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Microalbuminuria; Risk Predictive Tool and Determinant of Early Treatment in Diabetic Nephropathy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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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

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(ACE) inhibitors and angiotensin II receptor blockers (ARBs) as effective therapeutic strategies. Also, nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2DM, eGFR ≥25 mL/min/1.73 m2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite the maximum tolerated dose of the renin-angiotensin system (RAS) inhibitor. 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. 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 and 20 to 40% of type 2 patients eventually develop nephropathy" [5,6].

"The development of DN consists of several stages. Microalbuminuria (MAU) is considered the earliest sign of diabetic nephropathy among diabetes patients, 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" [7,8].

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 DM are 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. OVERVIEW OF DM NEPHROPATHY

2.1 Brief Pathophysiology

Diabetes mellitus is associated with deviations from normal metabolism in proteins, fats, and carbohydrates, which changes the glomerular membrane's permeability over 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 gene have 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 m^2, becomes evident, and patients may progress to CKD and eventually End-Stage Renal Disease (ESRD) [20].

“Therefore, the process of DM complicated with chronic CKD is a typical disease development with clinical manifestations of increased urinary albumin excretion, microalbuminuria, macroalbuminuria (with reduced glomerular filtration), and ESRD” [21] However, some DM patients show proteinuria in the normal range but were accompanied by renal insufficiency [estimated global filtration rate (EGFR) < 60 ml/(min/1.73 m2)] [21]. This phenomenon, first noticed by Lane et al. in 1992 [22] is later called normoalbuminuric diabetic kidney disease (NADKD).

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 [20,23] 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 [24]. 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 [24].

3. CONSIDERATION FOR EARLY OR PROPHYLACTIC TREATMENT

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 treatment is 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 tissue [25]. 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 [26], 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 supports their usage. Maintaining tight glycemia and blood pressure control is critical for optimizing patient outcomes. Landmark studies such as the Diabetes Control and Complications Trial (DCCT) [27] and the UK Prospective Diabetes Study (UKPDS) [28] 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 [29]. 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.

3.1 Highlights from ADA/KDIGO Guidelines

"The 2022 American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease each provides evidence-based recommendations for management" [30]. Representatives from the ADA and KDIGO collaborated to review and create a set of consensus statements that will direct clinical care based on their respective guidelines. The published guidelines are in agreement when it comes to goals of treatment, glycemia monitoring, lifestyle treatments, and CKD screening and diagnosis.

The summary of the consensus is as follows:

- "To optimize nutrition, exercise, smoking cessation, and weight management, all patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) and chronic kidney disease (CKD) should follow a comprehensive treatment-approved plan. This plan should include evidence-based pharmacologic therapies aimed at preserving organ function as well as other therapies chosen to achieve intermediate targets for glycemia, blood pressure (BP), and lipids. An ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB) is recommended for patients with T1DM or T2DM who have hypertension and albuminuria, titrated to the maximum antihypertensive or highest tolerated dose" [30,31].
- "A statin is recommended for all patients with T1DM or T2DM and CKD, moderate intensity for primary prevention of atherosclerotic cardiovascular disease (ASCVD) or high intensity for patients with known ASCVD and some patients with multiple ASCVD risk factors. Metformin is recommended for patients with T2DM, CKD, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2; the dose should be reduced to 1,000 mg daily in patients with eGFR 30–44 mL/min/1.73 m2 and in some patients with eGFR 45–59 mL/min/1.73 m2 who are at high risk of lactic acidosis" [30,31].
- "A sodium-glucose cotransporter 2 inhibitor (SGLT2i) with proven kidney or cardiovascular benefit is recommended for patients with T2DM, CKD, and eGFR ≥20 mL/min/1.73 m2. Once initiated, the SGLT2i can be continued at lower levels of eGFR. A glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended for patients with T2DM and CKD who do not meet their individualized glycemic target with metformin and/or an SGLT2i or who are unable to use these drugs. A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2DM, eGFR ≥25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite the maximum tolerated dose of the renin-angiotensin system (RAS) inhibitor" [30,31].

4. 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 and ns-MRA among those who fulfilled the treatment criteria. 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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The authors declared that no competing interests exist.

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