Significance of microalbuminuria in cardiovascular disease and nephropathy in diabetic patients

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ABSTRACT

Type 2 diabetes is the commonest form of diabetes constituting 90\% of the diabetic population. The global prevalence of diabetes is estimated to increase from 4\% in 1995 to 5.4\% by the year 2025. Diabetic nephropathy is a major cause of illness and death in diabetes. The excess of cardiovascular events and mortality occurs already in diabetic patients with persistent microalbuminuria. 

Keywords: Microalbuminuria, Diabetes, Nephropathy, Cardiovascular events.
INTRODUCTION

Type 2 diabetes is the commonest form of diabetes constituting 90% of the diabetic population. The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025. The countries with the largest number of diabetic patients are, and will be India, China and United States [1]. A long term complication of type 2 diabetes is nephropathy which stands next only to cardiovascular disease in terms of morbidity and mortality.

Diabetic nephropathy is the most common cause of renal failure in the western world. Dialysis and renal transplantation are costly [2, 3] and most of poor patients cannot afford the same.

Diabetic nephropathy progresses from subclinical disease, through the earliest clinically detectable stage characterized by microalbuminuria i.e., urinary albumin 30 to 300mg/day to overt nephropathy with macroalbuminuria [4-6]. Detection of microalbuminuria identifies individuals at high risk of progression to later stages of renal diseases [7,8], cardiovascular events and death [9].

Recently, it has been suggested that microalbuminuria may be a risk factor for the development of cardiovascular disease in non diabetics and may therefore have a role in screening programs [10].

Pathophysiology of microalbuminuria:

Normal human urine contains only very small quantities of albumin, less than 30 mg of albumin being excreted by healthy adults in 24 h. The appearance of large amounts of albumin in the urine is a cardinal sign of kidney disease, especially glomerular disease, and is detectable by screening techniques using urinary dipsticks. Accurate quantification of the amount of albumin lost in the urine has important clinical connotations: excretion of amounts in excess of 300 mg in 24 h is termed ‘overt albuminuria’, excretion of lesser amounts of albumin, between 30 and 300 mg in 24 h, is termed ‘microalbuminuria’.

THE GLOMERULAR FILTRATION BARRIER

The glomerulus is the filtering unit of the mammalian kidney: it is a complex network of capillaries and filtration takes place across the capillary wall into Bowman’s space. Water and small molecules are freely filtered in large quantities: 180 liters of glomerular filtrate/day in a 70 kg adult. The glomerular filter comprises of three layers [11]:

1. Inner layer of glomerular endothelial cells: GEnC have characteristic fenestrations filled with glycocalyx.
2. **Outer [urinary side] layer of glomerular epithelial cells or podocytes**: Podocytes have complex branching and inter-digitating processes called foot processes.

3. **GBM [glomerular basement membrane]**: Has unique constituents with typical isoforms of laminin, type IV collagen and proteoglycans, the latter imparting a strongly negative electrostatic charge [Figure 1].

![Transmission electron micrograph of the glomerular capillary wall](image)

**Figure 1: Transmission electron micrograph of the glomerular capillary wall [31]**
Pod: podocyte foot process. * slit membrane in each filtration slit.

**Glomerular epithelial cells [podocytes]**

Recent advances have put the podocyte firmly at centre stage for the basis of filtration of albumin through glomerulus[12]. Filtration takes place through slits formed between inter-digitating processes of the podocytes on the urinary side of the glomerulus. Each filtration slit has a membrane across it, apparently bridging the adjacent foot processes. The molecular composition of the slit membrane was obtained [13] in the late 1990s when the gene mutated in Finnish type congenital nephrotic syndrome, encoding a protein termed as nephrin was identified. In normal kidney, nephrin is expressed exclusively in the podocyte and is located at the slit membrane.

The fact that these gene mutations primarily affect the podocyte only and lead to massive proteinuria has led to the conclusion that podocytes are the cells responsible for the prevention of proteinuria in health [12].
In recent work with cultured human podocytes, it has been shown that podocytes are insulin-responsive [14], taking up glucose in response to insulin with similar kinetics and magnitude to muscle cells, and changing their shape as a result of acting cytoskeleton reorganization after insulin treatment.

**GBM:**

The GBM is made up of an unusually highly restricted isoforms of laminin and type IV collagen together with various proteoglycans, including heparin sulphate, agrin and perlecan [11,15]. The latter impart a highly negative electrostatic charge on the GBM, and much of the older literature on glomerular permeability focused on the charge characteristics of the GBM as a means of resisting the passage of albumin molecules, which are also negatively charged [16].

**Glomerular and tubular mechanisms:**

The alterations in glomerular function and tubular reabsorption play an important role in microalbuminuria. The glomeruli receive 25% of cardiac output per day. Of the 70kg of albumin that passes through the kidneys every 24hr, less than 0.01% reaches the glomerular ultra filtrate and hence enters the renal tubules [17-19]. Almost all filtered albumin is reabsorbed by proximal tubule via a high affinity, low capacity endocytic mechanism with only 10-30mg/24hour appearing in the urine [20].

The passage of albumin through glomeruli depends on two main factors, charge and size. The negative charge on the glomerular membrane repels the anionic proteins thereby preventing the passage of albumin molecules through glomeruli normally. The loss of glomerular charge selectivity has been found in both diabetics and non-diabetic population with microalbuminuria [21, 22].

Established microscopic abnormalities include thickening of the glomerular basement membrane, accumulation of mesangial matrix, and increase in the numbers of mesangial cells With disease progression there is a close relationship between mesangial expansion and declining glomerular filtration [23]. Mesangial expansion also correlates inversely with capillary filtration surface area, which itself correlates with glomerular filtration rate. Changes in the tubulointerstitium, including thickening of tubular basement membrane, tubular atrophy, interstitial fibrosis and arteriosclerosis, have been well described. Interstitial enlargement correlates with glomerular filtration, albuminuria, and mesangial expansion. It has been suggested that the accumulation of protein in the cytoplasm of proximal tubular cells causes an inflammatory reaction which leads to tubulointerstitial lesions [24]. Similarly, rise in blood pressure plays an important role by altering the fraction of plasma filtered by the glomerules.
Changes in endothelial function:

Increased systemic capillary permeability has also been linked with microalbuminuria in healthy populations and recent study shows that endothelial dysfunction leads to impaired insulin action as well as to capillary leakage of albumin [25, 26].

Therefore, microalbuminuria may be a marker of generalized vascular disease, as the formation of atherosclerotic thrombi is related to endothelial dysfunction in arteries. Thus in addition to being an early marker of incipient diabetic nephropathy, urinary albumin excretion may represent common pathways for the development of both large and small vessel disease making microalbuminuria as a possible marker for cardiovascular diseases.

Diagnosis:

Patients with diabetes are at risk of microalbuminuria if they have any of the following factors

- The urine albumin excretion is above the normal range > 30mg/day
- The systolic blood pressure is greater than 130mmHg
- The total cholesterol level is greater than 5.24mmol/L

DISCUSSION

Diabetic nephropathy is a major cause of illness and death in diabetes. The excess of cardiovascular events and mortality occurs already in diabetic patients with persistent microalbuminuria.

Currently microalbuminuria should be considered as a marker of dynamic, rather than fixed renal injury in diabetic patients [27]. Microalbuminuria is a marker for increased risk for cardiovascular disease [28] associated with impaired aerobic work capacity and showing microangiopathy or other pathological process affecting myocardium [29].

The increase in the ratio of LDL: HDL has been described [30] indicating atherogenic lipid profile, Impaired fibronolytic activity and von-Willebrand factor are present in patients with microalbuminuria suggesting a generalized endothelial injury [28].

The present data shows, that early detection of microalbuminuria or proteinuria in patients with diabetes indicates a potential risk for the development of progressive kidney function impairment and also a marker for high risk cardiovascular complications. These patients should receive a multifactorial treatment and should be monitored carefully to prevent or slow the progression of both kidney and cardiovascular complications to increase life expectancy.
REFERENCES