Review Article

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Biochemistry Section

Proteinuria in Primary and Secondary Renal Diseases

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ABSTRACT

Proteinuria is a strong indicator of kidney disease. Various pathological conditions such as diabetes mellitus, cardiovascular disease and hypertension have been shown to provoke secondary kidney problems and significant proteinuria. Studies have demonstrated that the normal glomerulus filters substantial amounts of albumin and, This filtered albumin is then processed by proximal tubular cells by two distinct pathways; a retrieval pathway and degradation pathway. Dysfunction in either one of these pathways gives rise to discrete forms of albuminuria. Different proteinuric factors (PF) and glomerular permeability factors appears to be involved in the abnormal glomerular permeability and are responsible for the development of proteinuria in primary nephritic syndrome. Transforming Growth Factor-β1 (TGF-β1) has prosclerotic property, can induce nephrosclerosis and is implicated in proteinuria of hypertension. Proteinuria is an important marker in renal disease, and an useful prognostic marker for cardiovascular disease. Microalbuminuria is the earliest clue of renal complications of metabolic syndrome. Renal insufficiency was an independent risk factor for death in elderly patients after myocardial infarction.

Key Words: Albuminuria, Nephrotic syndrome, Hypertensive nephropathies, Diabetic Nephropathies, Nephrin

INTRODUCTION

In this review we have discussed, first, the patho-physiology of albuminuria in three different conditions. Second, we describe the progress of albuminuria. Thirdly albuminuria predict the extent of renal damage and outcome. Proteins filtration, re-absorbtion and excretion by the nephrons is a complex mechanism in renal physiology. The entire glomerular tuft is supported by mesangial cells lying between the capillaries. Basement membrane-like mesangial matrix forms a meshwork through which the mesangial cells are centered [1]. Studies have demonstrated that the normal glomerulus filters substantial amounts of albumin and, This filtered albumin is then processed by proximal tubular cells by two distinct pathways; a retrieval pathway and degradation pathway. Dysfunction in either one of these pathways gives rise to discrete forms of albuminuria. Albuminuria in the nephrotic range would arise from retrieval pathway dysfunction. Dysfunction in the degradation pathway leads to albuminuria below the nephrotic range.Tubular reabsorption plays a central role in mediating the effects of albumin on renal function. Receptor-mediated endocytosis plays a role in urinary albumin degradation [2]. The kidney degrades large amounts of albumin and that the degradation fragments appear in the urine which are not reabsorbed into the blood stream [3].

ALBUMINURIA IN THE DIABETES MELLITUS

Glucose and Methylglyoxal (MGO) derived modifications of Extracellular membrane (ECM) proteins make distinct contributions to development of characteristic diabetic nephropathy glomerular lesions via perturbation of glomerular cell-matrix interactions. It has been suggested that hyperglycaemia causes early but transient mesangial cell proliferation followed by a decrease in proliferation and development of cell hypertrophy [4]. In early diabetes during the stages of glomerular hyperfunction, hypertrophy develops acutely at the onset of diabetes, leading to an increase in capillary surface corresponding to the increase in filtration rate. In the advanced stages when glomerular closure involves a proportion of the nephrons compensatory hypertrophy develops, thereby probably helping to preserve capillary surface for a period of time. The end-stage is glomerular closure, with elimination of glomerular function [5]. The reductions in podocyte numbers in both younger and older diabetic patients indicate a significant risk for functional abnormalities as diabetic nephropathy progresses [6]. The glomerulus, particularly the mesangium, has been studied in diabetes, tubulointerstitial injury is also a major feature of diabetic nephropathy and an important predictor of renal dysfunction. In the diabetic state, this includes large quantities of advanced glycation end products and glucose and, at later stages in the evolution of diabetic nephropathy, protein, all of which are factors that may induce TGF-β expression and fibrosis. Diabetic nephropathy should therefore be viewed as a disease affecting the entire nephron [7]. Non-enzymatic glycation of albumin increases its renal clearance [8]. The glycation of albumin, and not of GBM, leads to enhanced permeability in an in-vitro GBM filtration system. Increased permeability of glycated albumin may contribute to albuminuria and/or renal injury in states of increased circulating glycated albumin such as diabetes [9].

ALBUMINURIA IN HYPERTENSION

Albuminuria in hypertension is linked to an inhibition of lysosomal processing as determined by size exclusion chromatography analysis of urine which was correlated with increased renal transforming growth factor-beta [10]. Increase in pressure in the glomerular capillaries which resulted in stretch/relaxation resulted in increase in the relative amounts of types I and III collagens produced/cell. Additionally, stretch/relaxation selectively increased the relative amount of type I-homotrimers produced. Thus, when

mesangial cells are exposed to cyclic stretch/relaxation, they exhibit significant alterations in morphology, growth, prostaglandin and collagen production [11]. High-pressure cyclic stretch leads to MC proliferation, preceded by marked activation of p44/42 and p38/HOG MAPKs. Cell proliferation is not seen with low-pressure stretch, and there is only modest p44/42 MAPK activation, suggesting that glomerular capillary hypertension may lead to cell proliferation and injury partly through differential activation of kinase cascades [12]. Stretch-induced activation of SAPK and p42/44 MAPK in MCs can be inhibited by NO. The effect of NO is mediated by the generation of cGMP. These mechanisms may be responsible, at least in part, for the protective effect of NO in animal models of glomerular injury characterized by glomerular capillary hypertension [13].

NEPHROTIC SYNDROME

Circulating permeability factor in serum from patients with focal segmental glomerulosclerosis can cause immediate and marked changes in glomerular permeability to albumin. The serum factor is strongly associated with the recurrence of focal segmental glomerulosclerosis after renal transplantation and may be responsible for proteinuria in patients with this disorder [14].Properties and mechanism of action of permeability factor was mentioned by M. Sharma et al [15]. Components of normal serum block the focal segmental glomerulosclerosis factor activity in-vitro [16]. Protein leakage in nephrotic syndromes also occurs through defective podocyte with disruption of glomerular slit diaphragms [17]. Nephrin is a protein, which is synthesized in the podocytes and localized in the slit diaphragm area. Nephrin is a cell adhesion molecule of the immune-globulin super family, and presumably is a part of the zipper-like structure of the slit membrane. Mutation of the gene coding nephrin induces congenital nephrotic syndrome of Finnish type, which is a prototype of nephrotic syndrome, it has been suggested that nephrin also plays a role in acquired proteinuric kidney disease [18]. Podocin interacts with nephrin and CD2AP. This forms a complex functional unit that anchors the slit diaphragm to the actin cytoskeleton and establishes its location in the lateral plasma membrane of the podocyte foot processes [19].

Applied aspect proteinuria is an important marker in renal disease, and an useful prognostic marker for cardiovascular disease. Micro-albuminuria is the earliest clue of renal complications of metabolic syndrome [20]. Renal insufficiency was an independent risk factor for death in elderly patients after myocardial infarction [21] is a marker of different pathologic processes. Micro-albuminuria the spectrum of renal vascular manifestations range from systemic endothelial dysfunction (microvascular disease) to systemic atherosclerosis (macrovascular disease) [22].

CONCLUSION

Whatever be the aetiology the progress of proteinuria varies, especially in secondary proteinuria. Progress of proteinuria of low range of micro-albuminuria to overt proteinuria as it depends on many factors. Studies showing in some patient where it progesses; in some patients micro-albuminuria remained stable. The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes [23-25] whereas in others micro-albuminuria reverted back to normal transiently or even permanently [26-27].

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