

Proteinuria in Nondiabetic Patients: Clinical Significance

¹Vijay Viswanathan, ²A Anitha Rani

ABSTRACT

Proteinuria is a major health care problem, which affects millions of peoples globally. It is a characteristic of Diabetic Nephropathy and a strong indicator of kidney disease and renal dysfunction. It occurs in different forms with varied degree of severity. Proteinuria can be classified based on the amount and type of the protein and the pathological damage. Process involved in proteinuria is complex and multifactorial which includes tubular absorption, hemodynamics of glomerular and diffusion gradients. A continuous function of kidney is necessary for regular urine formation. In normal physiological condition urine is free of protein and this action was efficiently performed by nephrons in the kidneys. Nephrons play a major role in filtration and reabsorption. Thus kidney disease is associated with the malfunction of reabsorption mechanism.

Keywords: Clinical, Diabetes, Glomerular filtration, Proteinuria, Renal function.

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INTRODUCTION

Proteinuria is recognized as an independent risk factor for cardiovascular disease (CVD) and renal disease and as a predictor of end organ damage.¹ In particular, detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease.² Further, it has been shown to be an independent risk factor for the progression of kidney disease rather than simply being a marker for glomerular dysfunction.³ It is a common clinical finding in primary care practice. It is defined as urinary protein excretion of greater than 150 mg of protein/day, of which approximately 20 mg is albumin. The daily excretion of more than 3.5 gm of protein is called nephrotic range of proteinuria. Urinary protein excretion in healthy persons

varies considerably and may reach proteinuric levels under several circumstances.

PROTEINURIA

Proteinuria denotes a sign of glomerular diseases and represents a marker of injury to the glomerular permeability barrier. Ultrafiltered proteins are partly lost in urine (proteinuria) and partly absorbed by endocytosis in the proximal tubules. During periods of heavy proteinuria, the ultrafiltered proteins accumulate in lysosomes in the proximal tubular cells, causing cell disruption and injury.^{4,5} Further data suggest that protein overload may also directly contribute to podocyte injury and eventual glomerulosclerosis.⁶ In addition, proteinuria, even at a subnephrotic range, is a well-known risk factor for CV mortality and morbidity and is strongly associated with the progression of kidney disease. Urinary protein excretion has been used as a surrogate end point for therapeutic interventions of chronic kidney disease (CKD) where decreasing proteinuria would delay the progression of CKD.⁷

Proteinuria is preceded by stages of excessive glomerular filtration and of microalbuminuria, which signals an increased risk of progression to overt nephropathy. A progressive increase in proteinuria subsequently leads to a variable decline in renal function.⁸ End-stage renal disease (ESRD) in several glomerular diseases is histologically characterized by glomerulosclerosis and tubulointerstitial fibrosis.

Glomerular hypertension in both diabetic and nondiabetic chronic nephropathies leads to increased glomerular permeability and excessive protein filtration. A large number of experimental studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, independently of the original etiology. The common pathway of renal injury includes systemic hypertension, increased glomerular pressure and tubular protein overload, secondary tubulointerstitial inflammation, and fibrosis.^{9,10} The reduction of proteinuria is assumed to play a key role in the treatment of renal disease and has a main impact on slowing progression of chronic renal disease.¹¹ Proteinuria is also an independent risk factor for the development of CVDs in diabetic and nondiabetic renal disease (NDRD). Patients with microalbuminuria and a normal or small reduced

¹Head and Chief, ²Post Doctoral Research Fellow

¹Department of Diabetology, M.V. Hospital for Diabetes and Diabetes Research Centre, Chennai, Tamil Nadu, India

²Department of Kidney, M.V. Hospital for Diabetes and Diabetes Research Centre, Chennai, Tamil Nadu, India

Corresponding Author: Vijay Viswanathan, Head and Chief Department of Diabetology, M.V. Hospital for Diabetes and Diabetes Research Centre, Chennai, Tamil Nadu, India, e-mail: researchcommunication@mvd diabetes.com

glomerular filtration rate have more frequent coronary events and death.^{12,13}

CLASSIFICATION OF PROTEINURIA

Proteinuria can be classified into three categories, such as overflow proteinuria, tubular proteinuria, and glomerular proteinuria (Table 1).

Overflow Proteinuria

Low-molecular-weight proteins filtered by the glomerulus are almost entirely reabsorbed in the proximal tubule. During states of increased low-molecular-weight protein production and subsequent filtration, the amount of filtered protein exceeds tubular reabsorptive capacity, leading to proteinuria. Most often, this is a result of the immunoglobulin overproduction that occurs in multiple myeloma. The resultant light-chain immunoglobulin fragments (Bence Jones proteins) produce a monoclonal spike in the urine electrophoretic pattern.¹⁴ This can be detected in the urine because of the limited reabsorptive capacity of the proximal tubule.

Tubular Proteinuria

Tubular proteinuria occurs when tubulointerstitial disease prevents the proximal tubule from reabsorbing low-molecular-weight proteins (part of the normal glomerular ultrafiltrate). When a patient has tubular disease, usually less than 2 gm of protein is excreted in 24 hours. Tubular diseases include hypertensive nephrosclerosis and tubulointerstitial nephropathy caused by nonsteroidal anti-inflammatory drugs.

Glomerular Proteinuria

Glomerular proteinuria is a sensitive marker for glomerular disease. It is the most common cause of pathologic proteinuria.¹⁵ Several glomerular abnormalities alter the permeability of the glomerular basement membrane, resulting in urinary loss of albumin and immunoglobulins.¹⁵ Glomerular malfunction can cause large protein losses; urinary excretion of more than 2 gm per 24 hours is usually a result of glomerular disease.

Pathophysiological Mechanism in Proteinuria

Protein in urine can sometimes be a sign of kidney disease, as well as other health problems. Protein is one of the major building blocks of the body along with fats and sugars. The correct proportion of the protein is important in our diets, for growth and repair mechanism.

Healthy kidneys filter only traces of protein from blood into the urine as most protein molecules are large for the filters (glomeruli). Thus, it is not usual to lose

Table 1: Pathophysiology in proteinuria

Type	Pathophysiology	Causes
Overflow proteinuria	Increased production of low-molecular-weight protein	Monoclonal gammopathy leukemia
Tubular proteinuria	Decreased tubular resorption of protein in glomerular filtrate	Tubular or interstitial disease
Glomerular proteinuria	Increased glomerular permeability to protein	Primary or secondary glomerulopathy
Postural proteinuria	Abnormal protein excretion in the upright posture, with normal urinary protein excretion in recumbency, probably due to exaggerated systemic and glomerular hemodynamic responses in the upright posture	Otherwise normal subjects with structurally normal kidneys. Occasionally might mark beginning of more serious renal disease
"Admixture" proteinuria	Gross hematuria with tests for urinary protein detecting protein present in blood mixed with urine. No renal pathology	Urological causes of hematuria, such as calculi and cancer. Daily protein excretion usually <1 gm. If the random protein to creatinine ratio is >1.0, underlying glomerular disease is the likely cause of gross hematuria
"Physiologic"/ transient proteinuria	Probably due to transient glomerular hemodynamic changes	Exercise, fever, congestive heart failure

protein to the urine. Proteinuria develops when protein is filtered through the glomeruli. There are several proteins filtered in the urine, but the most relevant to kidney disease is albumin. Healthy kidneys excrete less than 150 gm of protein/day, of which approximately 20 gm is albumin. When this level exceeds, the condition is known as microalbuminuria. It is defined as excretion of 30 to 300 gm of albumin/day and is an early and sensitive marker of diabetic nephropathy.¹⁶⁻¹⁸ Microalbuminuria is associated with an increased risk of CVD in patients with and without diabetes and/or hypertension.^{15,19,20} The presence of protein in the urine is a warning signal for kidney function.

Genetic Predisposition

Genetic factors play an important role in the development of renal disease and proteinuria. Genetic predispositions are found in both congenital and acquired renal diseases. In recent years, several mutations in genes expressed in glomerular cells and especially in podocytes are found in congenital and early-onset proteinuria.²¹ Apart from its role in congenital or early-onset proteinuria, genetic factors play an important role in acquired renal diseases.

They influence both severity of proteinuria and progression of renal disease. For example, diabetic nephropathy is associated with loci on chromosomes 10 and 18, and susceptibility to develop familial immunoglobulin A nephropathy has been linked to loci on chromosomes 2, 4, 6, and 17.²²⁻²⁴

Symptoms and Cause of Proteinuria

Generally, there are no symptoms for proteinuria. If the protein loss is heavy, the urine has a frothy appearance and would most likely be associated with other symptoms, e.g., edema, where there is an excess of water in the body tissues.

The common causes of benign proteinuria are dehydration, emotional stress, fever, heat injury, inflammatory process, intense activity, and most acute illness. Further, glomerular diseases, such as glomerulonephritis and urinary tract infection can also cause proteinuria. Proteinuria can also be a symptom of other medical conditions, such as congestive heart failure, a first warning of eclampsia in pregnancy. Temporary proteinuria may occur after vigorous exercise or during high fever. In children, proteinuria can be detected later in the day, but not in the morning. This is known as orthostatic proteinuria, and it is usually harmless.

Prolonged proteinuria with the warning signal, such as large amounts of protein in the urine, blood in the urine, abnormal kidney tests like creatinine or estimated glomerular filtration rate (GFR), and high blood pressure are more likely to lead to kidney problems. High proteinuria (>2–3 gm per day, or a protein/creatinine ratio of 200–300 or more) usually needs further investigation to find out the cause. In the absence of the above warning signals, it is necessary to monitor kidney tests, urine tests, and blood pressure occasionally. Patients with proteinuria are more likely to suffer from heart disease. Thus, it is important to check blood pressure, cholesterol (usually higher in patients with proteinuria), and factors which cause heart disease, such as smoking and obesity.

Risk Factors for Proteinuria

The two most common risk factors for proteinuria are diabetes and hypertension. Both diabetes and high blood pressure can cause damage to the kidneys, which leads to proteinuria. In patients with essential hypertension and in those with diabetes mellitus, the presence of increased amounts of urinary protein or albumin has been shown to be an important and independent risk for an increased incidence of CV morbidity and mortality.

Other than diabetes or hypertension, proteinuria can also be caused due to medications, trauma, toxins, infections, and immune system disorders, such as multiple

myeloma and amyloidosis. Other risk factors include race and ethnicity, obesity, age (>65 years), family history of kidney disease, and preeclampsia. Proteinuria is regarded as the most acceptable predictive variable in the prognosis of nondiabetic chronic renal disease progression.²⁵ Proper interpretation of proteinuria has to be in line with the clinical context, sometimes it may also be based on other factors. For instance, there had been reported cases of complete resolution of microalbuminuria among diabetic subjects who were found to be normoalbuminuria with 48 months of follow-up.²⁶ Unfortunately, these proteins' effectiveness as biomarkers suffered from lack of specificity and standardization of the techniques.

Recognition of Nondiabetic Proteinuria

The diagnosis of diabetic nephropathy is almost always based on clinical grounds and supported by persistent proteinuria, hypertension, and a progressive decline in renal function.²⁷ A previous study reported that 50% of proteinuric type 2 diabetics with typical diabetic nephropathy on biopsy did not have diabetic retinopathy.²⁸ Renal biopsy is necessary to diagnose NDRD. However, it is generally agreed that renal biopsy cannot be used as a routine diagnostic test in type 2 diabetic patients with proteinuria. Therefore, it is very important to determine the clinical predictive factors for NDRD in type 2 diabetic patients. Factors clinically associated with NDRD in patients with type 2 diabetes mellitus remain unclear. The clinical clues for NDRD in type 2 proteinuric patients are (i) short duration of diabetes, (ii) rapid loss of renal function, (iii) heavy proteinuria with normal renal function, (iv) significant renal dysfunction with minimal/normoalbuminuria, (v) active urinary sediment, (vi) gross hematuria, and (vii) absence of retinopathy.²⁹

Late age of onset of diabetes, absence of neuropathy, absence of retinopathy, and presence of other systemic diseases are reported as markers of NDRD in different studies. However, it remains unclear which clinical factors have greater value in the prediction of NDRD. As the reported incidence of NDRD in type 2 diabetics is high, it is necessary to predict, diagnose, and treat the concurrent glomerular diseases because of the prognostic and therapeutic importance.³⁰ So far, only few such studies had been published from India.

Diagnosis and Treatment of Proteinuria

Protein in the urine is not usually obvious, but can be detected by a simple urine dipstick testing; spot urine specimen analysis, timed urine collection, and the sulfosalicylic acid test are the most commonly employed tests. Proteinuria is not a specific disease; hence the treatment depends on identifying and managing its underlying cause. If that

cause is kidney disease, appropriate medical management is essential. Untreated CKD can lead to kidney failure. In mild or temporary proteinuria, treatment may not be necessary. Proteinuria is a risk factor for the progression of CKD and is associated with adverse CV outcomes. Controlling blood pressure particularly with strongly antiproteinuric agents slows the progression of CKD and delays/prevents CV outcomes. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists have a blood pressure-independent antiproteinuric effect and are considered first-line agents in this scenario.³¹ Proper treatment is necessary in patients with chronic disease, such as diabetes and high blood pressure. It is essential to prevent the progressive kidney damage, i.e., is causing the proteinuria.

Angiotensin-converting enzyme inhibitors and controlling blood pressure have greater benefit in patients with more significant degrees of proteinuria. In a meta-analysis, Jafar et al^{32,33} demonstrated that antihypertensive regimens containing ACEI have a significant benefit in delaying progression of NDRD.

In light of the high prevalence of NDRD, it is appropriate for performing renal biopsy in type 2 diabetics with clinical suspicion of NDRD, especially with overt proteinuria with or without retinopathy. Kidney biopsy is helpful in two ways: (i) It differentiates diabetic from nondiabetic glomerulopathy and (ii) knowledge of the underlying cause of proteinuria may play an important role in planning the correct treatment of these patients. Further, early diagnosis of NDRD is crucial as appropriate therapy could prolong renal survival, i.e., patient population.

Clinical Relevance of Proteinuria

Proteinuria is one of the most reliable predictors of renal disease progression, and many studies have demonstrated that limitation of proteins' glomerular ultrafiltration, either with diet or with antihypertensive medication, slows renal disease progression.³⁴ There are clinical evidence showing that the renin-angiotensin system blockade with ACEI or with angiotensin II type 1 receptor antagonists slows renal damage progression in diabetic nephropathy and chronic proteinuric nondiabetic nephropathies,³⁵⁻³⁸ and moreover, this renoprotective effect goes beyond simply the reduction of blood pressure levels.

Hypertension is associated with more rapid progression of CKD stages 3 and 4.³⁹ Several studies have shown that treating hypertension in patients with CKD and proteinuria may attenuate the decline in GFR.^{31,40} The underlying diagnosis of renal disease, the level of GFR, and level of proteinuria should be evaluated, as well as

the complications of decreased GFR, the risk of progression of kidney disease, the presence of clinical CVD and CVD risk factors, and comorbid conditions.⁴¹

Recently, magnitude of proteinuria has been established as one of the most important risk factors for progression of renal disease. When the protein concentration in the tubular lumen is increased, nuclear factor kappa B translocates to the nucleus of the tubular cells, binds to specific receptors, and enhances gene transcription and generation of inflammatory cytokines including angiotensin, endothelin-1, transforming growth factor beta, regulated upon activation, normal T cell expressed and secreted (RANTES), monocyte chemoattractant protein 1, interleukin 1, plasminogen activator inhibitor 1, and metalloproteinases.^{4,42} This ultimately leads to the presence of interstitial cellular infiltrates and increased matrix protein deposition, which are common observations in renal biopsies of patients with proteinuric renal disease.⁴² Transforming growth factor beta 1 production in renal tubular cells and fibroblasts is increased by angiotensin II, and ACEI have been shown to decrease levels in various forms of kidney disease, and this treatment has been associated with ameliorated damage to the renal interstitium.⁴³

Microalbuminuria has been identified as a reliable predictor of developing renal disease in people with diabetic nephropathy and those with renal disease secondary to systemic hypertension. The presence of microalbuminuria predicts worsening of renal disease to overt diabetic nephropathy and increased risk of CVD. Studies have shown the presence of abnormally high urine albumin concentrations in up to 30% of people with newly diagnosed type 2 diabetes. Of these, approximately 75% of diabetics will have only microalbuminuria and about 25% will have overt diabetic nephropathy.⁴⁴ The presence of microalbuminuria in this group of patients also has been associated with increased risk of developing ESRD. In the MICRO-HOPE study, e.g., the risk of progression to diabetic nephropathy over a 5-year period was 2% for normal patients, compared with 20% for microalbuminuric patients.⁴⁵ In another study of diabetics, those with a high urine albumin concentration at study entry were more likely to develop overt proteinuria, and mortality rate was significantly higher.⁴⁶ Microalbuminuria also is a common finding in people with primary hypertension and is a marker for developing renal insufficiency in those people. Microalbuminuria also is significantly more prevalent in hypertensive people than in normotensive ones.

Proteinuria has been linked to established hypertension and renal disease, and it also has been determined that it may precede hypertension. In people, higher rates of urinary albumin excretion in nonhypertensive indi-

viduals were associated with increased risk of developing hypertension.⁴⁷

Proteinuria as a Biomarker of Kidney Disease

Several large controlled therapeutic intervention studies during the past years have confirmed that proteinuria is a strong and independent predictor of renal failure in diabetics.⁴⁸ In the Modification of Diet in Renal Disease (MDRD) study, which was designed primarily to evaluate dietary protein restriction and strict blood pressure control in 840 patients with diverse renal diseases, multivariate analysis demonstrated that the degree of proteinuria significantly predicts the decline in GFR.⁴⁹

The presence of filtered high molecular and tubular proteins in urine has been the conventional biomarker indicating impairment and predicting sequence in chronic renal disease. The predictive usefulness of proteinuria was earlier discovered in known cases of type 1 diabetes.

CONCLUSION

Increased proteinuria would lead to a larger risk for renal failure in the long-term. It is therefore important to carefully examine such patients and follow them up, by controlling their blood pressure, quantitating their proteinuria, and determining their renal function and serum cholesterol. Early recognition and management of proteinuria may result in a delay in the progression to end-stage disease or the successful treatment of the underlying disease. Therefore, proteinuria requires immediate and thorough evaluation. Proteinuria is a well-recognized risk factor for CVD and renal disease; hence, its early pharmacological treatment is a matter of clinical relevance. Little treatment is available to promote the reduction of proteinuria once, i.e., established.

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