being type 2 diabetes. These figures clearly illustrate the rapid growth in the prevalence of DN. The development of

DN in individuals with diabetes significantly heightens the risk of cardiovascular diseases, infections, and cancers, as well as cardiovascular-related and overall mortality rates. Recent research has shown that the excess mortality linked to diabetes is particularly pronounced in those who develop kidney disease. Individuals with diabetes alone face a twofold higher risk of cardiovascular mortality compared to the nondiabetic population, while those with both diabetes and kidney disease face a threefold to twelvefold higher risk of mortality. Due to the elevated mortality rates associated with DN, only a small percentage of individuals with the condition manage to survive ESRD. The increasing prevalence of DN underscores the urgent need for enhanced strategies in diabetes management and kidney disease prevention to mitigate the escalating burden of this condition on a global scale.

Poorly managed diabetes can lead to a range of serious health complications, with one of the most concerning being diabetic kidney disease (DKD). DKD is a significant contributor to end-stage renal disease (ESRD) in individuals with diabetes, resulting in a mortality risk that is 10 to 100 times higher compared to those with normal kidney function at the same age. This alarming increase in mortality emphasizes the devastating impact of DKD. Between 1990 and 2012, the number of deaths worldwide attributed to DKD rose by a staggering 94% due to the growing prevalence of diabetes and its associated complications. As cases of DKD and diabetes-related ESRD continue to rise, it is crucial to address this global health crisis, particularly in regions with limited access to renal replacement therapy. Detecting kidney disease in its early stages can be challenging as there may be no obvious symptoms. This underscores the importance of annual screening to identify any problems early on when treatment can still slow down the progression of the disease. If kidney disease goes untreated, noticeable signs such as swollen extremities, blood in urine, fatigue, shortness of breath, and nausea may start to manifest. However, it is important to note that these symptoms can also be caused by other conditions. Therefore, it is crucial to consult a doctor and discuss any concerning symptoms for proper evaluation and recommendations. Taking prompt action is essential in preserving kidney function and avoiding the negative health outcomes associated with advanced DKD. Fortunately, there are steps that individuals with diabetes can take to reduce their risk of developing this life-threatening complication. Early detection, coupled with lifestyle changes, medication, and careful monitoring, can significantly decrease the likelihood of developing advanced DKD. By actively managing their diabetes and working closely with healthcare professionals, individuals can mitigate the impact of DKD and improve their overall health outcomes. This is particularly important in regions where access to renal replacement therapy is limited, as prevention and early intervention become even more crucial. Addressing the global health crisis posed by DKD requires a comprehensive approach that encompasses education, awareness, and improved healthcare infrastructure to ensure that individuals with diabetes receive the necessary support and resources to manage their condition effectively.

III. TEST FOR KIDNEY DISORDER

The two tests for kidney disorder are.

Urine test (ACR): The urine test, known as the albumin: creatinine ratio (ACR), is a straightforward method of detecting protein leakage in the urine. This leakage is an indication of the early stages of kidney disease. By measuring the levels of albumin and creatinine in the urine, healthcare professionals can determine if there is any abnormal protein excretion, which can be a sign of kidney damage.

Blood test (eGFR): On the other hand, the blood test focuses on assessing the efficiency of the kidneys by measuring the levels of creatinine, a waste product in the body. This test, known as the estimated glomerular filtration rate (eGFR), takes into account various factors such as age, gender, and ethnicity to estimate how well the kidneys are functioning. By analyzing the eGFR, healthcare professionals can gain valuable insights into the overall health of the kidneys and identify any potential issues.

Diabetic nephropathy, a complication of diabetes, can be categorized into different stages based on the presence of albuminuria (the presence of albumin in the urine) and the level of renal impairment. These stages include microalbuminuria and macroalbuminuria. It is now understood that microalbuminuria is not just a predictor but an early stage of diabetic nephropathy. However, the presence of microalbuminuria does indicate a higher likelihood of developing more severe renal impairment in the future. Interventions aimed at reducing microalbuminuria and bringing it closer to normal levels have been proven to delay the onset of renal impairment and, in some cases, even reverse the progression of kidney damage caused by diabetes. Macroalbuminuria, on the other hand, is more commonly observed in patients with type-2 diabetes. Incipient nephropathy refers to the initial presence of small but normal amounts of urine albumin, known as microalbuminuria. Overt nephropathy, or macroalbuminuria, develops after several years in type 1 diabetes but may already be present at the time of diagnosis in type-2 diabetes. Patients who progress to macroalbuminuria are at a higher risk of developing end-stage renal disease (ESRD), which is the final stage of kidney disease where the kidneys can no longer function properly. Therefore, early detection and management of albuminuria are crucial in preventing the progression of diabetic nephropathy and preserving kidney function.

In individuals with untreated type-1 diabetes, a significant portion of patients with sustained microalbuminuria will observe a gradual increase in albumin excretion ranging from 10% to 20% annually until the development of overt nephropathy, a process that typically occurs throughout 10 to 15 years. Following the onset of overt nephropathy, there is a notable decline in the glomerular filtration rate (GFR) at a rate of 2 to 20 ml/minute per year, leading to the development of end-stage renal disease (ESRD) in approximately 50% of patients within a decade and 75% within two decades. Structural alterations within the kidneys, such as thickening of the glomerular basement membrane and enlargement of the mesangial cells, can be identified as early as 2 to 8 years after the initiation of diabetes, highlighting the progressive nature of renal complications in untreated type-1 diabetes.

IV.SYMPTOMS

The early stages of diabetic nephropathy may not exhibit any symptoms, posing a challenge in its identification. However, as the disease advances, a range of signs may become apparent, including uncontrolled hypertension, swelling in the limbs, frothy urine, cognitive decline, breathing difficulties, reduced appetite, queasiness, skin irritation, tiredness, and muscle weakness. If diabetes remains unregulated over an extended period, it can lead to the breakdown of the blood vessels in the kidneys that are responsible for eliminating toxins from the blood. This impairment can result in diminished kidney function and the onset of high blood pressure. The heightened stress on the kidney's filtration mechanism due to hypertension can worsen kidney damage, establishing a harmful cycle of deteriorating renal health. Effective management of diabetes is essential to either prevent or decelerate the

progression of diabetic nephropathy and its associated complications. By controlling blood sugar levels, individuals can reduce the risk of kidney damage and maintain optimal kidney function. Regular monitoring, lifestyle modifications, and adherence to prescribed medications are crucial components of diabetes management to safeguard against the detrimental effects of diabetic nephropathy [3].

V. CAUSES

Diabetic nephropathy, a complication commonly associated with both type 1 and type 2 diabetes, is often accompanied by high blood pressure, also known as hypertension. This condition is believed to have a significant impact on the development and progression of diabetic nephropathy. It is thought that hypertension can contribute to the onset of the disease, while also being a consequence of the damage caused by the condition itself. Over time, as kidney function deteriorates, structural changes occur within the kidneys that can lead to an increase in blood pressure levels. This elevation in blood pressure can further worsen the progression of diabetic nephropathy, potentially hastening the advancement of the disease to its most severe stage, stage five. Apart from hypertension, the elevated levels of blood sugar associated with diabetes can also inflict damage on the kidneys through various complex mechanisms. This damage primarily affects the blood vessels responsible for filtering the blood to produce urine, making the management of diabetic nephropathy even more challenging. These intricate interactions between high blood pressure, elevated blood sugar levels, and kidney damage contribute to the complexity of diabetic nephropathy and highlight the importance of comprehensive management strategies [4].

VI. RISK FACTORS

Diabetic individuals face an elevated risk of developing diabetic nephropathy due to various factors. These factors encompass uncontrolled hyperglycemia, uncontrolled hypertension, smoking, high blood cholesterol levels, obesity, a family history of diabetes, and pre-existing kidney disease [3]. Inadequate management of blood sugar levels and high blood pressure can significantly heighten the chances of diabetic nephropathy in diabetic patients. Furthermore, smoking and elevated blood cholesterol levels can exacerbate the risk of this condition. Obesity also contributes to the increased likelihood of diabetic nephropathy in individuals with diabetes. Additionally, a family history of diabetes and pre-existing kidney disease can predispose individuals to this complication. To minimize the risk of developing diabetic nephropathy, individuals with diabetes must effectively manage these risk factors.

VII. STAGES OF DIABETES-RELATED NEPHROPATHY

Diabetes-related nephropathy stages can be categorized based on the estimated glomerular filtration rate (eGFR). The eGFR is a measure of kidney function, with a normal value being around 100. At the lowest end of the spectrum, an eGFR of 0 indicates complete loss of kidney function. This information helps in understanding the severity of kidney damage in individuals with diabetes. The stages of any kidney disease, including diabetes-related nephropathy, include:

Stage I	Your glomerular filtration rate (GFR) is 90 or higher. At this stage, your kidneys have mild damage but still function normally.
Stage II	Your glomerular filtration rate (GFR) may be as low as 60 or as high as 89. You have more damage to your kidneys than in stage I, but they still function well.
Stage III	Your glomerular filtration rate (GFR) may be as low as 30 or as high as 59. You may have mild or severe loss of kidney function.
Stage IV	Your glomerular filtration rate (GFR) may be as low as 15 or as high as 29. You have severe loss of kidney function.
Stage V	Your glomerular filtration rate (GFR) is below 15. Your kidneys are nearing or at complete failure.

VIII. THERAPY

Timely initiation of treatment can significantly delay or even stop the advancement of diabetic nephropathy. The main goal of the treatment protocol is to efficiently control and regulate both blood glucose levels and blood pressure. This comprehensive treatment plan may involve the prescription of different medications customized to suit the unique requirements and overall health status of the individual.

1. Drug Treatment

ACE inhibitors and ARBs are commonly used medications to lower blood pressure, protect kidney function, and prevent further damage in patients with chronic kidney disease (CKD). However, Kerendia (finerenone) stands out as a prescription drug specifically formulated to reduce the risk of a permanent decline in glomerular filtration rate (GFR), end-stage renal disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adults with CKD associated with type 2 diabetes. Along with these medications, doctors may also recommend vitamin D supplements to address deficiencies often seen in individuals with kidney disease, as well as statins to manage cholesterol levels. Noteworthy, the American College of Cardiology has endorsed the use of SGLT2 inhibitors or GLP-1RA for individuals with type 2 diabetes and CKD, as these medications have demonstrated potential in reducing the progression of CKD and lowering the risk of cardiovascular events [5].

2. Dietary Changes

If a person has kidney disease, their doctor may ask them to monitor the following nutrients.

- **Water:** Although essential, too much water or fluids can increase the risk of swelling and high blood pressure
- **Sodium**: Can raise blood pressure because it is a component of salt.
- **Protein:** In people with kidney disease, protein can cause waste to build up in the blood, putting more pressure on the kidneys.
- **Phosphorus:** Found in many protein and dairy foods. Too much phosphorus can weaken bones and put pressure on the kidneys.
- **Potassium:** People with kidney disease may have higher than healthy levels of potassium, which can affect nerve cells.

- **Blood sugar management**: Reducing the risk of diabetes complications, such as kidney disease, cardiovascular disease, and diabetic neuropathy, is crucial for maintaining good health. These conditions can have severe consequences, and it is important to take proactive measures to prevent them. By effectively managing blood sugar levels, individuals can significantly reduce the likelihood of developing these complications and safeguard their overall well-being.
- **Treatment options in the last stage:** If diabetic nephropathy advances to end-stage renal disease (ESRD), individuals will require either dialysis or a kidney transplant. Typically, dialysis will be necessary for the remainder of their lives, unless a suitable kidney becomes available for transplantation [4].

IX.SUMMARY

The examination of this chapter in the book leads us to the deduction that Diabetic Nephropathy is a prevalent and severe chronic complication of microvascular kidney disease. In numerous Asian urban areas, particularly in Asia, diabetic nephropathy has emerged as the primary cause of end-stage renal disease, aligning with economic progress, predominantly linked to type 2 diabetes. It is estimated that approximately 30-40% of individuals with type 2 diabetes will develop diabetic nephropathy, with genetic and environmental factors playing a role in its development. The genes associated with the onset and advancement of diabetic nephropathy are still being investigated, indicating a need for further exploration in this area. Several risk factors have been identified as contributing to an increased likelihood of developing diabetic nephropathy, encompassing both environmental and hereditary elements. Significant progress has been made in managing blood glucose levels, implementing antihypertensive therapies to inhibit the renin-angiotensin system in cases of elevated albuminuria, and promoting lifestyle modifications. These interventions have had a positive impact on the prognosis of the condition. However, despite these advancements, the incidence of diabetic nephropathy remains high, and the associated morbidity and mortality rates continue to pose significant challenges. Therefore, there is an urgent need for the development of new therapies to address this ongoing issue and improve outcomes for individuals affected by diabetic nephropathy. Further research and exploration into the genetic and environmental factors contributing to the development of diabetic nephropathy are crucial to better understand the disease and develop targeted treatments. By addressing the underlying causes and risk factors, it is hoped that the incidence and severity of diabetic nephropathy can be reduced, ultimately improving the quality of life for those affected by this condition.

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