Using Microalbuminuria as Early Screening Tool for Prevention of Renal Disease Progression in Diabetes Mellitus: A Review Article of Current Insights

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Abstract

Diabetic kidney disease is one of the primary causes of end-stage renal disease. Early diagnosis is very important in preventing its development. Microalbuminuria (MA) is a surrogate marker for renal outcomes. Diabetic Nephropathy (DN) progresses from sub clinical disease, though the earliest clinically detectable stage characterized by microalbuminuria to overt nephropathy with MA, which is an early sign of renal damage. Several factors were identified to be associated with MA. This include HbA1, low-density lipoprotein, duration of Insulin Dependent Diabetes Mellitus (IDDM), maleness, systolic blood pressure, diabetes severity, smoking habit, BMI, physical inactivity, metabolic syndrome, diastolic blood pressure, fasting plasma glucose, and others. Early detection of MA and halting the factors which may exacerbate MA will result in early prevention of DN. In addition to this, the use of Angiotensin Converting Enzyme (ACE) Inhibitor, Aldosterone Receptor Blocker (ARB) reduces the risk for development of MA, along with cardiovascular risk reduction with stations. Fenofibrate and Canagliflozin treatment were also explained to have beneficial effects. Reducing MA is considered to be an important for therapeutic success and also can improve patient's quality of life.

Keywords: Microalbuminuria; Renal Disease; Diabetes Mellitus; Screening

Introduction

The increasing in chronic kidney disease and end-stage renal disease become a challenge worldwide. Even though infectious diseases remain the leading cause of mortality in Sub-Saharan Africa (SSA), non-communicable diseases are coming to the forefront. Diabetes mellitus (DM) affects 9.4 million people in Africa. The prevalence of diabetic nephropathy (DN) is estimated to be 6 - 16% in SSA [1]. Progression of kidney disease most frequently occur after the development of persistent microalbuminuria (PMA) in type 1 diabetes, suggesting that PMA diagnosis indicate a crucial time to assess and target renal interventions. In particular, intensive diabetes therapy seems to improve renal outcomes after the development of PMA in addition to preventing progression to microalbuminuria [2].

Diabetic kidney disease (DKD) is one of the primary causes of end-stage renal disease (ESRD). Early diagnosis is very important in preventing the development of DKD. Microalbuminuria is a surrogate marker for renal outcomes, though the earliest clinically detectable stage characterized by microalbuminuria to overt nephropathy with macroalbuminuria. Based on this, the natural history of DKD has been divided into three stages: normoalbuminuria, microalbuminuria, and macroalbuminuria. Due to this, proteinuria is a strong predictor of progression of chronic kidney disease and is associated with worse renal prognosis. Pharmacological treatment aimed to reduce albuminuria levels delays the progression of renal disease [3-6].

MA is an early sign of renal damage and it predicts the development of nephropathy and other complications of hypertension. It is defined as Urine albumin excretion (UAE) in the range of 30 - 300 mg/24h, 20 - 200 mg/L in the first morning sample, 20 - 200 μg/min in a timed overnight 24h sample, or Urinary albumin to creatinine ratio (UACR) of > 30 mg/g (30 - 300 mg/g) in a first morning midstream sample [7]. Approximately 20% to 40% of patients with DM develop DKD. DKD is a clinical syndrome characterized by persistent albuminuria (> 300 mg/24h, or > 300 mg/g creatinine), a relentless decline in glomerular filtration rate (GFR), raised arterial blood pressure, and enhanced cardiovascular morbidity and mortality [8].

Using the UACR rather than 24-hour proteinuria was recommended to monitor proteinuria and its prognosis [9]. It further classified as Macroalbuminuria with an abnormal increase in albumin excretion rate in the range ≥300 mg albumin/g creatinine and Microalbuminuria with an abnormal increase in UAE rate within the specific range of 30-299 mg of albumin/g of creatinine [10]. Diabetic nephropathy is the most hazardous of the complications of diabetes, and is responsible for excess morbidity and mortality in patients with both types of DM. It is now established as the earliest risk marker for nephropathy in type 1 diabetes and cardiovascular disease in type 2 diabetes [11].

**Aim of the Study**

The aim of this study was to summarize the existing evidence.

**Mechanism of microalbuminuria**

MA (amount greater than 30 - 300 mg/day) reflects an abnormal glomerular capillary permeability to protein. Three mechanisms were proposed. First, loss of negatively charged surface of the glomerular capillary wall allows the albumin with negatively charged surface to freely escape into the urine. Second, intra-glomerular hypertension and hemodynamic maladjustment increases filtration pressure and enhances sized selective proteinuria leakage. Third, podocyte injury leads to a vicious cycle of hemodynamic maladjustment and endothelial and podocyte injuries. In short form, persistent proteinuria may result from either a lack of adequate repair and/or injury to further components of the filtration barrier [5,12,13].

The most likely initiating step in diabetic microalbuminuria is Glomerular endothelial dysfunction, and in particular damage to its glycocalyx. Podocyte damage and loss is one of by predictable structural changes in the glomerulus which indicate progression of microalbuminuria to overt nephropathy. This is due to ongoing diabetic Mellitus and disturbed cell-cell communication, which is secondary to increased penetration of the glomerular filtration barrier (GFB) by serum proteins [14].

The hyperglycemia (HG) is the major initiating factor in the pathogenesis of diabetic complications (DC), including microalbuminuria. However, most adverse effects of glucose are mediated indirectly through diverse metabolic pathways. Four major hypotheses have highlighted how the HG leads to including the roles of AGEs, increased activity of the polyol pathway, activation of protein kinase C and increased flux through the hexosamine pathway. Activation of these pathways in turn causes dysregulation of a number of effectors molecules which cause cellular damage and dysfunction [14].

**Prevalence of microalbuminuria in Diabetes mellitus**

In type 2 diabetic patients in Egypt, prevalence of microalbuminuria (incipient diabetic nephropathy) was 34.2% and that of macroalbuminuria (overt diabetic nephropathy) was 12.8% in the studied group [15]. Similarly, prevalence of albuminuria among Palestinian population with type 2 diabetes was found to be 34.6%, microalbuminuria (29.3%) and macroalbuminuria (5.3%) [16]. In Pakistan, the prevalence of the microalbuminuria in patients with Type-2 diabetes is 31.56% [17]. In similar way Prevalence of microalbuminuria was 36.3% in southern India [18]. However, Diabetic patients in Nepal have prevalence of microalbuminurea 20.3%, which is little bit lower [19].
Nature history of Diabetic renal disease

![Figure 1: Nature history and renal changes in type 1 diabetes mellitus. DN: Diabetic Nephropathy; ESRD: End-Stage Renal Disease; GBM: Glomerular Basement Membrane; GFR: Glomerular Filtration Rate; BP: Blood Pressure [20].]

Factors associated with albuminuria in diabetes mellitus

Elevated levels of MA strongly predict the development of clinical diabetic nephropathy. However, this are potentially reversible, and their detection and treatment may prevent diabetic renal disease [21].

Distinguishing patients with T2DM who exhibit an increased risk of albuminuria is crucial for preventing diabetic nephropathy [22]. In contrast, albuminuria outcomes in type 1 DM were more favorable in absence of other associated factors and with adequate treatment [2].

HbA1c, low-density lipoprotein, duration of Insulin Dependent Diabetes Mellitus (IDDM), males, systolic blood pressure, diabetes severity, smoking habit, BMI, physical activity, metabolic syndrome, diastolic blood pressure, fasting plasma glucose, elevated plasma levels of Chemokine ligand 16 (CXCL16), angiopoietin-2, Transforming growth factor beta 1 (TGF-β1), Yang deficiency and Phlegm stasis were the significant independent predictors of microalbuminuria in IDDM [16,18,19,22-25]. After adjustment for several variables, angiopoietin-2 and TGF-β1 were significant predictors of new-onset MA [24].

Sex-specific analyses showed difference of these predictors in men and women. Accordingly, HbA1c, age, and baseline albumin excretion rate (AER) were particularly important for men; whereas, for women, the main predictors were duration of IDDM and triglycerides [23].

A significant fraction of microalbuminuric Type 1 diabetic patients will progress to overt proteinuria. Patients with higher AER values, sub-optimal metabolic control, and excess body fat and peripheral neuropathy may carry a particularly high risk of clinical nephropathy requiring aggressive therapeutic intervention [26].

Treatment of microalbuminuria do decrease its risk

The most important task is prevention. Prevention of DN can be achieved by tight glycaemic and blood pressure control. This cannot always be realized. Once MA develops, in patients with type 2 diabetes early intervention with Angiotension Converting enzyme (ACE)
or Aldosterone receptor blocker (ARB)s reduces the risk for development of MA by inhibition of Renin angiotensin aldosterone (RAS), along with cardiovascular risk reduction with stations [11,27]. In addition, in the patients with hypertriglyceridemia and type 2 DM, fenofibrate can improve MA and do not increase the deterioration of GFR [28].

Regarding the nutritional supplementation, reducing protein intake from animal sources and increasing the intake of lipids from vegetable origin might reduce the risk of MA in type 2 diabetic patients. This is because, high intake of protein and the low intake of Poly unsaturated fatty acid (PUFAs), particularly from plant oils, were associated with the presence of MA [29].

Canagliflozin treatment reduces sustained loss of kidney function, attenuated eGFR decline and causes a reduction in MA, with possible renoprotective effect of this drug in people with type 2 DM [30]. Reducing MA is considered to be an important therapeutic objective and a bio-measure of therapeutic success in type 2 diabetic patients to improve patients quality of life [31].

Conclusion

Diabetic nephropathy is one of the common complication of DM which causes the significant proportion diabetes mellitus associated death. The most effective way in preventing DM complication is early screening. Micro albumin can be detected before the development of overt DN. Once MA was detected the focus will be in halting the factors that may accelerate the progression of MA to overt DN. In addition to this, the use of ACE, ARB reduces the risk for development of MA, along with cardiovascular risk reduction with stations. Fenofibrate and Canagliflozin treatment were also explained to have beneficial effects. Reducing MA is considered to be an important for therapeutic success and also can improve patient’s quality of life.

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