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Original Research Paper

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DIABETES & MICROALBUMINURIA- A MULTI-SYSTEM DISEASE

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KEYWORDS :

In diabetic patients, the presence of microalbumin in the urine is perhaps the most significant early signal for the onset of systemic vasculopathy and associated target organ damage viz., brain, heart, and kidneys[1]. Microalbuminuria is considered to be a predictor of the development of overt diabetic nephropathy in type 1 and 2 diabetes[2]. Diabetic patients are at considerable risk of either having or developing the renal disease and/or related cardiovascular diseases, usually starting with microalbuminuria often related to insulin resistance (or metabolic syndrome)[1]. Thus, microalbuminuria is a relatively common accompaniment of metabolic syndrome and the foremost predictor of renal disease as well as cardiovascular disease[3,4]. Hypertension and microalbuminuria often coexist in diabetic patients, and reducing blood pressure reduces microalbuminuria in type 1 diabetes[2]. However, the relationship between hypertension and microalbuminuria in diabetes is complex. Furthermore, microalbuminuria is also associated with other inflammatory states, including rheumatoid arthritis and inflammatory bowel disease. Also, male sex and hormone replacement therapy in women seems to increase the susceptibility of a person to microalbuminuria, although the basis for this is yet not clear[2].

Microalbuminuria represents an abnormally elevated urine albumin level that cannot be detected with the use of a urinalysis dipstick. The presence of microalbuminuria predicts worsening of renal disease to overt diabetic nephropathy and an elevated risk of cardiovascular disease[5]. In general, urinary albumin excretion is classified as: normoalbuminuria (< 30 mg per day or urinary albumin-to-creatinine ratio i.e. UACR < 30 mg/g), microalbuminuria (30–300 mg per day or UACR 30–300 mg/g) and macroalbuminuria (> 300 mg per day or UACR > 300 mg/g). It is very important to note that even the low-degree or microalbuminuria is not merely a determinant of nephropathy in patients with diabetes but more of an early and sensitive marker of widespread vascular damage with established cardiovascular prognostic value[6].

Mechanistically, increased urinary albumin excretion is the net result of glomerular capillary passage and tubular reabsorption. Albumin is only minimally filtered in the glomeruli under normal physiological conditions. However, functional (physiological—reversible) and structural (pathological—irreversible) changes such as elevated glomerular hydraulic pressure,increased glomerular filtration coefficient, change in size and charge selectivity of the glomerular membrane, increases the glomerular albumin passage [2].

In the non-diabetic population, hypertension is the major risk factor for microalbuminuria, and the prevalence of microalbuminuria in essential hypertension is around 25%. Individuals with essential hypertension who develop microalbuminuria have a higher incidence of biochemical disturbances, implying that hypertension per se may not be the cause of microalbuminuria, rather, additional derangements involving inflammatory imbalance may be causative of microalbuminuria[2].

While in the case of diabetic patients, diabetes induces abnormalities in all three distinct layers of the glomerular membrane—endothelial cell layer, basement membrane, and podocyte layer. These abnormalities can be structural e.g. increased pore size or biochemical viz., loss of negatively charged molecules. Also, poor glycaemic regulation in diabetes reduces the glycocalyx, leading to micro- and macroalbuminuria. The glycocalyx is a thick layer of proteoglycan/glycosaminoglycans that cover the outer endothelial layer in the kidney and the other capillary beds of the body. Key players involved in inducing this damage are reactive oxygen species (ROS), VEGF, and proinflammatory cytokines[7].

Microalbuminuria may be detected 1 year after the onset of diabetes in post pubertal patients with type 1 diabetes, and at diagnosis in type 2. There is a significant structural glomerular disease even at this early phase, and the glomerular filtration rate (GFR) starts to decline during the phase of microalbuminuria, although it can remain within the normal range until the albumin excretion rate (AER) approaches 200 micrograms/minute (300 mg/day). In healthy adults, the normal AER ranges between 1.5 and 20 micrograms/minute, with a median value of around 6.5 micrograms/minute. An increase in AER to a persistent value > 200 micrograms/minute (> 300 mg/day) marks the onset of historically clinically defined 'overt diabetic nephropathy', and is a harbinger of renal failure and cardiovascular complications in both types of diabetes. Blood pressure rises progressively in this phase in both type 1 and type 2 diabetes. Stabilization of kidney function can be harder to achieve in this stage, and therefore early detection and 'aggressive' treatment is warranted. Over time, the protein loss can increase to > 3-4 g/day and occasionally lead to nephrotic syndrome with hypoalbuminemia, hypercholesterolemia, and peripheral oedema[3].Diabetic nephropathy even at the stage of microalbuminuria is strongly predictive of death from cardiovascular disease, particularly in older patients with type 2 diabetes. Microalbuminuria is also associated with retinopathy, peripheral vascular disease, and neuropathy. Blood pressure increases in patients with microalbuminuria and lipid abnormalities develop; these include increased low-density lipoprotein (LDL)-cholesterol, total triglycerides (triacylglycerols) and apolipoprotein B, and reduced high-density lipoprotein (subclass 2)-cholesterol. These progressive abnormalities are seen in both type 1 and type 2 diabetes[3].

Microalbuminuria is strongly associated with vascular disease. The most favored mechanistic explanation linking microalbuminuria with vascular disease is that of microalbuminuria as a marker of generalized endothelial dysfunction. It is thought that persons with increased urinary albumin excretion (UAE) generally have a loss of glomerular charge selectivity and size selectivity, as well as an increased transcapillary escape rate of albumin. This elevated albumin leakage in the glomerulus appears tied to greater capillary permeability for albumin in the systemic vasculature, probably leading to generalized hemodynamic strain and disequilibrium, and then ultimately initiating atherosclerosis with attendant symptomatic vascular sequela[8].

Proinflammatory cytokines produced by visceral adipocytes (adipokines) have recently emerged as important mediators of the increased cardiovascular risk associated with the insulin resistance syndrome. These adipokines represent a possible link from insulin resistance and obesity to microalbuminuria in the non-diabetic population[2].

Thus, in the diabetic as well as in the general population the risk factors for the development of microalbuminuria can be grouped into- endothelial dysfunction, inflammation, and insulin resistance. Thus, microalbuminuria is a strong biomarker for diabetic nephropathy, end-stage renal disease, fatal and nonfatal cardiovascular events not only in type 1 and 2 diabetes but also in essential hypertension and the general population[7].

The renal consequences of increased urinary albumin excretion are mainly due to the tubular uptake of albumin, which plays a role in the initiation and progression of chronic tubulointerstitial damage. In fact, tubular uptake of albumin triggers the activation of a wide array of cytotoxic signals that affect the interstitium, the fibroblasts, and the nearby blood vessels, and may cause tubulointerstitial dysfunction, leading to a worse renal prognosis.Albuminuria is not only a risk indicator but also an important causal factor for the development and worsening of kidney disease[7].

In agreement, various studies have demonstrated a renoprotective effect of improved glycaemic regulation, arterial blood pressure reduction, blockade of the renin-angiotensin system independent of blood pressure. However, the impact or risk progression depends on the progression from normoalbuminuria to microalbuminuria (primary prevention), and microalbuminuria to diabetic nephropathy (secondary prevention). The vascular risk may actually start within the currently defined normal range of albuminuria i.e. UACRs <30 mg/g, and rise continuously even among persons without diabetes. The progression of renal disease in diabetics and its prevention modalities are shown in Fig 1.

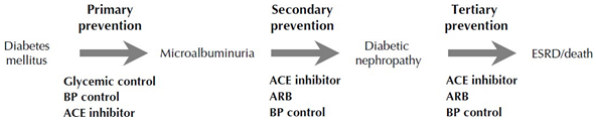

Fig 1: Progression of renal disease in diabetics and its prevention modalities *(ARB: Angiotensin II receptor blockers; ESRD: End stage renal disease)* [5]

In the HOPE trial, even from a UACR as low as 0.5 mg/mmol (equivalent to 4.4 mg/g), for every 0.4 mg/mmol rise in the UACR level, the adjusted hazard of major vascular events rose by 5.9%. Similarly, an analysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that for every 10-fold increase in UACR, the hazard ratio (HR) for the composite vascular endpoint increased by 57% with similar results for the diabetic subjects[9].

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glycemic control therapy reduced the occurrence of microalbuminuria by 39%, and that of albuminuria by 54%. Long-term follow-up of the patients from DCCT in the EDIC study revealed that the reduction in the development of micro-and macroalbuminuria translated into a 50% reduced risk of development of an eGFR < 60 ml/min/1.73 m^2, indicative of renal health[7].Microalbuminuria has also been found to be an early marker of preclinical brain damage in the form of asymptomatic cerebral ischemic lacunae observed on neuroimaging. Patients with microalbuminuria tend to have significantly higher carotid artery intima-media thickness than normoalbuminuric patients. Further, microalbuminuria is a frequent finding in several acute clinical conditions and the UAE level appears to be directly proportional to the severity of many acute inflammatory processes including trauma, sepsis, surgery, muscle ischemia, and acute myocardial infarction[8].

CONCLUSION

Microalbuminuria indicates an increased risk for the development of diabetic nephropathy in diabetic patients. It also heralds end-stage renal disease, fatal and non-fatal cardiovascular events in diabetes as well as in hypertensive as well as the general population. It marks the need for intensified treatment with multifactorial intervention targeting glycaemic control, blood pressure including the blockade of the renin-angiotensin system, and dyslipidemia. This intervention has demonstrated to reduce complications and improve prognosis significantly since albumin in the urine is not only a biomarker for renal and cardiac complications but also a casual causative factor for the worsening of renal disease. The appearance of albumin in the urine is the foremost biomarker for the onset of systemic vasculopathy and multiple associated target organs damage viz., brain, heart, and kidneys. Thus, screening for and treatment of microalbuminuria can significantly affect diabetes care and patient outcome.

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