Review Article

Microalbuminuria;Risk Predictive Tooland Determinant ofEarly Treatment in Diabetic Nephropathy

Abstract

In people diagnosed with diabetes mellitus (DM), microalbuminuria (MAU) is thought to be the first indication of diabetic nephropathy. Early identification of microalbuminuria is essential, to properly manage diabetic nephropathy and its complications.Patients with DM, both newly and previously diagnosed, should be screened for microalbuminuria. A pivotal question in diabetes management is whether diabetic patients with microalbuminuria should be considered for early prophylactic treatment. However, current evidence strongly supports the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) as effective therapeutic strategies. Therefore, recent clinical guidelines have increasingly emphasized the necessity of routine screening for microalbuminuria in diabetic patients, particularly among those with both type 1 and type 2 diabetes mellitus. Thus, this review aims to reiterate the significance of early detection of microalbuminuria in the early treatment commencement of diabetic nephropathy among patients diagnosed with diabetes mellitus.

Keywords: microalbuminuria, diabetes mellitus, diabetic nephropathy

1.0 Introduction

Diabetes mellitus (DM) is becoming more prevalent worldwide at an alarming rate and is now a public health concern.[1]The 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas projects that there will be 537 million diabetics globally, with a current prevalence estimate of more than 10%.[2] In Africa, the number of people with diabetes is expected to increase by 162.5% by the year 2045.[2]

One of the common complications in people diagnosed with diabetes is diabetic nephropathy (DN), which is characterized by elevated arterial blood pressure, a progressive reduction in glomerular filtration rate (GFR), and chronic albuminuria.[3]It is the leading cause of end-stage renal disease and premature mortality in diabetic patients due to its insidious onset.[4] Approximately one-third to half of patients with diabetes develop these renal manifestations[5] and 20 to 40% of type 2 patients eventually develop nephropathy.[6]

The development of DN consists of several stages.Microalbuminuria (MAU) is considered the earliest sign of diabetic nephropathy among diabetes patients,[7] which can progress to overt proteinuria and ultimately end-stage renal disease (ESRD).The best-documented indicator of the high risk of developing diabetic nephropathy in patients with diabetes mellitus is still

microalbuminuria (MAU), which is defined as an albumin/creatinine ratio (ACR) of 30–300mg albumin/g of creatinine or a urinary albumin excretion rate of between 30–300 mg/24 hours.[8]

The prevalence of MAU among diabetes patients in Africa was reported as 37.11%higher than the European prevalence of (26% to 29%), Australia (26.1%), North India (25.5%), and Iran (14.2%).[7]The increased incidence of MAU among diabetics in Africa may be related to comorbid conditions like hypertension, which worsens systemic vasculopathy and other microvascular problems.[7]However, it has been demonstrated that early detection, medical intervention, and appropriate lifestyle changes can stop or reverse the progression from micro to macroalbuminuria.[9]Some data show that after 10 to 15 years of untreated type 1 diabetes with persistent MAU, over 80% of patients will develop overt nephropathy, and 50% will eventually progress to end-stage renal disease (ESRD). Also, after 20 years from the time of onset, 20–40% of type 2 diabetics with MAU develop overt nephropathy, and approximately 20% develop ESRD.[10]

MAU may serve as a risk indicator for cardiovascular events as well as the onset of kidney disease. However, its existence on its own does not signify existing kidney disease, particularly if the estimated glomerular filtration rate is more than 60mL/min/1.73 m^2.

Regardless of the presence of diabetes, MAU is recognized as a cardiovascular (CV) risk factor for myocardial infarction and stroke.[9]An increase in MAU, when blood pressure and other risk factors are controlled, portends a poor prognosis for kidney outcomes over time. Patients with long-standing, poorly controlled DMare more likely to have MAU than those without diabetes,likewise,those with MAU are at greater risk for developing hypertension, a risk factor known to increase CV risk.[9]Also, irrespective of diabetes status, individuals whose nocturnal blood pressure does not dip on 24hr ambulatory blood pressure monitoring for any reason, including sleep apnea, are more likely to have MAU.[11]

Aggressive risk factor treatment, emphasizing blood pressure and glucose targets, is crucial early in the course of DM to prevent cardiovascular disease and prevent/delay the onset of renal disease or manifestation[9]since microalbumin is an early indicator of systemic vasculopathy and other microvascular problems manifested in the urine of DM patients.[7]This study therefore sought to reaffirm the importance of MAU screening in patients with DM, and the necessity of focused treatment to prevent the development of out-blown macroalbuminuria and DN.

2.0 Overview of DM Nephropathy

2.1 Brief Pathophysiology

Diabetes mellitus is associated with deviations from normal metabolism in proteins, fats, and carbohydrates which brings about changes in the permeability of the glomerular membraneover time,a key factor in kidney-related complications.

The pathophysiology underlying microalbuminuria in diabetes is multifaceted, involving a complex interplay of hyperglycemia, hypertension, and dyslipidemia. Glycated albumin,

connected to the generation of reactive oxygen species and other cellular toxins, is the cause of vascular damage in diabetics. Following such an event, vascular injury advances more rapidly due to the increased influence of pressure hormones such as angiotensin II. The ultimate consequence is direct damage to the proximal tubular cells and podocyte basement membrane of the nephron, as well as to the vascular smooth muscle cells, endothelial cells, and visceral epithelial cells (podocytes) of the glomerular capillary wall membrane, which results in the formation of MAU.[12,13]The prevalence of MAU and level of albuminuria are higher in patients with isolated impaired glucose tolerance than those with impaired fasting glucose.[14]

Microalbuminuria serves as an early indicator of kidney damage and has been recognized as a significant risk factor not only for nephropathy but also for cardiovascular morbidity and mortality in diabetic patients (Vartian et al., 2021).

2.2 Genetic predisposition

Cubilin, a proximal tubule receptor protein involved in albumin reabsorption, is linked to impaired tubular reabsorption of albumin, a genetic defect that predicts the development of MAU.[15]Also, susceptibility loci and a missense variant in the cubilin genehave been identified to be associated with the development of MAU.[16] This missense variant was associated with a 41% increased risk for persistent MAU development over some years among participants with type 1 diabetes.[16]Since an increase in MAU is a known marker of nephropathy progression, particularly in those with a family history of nephropathy, the progressive rise in albuminuria levels associated with nephropathy may be related to the genetic susceptibility of nephropathy in some patients.[17]

2.3 Disease progression and complications

The early stages of diabetic nephropathy are frequently asymptomatic, making early identification difficult. Diabetic nephropathy usually presents clinically in multiple stages, each distinguished by unique features. The first indication of diabetic nephropathy, microalbuminuria, is seen at an early stage before any clinical symptoms manifest. Even though MAU patients may not exhibit any symptoms at this point, early action is essential to stop the disease from progressing.[18]As the disease progresses unchecked, patients enter the stage of overt nephropathy, characterized by macroalbuminuria (urinary albumin excretion >300 mg/day). Symptoms such as edema due to protein loss, which reduces oncotic pressure are experienced.[19] At the advanced stages of DM nephropathy, patients may present with nephrotic syndrome, marked by severe proteinuria, hypoalbuminemia, hyperlipidemia, and generalized edema. The decline in glomerular filtration rate (GFR)below 15 mL/min/1.73 m², becomes evident, and patients may progress to CKD and eventually End-Stage Renal Disease (ESRD).[20]

In the final instance, patients with ESRD due to DM nephropathy require renal replacement therapy, such as dialysis or kidney transplantation. At this stage, the management focuses on alleviating symptoms and preparing for long-term dialysis or transplantation.[20,21] The progression of DM nephropathy is influenced by factors such as glycemic control, blood pressure, and cardiovascular risk factors, with chronic hyperglycemia and hypertension accelerating kidney damage through mechanisms like glomerular hyperfiltration and

glomerulosclerosis.[22] Complications associated with DN are extensive and include cardiovascular disease, diabetic retinopathy, and diabetic neuropathy, reflecting the systemic nature of diabetes and its impact on multiple organs and systems.[22]

4.0 Consideration for Early or ProphylacticTreatment

Diabetic nephropathy causes a decline in renal function that leads to renal insufficiency. At this point, therapy is necessary to slow the rate of advancement. Kidney failure and the need for dialysis or kidney transplants can result from renal malfunction if not commenced.[7]

The main factor leading to microalbuminuria is hyperglycemia. Extended periods of exposure to increased glucose levels cause proteins to be glycosylated, which in turn produces advanced glycation end-products (AGEs). It is well recognized that these AGEs cause oxidative stress and trigger inflammatory reactions, which impair regular cellular operations. Furthermore, prolonged hyperglycemia triggers the polyol pathway through aldose reductase, resulting in the conversion of excess glucose into fructose and sorbitol. The activation of this pathway increases vascular permeability in the kidneys by causing endothelial dysfunction in addition to osmotic and oxidative stress in renal tissues.[23] The cumulative effects of chronic hyperglycemia create an environment conducive to renal injury, accelerating the progression toward nephropathy. Consequently, detecting microalbuminuria can prompt clinicians to initiate interventions aimed at mitigating renal risk and improving overall prognosis.

The importance of routinely screening diabetic patients for microalbuminuria has been highlighted by recent clinical guidelines. This is especially crucial for individuals who have both type 1 and type 2 diabetes mellitus.According to the American Diabetes Association[24], screening for microalbuminuria could commence five years after the initial diagnosis of type 1 diabetes, while it should begin at the time of diagnosis for individuals with type 2 diabetes. Patients who are identified as having microalbuminuria must be promptly engaged in early intervention strategies. These strategies are vital for effectively slowing the progression of renal disease, thereby preserving kidney function and enhancing overall health outcomes for diabetic patients.

Whether diabetic individuals with microalbuminuria should be considered for early preventative therapy is a crucial concern in the management of diabetes. Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors are useful treatment options, and the available data clearly supports their usage. Additionally, maintaining tight control of glycemia and blood pressure is critical for optimizing patient outcomes. Landmark studies such as the Diabetes Control and Complications Trial (DCCT)[25] and the UK Prospective Diabetes Study (UKPDS)[26] have consistently demonstrated that intensive glycemic control significantly reduces both the onset and progression of microalbuminuria. Furthermore, ACE inhibitors and ARBs have been shown to exhibit nephroprotective effects, effectively reducing urinary albumin excretion and delaying the advancement to established diabetic nephropathy.[27]In light of these findings, it may be necessary to implement early intervention using these pharmaceutical agents in conjunction with strict blood pressure and blood glucose management in this high-risk population to reduce the long-term problems linked to diabetic kidney disease.

Prophylactic therapy of microalbuminuria in diabetic patients has several advantages, both in terms of clinical and financial outcomes. Proactive management of microalbuminuria can result in significant financial savings by lowering the rate of complications and hospitalizations related to advanced renal disease. In particular, the financial burden on healthcare systems can be reduced by effectively managing renal function through early intervention with pharmaceutical therapy, which can also stop the progression to more severe stages of diabetic nephropathy.

Furthermore, maintaining renal function is essential to improving patients' overall quality of life. Patients are better equipped to control their diabetes and related problems by assuring improved renal health. With the support of this all-encompassing strategy, patients can preserve more independence and participate in their everyday activities while also promoting their physical well-being and improving their psychological and social well-being. Early preventative treatment for microalbuminuria is a cost-effective solution that improves patient outcomes.

Conclusion

Microalbuminuria should be screened for, in newly and already diagnosed DM patients. Because very early in the course of diabetes, the presence of MAU would argue for good glycemic control but not the presence of nephropathy.Diabetic patients with microalbuminuria should be considered for early or prophylactic treatment due to the significant risk of progression to diabetic nephropathy and associated cardiovascular complications. Current clinical evidence and guidelines support the initiation of treatment strategies, including the use of ACE inhibitors, ARBs, and intensive glycemic control, as effective means to mitigate renal damage. Ultimately, an early intervention approach can foster improved clinical outcomes, enhanced quality of life, and offer economic benefits by preventing costly complications associated with advanced diabetic kidney disease.

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