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Diabetic Nephropathy is One of the Biggest Complications of Diabetes

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Abstract

The kidneys consist of countless glomeruli, which are clusters of capillaries responsible for filtering blood, allowing the urine formed to travel through the ureters to the bladder, from which it is expelled via the urethra. In the initial phases of diabetic nephropathy, the glomeruli experience enlargement attributed to early changes in hemodynamics and elevated pressure within them. This leads to impairment of the glomerular membrane, resulting in the leakage of albumin and additional proteins into the urine. The thickness of the glomerular membrane can reach up to three times its normal size, particularly in individuals exhibiting microalbuminuria. As the condition progresses, glomerular sclerosis takes place, demonstrated by a decline in kidney functionality. The early identification approach for nephropathy relies on detecting microalbumin in a sample of first-morning urine, while ongoing monitoring necessitates evaluating albumin in a 24-hour urine sample. Measuring serum creatinine serves as a solid gauge of kidney health. As blood pressure may be mildly elevated during the initial phases, conducting a 24-hour Holter blood pressure analysis is essential to ensure that pressure does not lower during the night, which can frequently indicate the onset of diabetic nephropathy.

Keywords: Diabetic nephropathy; Diabetes; Kidney; Stages; Health

Introduction

Diabetic Nephropathy is a significant contributor to chronic kidney disease [1]. There is observable thickening of the glomerular basement membrane, along with glomerular sclerosis and mesangial expansion. Recognized as one of the primary complications of diabetes mellitus, diabetic nephropathy leads to kidney failure and mortality if left untreated. The alterations that occur result in elevated pressure within the glomeruli and a gradual decrease in the glomerular filtration rate. In the presence of systemic hypertension, the advancement of diabetic nephropathy can accelerate. Typically, it shows no symptoms until nephrotic syndrome or kidney failure occurs. The identification of urinary albumin is critical for diagnosing diabetic nephropathy. Following a diabetes diagnosis, urinary albumin levels should be consistently monitored at least annually through the albumin: creatinine ratio measurement. The management of diabetic nephropathy involves rigorous control of blood glucose and blood pressure.

It is commonly characterized by exceeding 500 mg of albumin in a 24-hour urine collection, which is recognized as overt nephropathy [2]. However, patients initially experience stages of lower protein excretion, referred to as microalbuminuria. Proteinuria affects 15% to 40% of individuals with Type 1 diabetes, with the occurrence peaking around 15 to 20 years after diabetes onset. In those with Type 2 diabetes, the prevalence ranges from 5% to 20%.

Diabetic nephropathy first presents itself with the presence of albumin in urine; as kidney function deteriorates, there is a buildup of urea and creatinine in the bloodstream [3]. The optimal approach to evaluate albumin excretion is by measuring the albumin-creatinine ratio from a urine sample taken from a patient upon waking in the morning. In this early morning sample, a normal albumin (mcg/L) to creatinine (mg/L) ratio is identified as being under 30 mcg/mg of creatinine, while a ratio between 30 and 300 mcg/mg indicates unusual microalbuminuria. To confirm a diagnosis of microalbuminuria, it is necessary for at least two early morning urine samples collected over a span of three to six months to show abnormal results. Factors like brief periods of high blood sugar, physical activity, urinary tract infections, heart

failure, and sudden fever can lead to short-lived albuminuria, thus any microalbuminuria assessments should wait until these issues are resolved.

The development of end-stage kidney disease can be anticipated if there are ongoing urinary albumin excretion rates that are more than 30 mcg/mg creatinine. Managing blood sugar levels as well as adhering to a protein intake of approximately 0.8 g/kg/day can mitigate hyperfiltration and diminish elevated microalbuminuria in individuals with early diabetes or those facing initial stages of diabetic nephropathy. The use of antihypertensive medications contributes to the reduction of microalbuminuria. Research from various studies indicates that ACE inhibitors play a specific role in lowering the pressure within the glomeruli in addition to managing overall blood pressure. In diabetes patients who are normotensive, administering an ACE inhibitor such as captopril at 50 mg twice daily can slow the advancement to proteinuria and help maintain a stable albumin excretion rate. SGLT-2 inhibitors should be prescribed for individuals with type 2 diabetes experiencing worsening kidney issues, even when they are on optimal antihypertensive treatment that includes either an ACE inhibitor or an ARB.

Nephropathy

Increased activity through the polyol pathway results in a reduction of myo-inositol, decreased Na/K ATPase function, and sodium accumulation in diabetic nerves [4]. Supporting evidence has highlighted the connection between these biochemical alterations and nerve dysfunction, which has emerged from studies showing that ARIs can inhibit polyol pathway function, prevent the reduction of myo-inositol, stop sodium buildup, and maintain Na/K ATPase activity along with nerve integrity. Nevertheless, the underlying pathophysiological processes of diabetic neuropathy may differ from those affecting diabetic nephropathy. Observations in the kidney cortex of diabetic rats indicate that levels of polyols, as well as those in the medulla and red blood cells, rise substantially, while myo-inositol levels decrease by 30% exclusively in the kidney cortex, and Na/K ATPase activity diminishes by 59% solely in red blood cells. Conversely, in rats treated with the ARI tolrestat, only the Na/K ATPase activity in red blood cells showed improvement, while myo-inositol levels, Na/K ATPase activity, and conduction velocity within the sciatic nerve remained unchanged.

The thickening and duplication of the tubular basement membrane have been proposed as an initial occurrence in diabetic nephropathy. When confluent monolayers of LLCPK1 cells in tissue culture were incubated, the treatment with D-glucose resulted in a marked increase of fibronectin in the basolateral area. The rise in fibronectin levels triggered by glucose exposure could be countered by sorbinil. Furthermore, the activation of the polyol pathway by glucose could potentially contribute to a lack of contractility in renal arteriolar smooth muscle and glomerular mesangial cells.

CKD

Diabetic nephropathy serves as the leading factor for Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD), with approximately 50% of individuals undergoing dialysis globally being diabetic [5]. The estimated occurrence of CKD in those with diabetes is around 40%. Although recent studies indicate a decline in ESRD rates among patients with Type 1 Diabetes Mellitus (T1DM) attributed to better monitoring, improved blood sugar levels, and the use of RAAS inhibitors such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, the overall incidence of nephropathy is escalating due to rising cases of Type 2 Diabetes Mellitus (T2DM), creating a considerable strain on both patients and healthcare resources.

Even brief instances of acute renal injury can signal more severe repercussions. An observational study involving diabetic patients found that 29% of those hospitalized encountered a single acute kidney injury episode, which heightened their risk of advancing to ESRD. This highlights the necessity for diligent monitoring of hospitalized Diabetes Mellitus (DM) patients alongside the adjustment of their anti-hyperglycemic medications, since a decreasing Glomerular Filtration Rate (GFR) under a previous treatment plan may result in hypoglycemia. Both hyperglycemia and hypoglycemia independently contribute to inpatient results. Patients with renal issues in hospitals face a heightened risk of hypoglycemia due to variations in kidney performance, food consumption, medications, and various factors associated with their condition.

Insulin has been the benchmark for managing diabetes in hospital settings for a long time; however, newer diabetes medications that are deemed safe and effective for those with impaired renal function have begun to be studied more recently. Their adoption is rising as several trials have proven their effectiveness. DPP-4 inhibitors, such as sitagliptin and linagliptin, have been researched for diabetes management in hospitals and nursing homes as well as during the transition from hospital care to home. Emerging data regarding the use of SGLT-2 inhibitors in hospital settings show trials assessing their initiation in terms of Heart Failure (HF) outcomes when started shortly after admission or just before or after discharge. The safety profiles of these medications in HF studies can be applied to glucose regulation. Additionally, GLP-1 Receptor Agonists (GLP-1RAs) and SGLT-2 inhibitors have demonstrated the ability to slow the progression of renal disease, assuming appropriate dosage modifications for the CKD population. Using insulin in hospital settings is associated with a risk of hypoglycemia. Research involving hospitalized CKD patients emphasizes the critical need for dosage adjustments correlated with CKD severity to avert hypoglycemia.

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Factors

At most, it is likely that about 40% of individuals with diabetes will experience nephropathy [2]. Evidence indicates that there is familial aggregation regarding this complication, suggesting that genetic factors contribute to the onset of nephropathy in both types 1 and 2 diabetes mellitus. In this context, several modifiable elements can trigger the onset and advancement of nephropathy, including elevated blood sugar levels and high blood pressure. Additional causative factors comprise glomerular hyperfiltration, the presence of protein in urine, smoking, abnormal lipid levels, and dietary influences, particularly concerning protein and fat intake.

Diabetes Mellitus (DM) is primarily an oxidative and metabolic condition that affects carbohydrate metabolism, although in severe instances, protein and lipid metabolism can also be impacted [6]. It is marked by elevated blood glucose levels beyond the normal range due to either a complete or partial lack of insulin. Continuous high blood sugar levels over time are the main contributor to the onset of complications in diabetes. DM is linked with various complications involving the eyes, kidneys, heart, and liver. Among the biochemical problems associated with it are hypoglycemia, hyperglycemic crisis, diabetic ketoacidosis, and hyperglycemic hyperosmolar state. Diabetic kidney disease (nephropathy) stands as a significant cause of chronic kidney failure, increasing morbidity and mortality levels. It is identified by a reduced Glomerular Filtration Rate (GFR), thicker glomerular basement membrane, collapsed glomeruli, tubulo-interstitial fibrosis, lower albumin excretion rates, and diminished creatinine clearance. Continuous and unmanaged high blood sugar levels create oxidative stress, which contributes to the harmful developments in the diabetic kidney condition. Recent studies have shed light on the evolving nature of diagnostic and prognostic indicators related to diabetic nephropathy.

Changes

The typical histological alterations seen in diabetic nephropathy involve thickening of the Glomerular Basement Membrane (GBM) and expansion of the mesangial area [2]. The GBM not only becomes thicker, but it also becomes biochemically and functionally impaired, leading to albumin seepage into the urine. The impaired performance of the GBM, combined with elevated transglomerular pressure resulting from excessive constriction of the efferent glomerular arteriole relative to the afferent arteriole, causes proteinuria. Furthermore, the growth of the mesangium reduces the glomerular capillary lumen, which, in turn, diminishes glomerular filtration.

The involvement of hyperglycemia in the pathophysiology is intricate and influences this through enhanced growth factors (such as transforming growth factor-β and vascular endothelial growth factor), stimulation of protein kinase C, increased oxidative stress, heightened creation of advanced glycosylation end products, and an augmented flow through the aldose reductase pathway.

The Glomerular Basement Membrane (GBM) is a delicate structure located within the kidney nephrons [1]. Each nephron is comprised of three components: a small blood vessel that supplies unfiltered blood, the glomerulus, and another small blood vessel that carries filtered blood back to the body. The initial alteration in the kidneys that frequently occurs due to diabetes is the thickening of the GBM, which acts as a barrier between blood and urine. When the membrane is compromised, proteins can leak from the blood into the urine. Even in the early and mild stages of kidney disease, albumin can often be found in the urine. Electron microscopy reveals damage to the GBM. If the condition continues to progress over time, the kidneys may eventually fail to function properly, resulting in renal failure. GBM nephropathy is also referred to as thin basement membrane nephropathy.

GBM nephropathy is believed to impact roughly 1% to 10% of the population, with many specialists asserting that the true figure is likely around 1% or 2%. This form of nephropathy is observed more frequently in individuals with type 1 diabetes compared to those with type 2 diabetes. In addition to its association with diabetes, it ranks as the most prevalent hereditary kidney disorder. Reports have documented GBM across various ethnicities, including Caucasians, Africans, Chinese, and Indians. The median age at which the condition manifests is 37 years for adults and 7 years for children. The disease has been noted to cause hematuria in individuals aged between 1 and 86 years. It is 1. 6 times more prevalent in females than in males.

Blood Pressure

Research has shown a strong link between blood pressure levels and the diminishing rate of Glomerular Filtration Rate (GFR) [7]. This indicates that elevated systemic blood pressure may hasten the advancement of diabetic nephropathy. Previously, it was believed that the negative effects of systemic hypertension on kidney structure and function occurred primarily through vasoconstriction and arteriolar nephrosclerosis. However, studies involving rat models indicate that systemic hypertension impacts individual glomeruli, causing an increase in glomerular hydrostatic pressure, which in turn leads to hyperperfusion and elevated capillary pressure. Instances of intraglomerular hypertension have been observed directly in rats suffering from streptozotocin-induced diabetes and are estimated to be common in human diabetic patients, especially those whose diabetes has caused renal complications. The reduction or loss of renal autoregulation of GFR and renal plasma flow, as shown in nephropathy-afflicted type 1 and type 2 diabetic patients, heightens the risk of hypertension or ischemic damage to glomerular capillaries.

Elevated nighttime blood pressure (often referred to as "nondipping") is more prevalent among those with nephropathy. An exaggerated blood pressure response during physical activity

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has also been noted in patients with prolonged type 1 diabetes who exhibit microangiopathy.

Multiple elements of the Renin-Angiotensin-Aldosterone System (RAAS) are heightened and are thought to play a role in the advancement of diabetic nephropathy. Consequently, inhibiting the RAAS has been shown to offer renal protection. The initial focus was on the detrimental impacts of angiotensin II. Aldosterone is yet another factor of the RAAS that is considered significant in the mechanisms behind diabetic nephropathy. Aldosterone is crucial for managing electrolyte levels and fluid balance and exerts extensive effects through both genomic and nongenomic pathways, influencing not only the kidneys but also blood vessels, the central nervous system, and the heart, which were not previously seen as target tissues.

It has been proposed that levels of uric acid are associated with hypertension, metabolic syndrome, and renal issues. Recently, high serum uric acid has been discovered to be a significant predictor of the onset of diabetic nephropathy among type 1 diabetic patients. A multicenter trial was launched to examine whether lowering uric acid using allopurinol compared to a placebo in 530 type 1 diabetes patients with early signs of diabetic nephropathy would help maintain kidney function, but after three years, no significant difference in the decline of GFR was observed.

Diagnosis

The identification of the condition is straightforward in individuals with long-standing (>10 years) Type 1 Diabetes Mellitus (T1DM) who experience kidney function issues and protein in the urine, particularly when retinopathy is also present, which is referred to as the retinal–renal syndrome [2]. In contrast, the diagnosis in those with Type 2 Diabetes Mellitus (T2DM) may be less definitive, primarily because the precise initiation of the illness is often ambiguous; additionally, around 25% of patients might not exhibit retinopathy.

A clinical diagnosis of diabetes-related kidney disease can occur when there is consistent albuminuria and/or sustained reductions in the Glomerular Filtration Rate (GFR). Proteinuria screening can be easily performed through a spot urine sample. Given the recognized fluctuations in daily urinary albumin release, a diagnosis should only be established if two separate samples show abnormal results. Furthermore, it is essential to rule out other causes that may elevate urinary albumin levels, including urinary tract infections, blood in urine, acute fever, uncontrolled high blood pressure, heart failure, intense physical activity, and brief episodes of significant high blood sugar. A decreased GFR is classified as an Estimated GFR (eGFR) of less than 60 mL/min/1.73 m2 using a formula based on creatinine levels. The persistence of these anomalies for a minimum of three months must be verified since temporary fluctuations, which can arise from various unrelated conditions, are not uncommon.

It's vital to emphasize that albuminuria is not a prerequisite for the clinical diagnosis of diabetic kidney disease. A notable portion of diabetes patients with reduced eGFR may have less than 30 mg/g of albuminuria, and these individuals frequently exhibit histopathological changes indicative of diabetic kidney disease.

Comorbidities

Patients suffering from diabetic nephropathy usually present with other microvascular complications. Significant retinopathy is nearly always found in those with type 1 diabetes and albuminuria, although this correlation is weaker in those with type 2 diabetes [8]. Additionally, peripheral neuropathy tends to be more prevalent among those with diabetic nephropathy and is linked to both albuminuria and lowering GFR. Autonomic neuropathy, identified through the absence of nighttime blood pressure decline, is frequently observed and serves as a predictor for the deterioration of kidney function.

Both albuminuria and reduced GFR independently and interactively enhance cardiovascular risk and are associated with rising morbidity and mortality rates. Individuals with T1DM exhibiting normoalbuminuria do not experience an elevated risk of early death; however, those with moderately high albuminuria face a two- to threefold increased risk, whereas those with severely high albuminuria have a ninefold amplified risk. Those with End-Stage Kidney Disease (ESKD) face an eighteenfold higher risk of premature death compared to the general non-diabetic population. Cardiovascular Disease (CVD) occurs 1.2 times more frequently in diabetes patients with moderately raised albuminuria and is ten times more prevalent among those with severely high albuminuria in comparison to individuals with normoalbuminuria.

In the case of T2DM, the risk for CVD is elevated two- to fourfold in those with moderately increased albuminuria and is nine times higher in those with severely increased levels. When serum creatinine levels exceed the normal range, the risk for cardiovascular complications escalates significantly.

Stages

Kidney disease related to diabetes mellitus affects around 25 to 40 percent of individuals with type 1 diabetes [6]. The progression of this condition is categorized into five stages, which are determined by assessing kidney function.

First Stage

In the initial stage, there is an increased rate of filtration caused by heightened demand on the kidneys. This results in elevated Glomerular Filtration Rate (GFR) and hypertrophy of the glomeruli.

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Second Stage

During the second phase, GFR remains either normal or elevated, but the damage to the glomeruli has intensified. There is considerable microalbuminuria stemming from ongoing hyperfiltration. This is shown by the enlargement of the mesangial area or the thickening of the basement membrane. In this stage, individuals excrete more than 30 mg of urinary albumin daily. If microalbuminuria continues, chronic kidney disease can develop. It is recommended that all individuals with diabetes have routine tests for microalbuminuria annually.

Third Stage

In the third stage, microalbuminuria continues, and the injury to the glomeruli advances to clinical albuminuria. Urine tests at this point will show a positive result for albumin using a dipstick. The urine contains over 300 mg of albumin daily. Hypertension often develops at this third stage, alongside mesangial sclerosis.

Fourth Stage

This stage arises in the later phases of diabetes mellitus. There is noticeable proteinuria and hypertension. Additionally, there is a progressive scarring of the glomeruli with increasing microalbuminuria. As the filtering ability of the kidneys begins to diminish, signs of kidney failure appear, indicated by rising levels of urea nitrogen and creatinine in the blood. Approximately 10 percent of GFR is lost each year.

Fifth Stage

This is the chronic renal disease stage. The Glomerular Filtration Rate (GFR) drops below 10 mL/min. There is fibrosis and sclerosis of the glomeruli. The primary treatments include renal replacement therapy, such as hemodialysis, peritoneal dialysis, or kidney transplantation.

Treatment

Effective management of blood sugar levels has been proven to help maintain kidney health and represents a crucial aspect of treatment [2]. Equally vital is managing blood pressure. The target should be under 140/90 mmHg (less than 125/75 mmHg if serum creatinine levels are elevated and proteinuria exceeds 1 gram every 24 hours). Treatment may begin with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, Renin-Angiotensin System (RAS) blockade, or SGLT-2 inhibitors, and many patients may require three to four different medications to reach their targets. Furthermore, certain GLP-1 receptor agonists have demonstrated a reduction in the likelihood of composite kidney outcomes (including new onset of albuminuria over 300 mg/day, doubling of serum creatinine, End-Stage Kidney Disease (ESKD), or kidney-related mortality). As SGL-2 inhibitors and GLP-1 receptor agonists also lower cardiovascular disease risks, they are significant in managing diabetes. Evidence suggests that statin medications might help preserve kidney function, along with dietary restrictions on protein intake.

Conclusion

30-40% of individuals diagnosed with diabetes will experience diabetic nephropathy at some point in their lives, which is one of the significant long-term complications associated with diabetes. The primary contributor to nephropathy is diabetes that is not well-managed. The onset of diabetic nephropathy occurs over an extended latency period, typically taking an average of 10 to 15 years following the initial diabetes diagnosis before kidney disease manifests. Elevated blood sugar levels lead to calcification in the larger blood vessels of the kidneys and also harm the smaller ones. This results in the body expelling more protein through urine, which can be identified through a urinalysis. Early detection and intervention are crucial in halting the disease's advancement and extending lifespan.

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