

“The ghosts of dead patients that haunt us do not ask why did not employ the latest fad of clinical investigation. They ask us, why did not test my urine”

Sir Robert Hutchison

Kidney plays an important role in maintaining body homeostasis by changing the composition of urine to maintain electrolytes and acid-base levels and also got endocrine function which maintains metabolism.¹

Glomerular filtration rate (GFR) is normally used to assess the kidney function which may not be useful in many clinical settings. Abnormalities kidney function can not only be the early sign of kidney disease but can also reflect many systemic conditions.

Normally plasma proteins crosses glomerular capillaries and mesangium without entering urinary space except a small portion of small density proteins which are excreted into the tubules and are reabsorbed by the proximal renal tubule.²

Proteinuria which may be a incidental finding in many patients can be the early sign of a serious kidney and systemic disorder. Several studies have revealed that proteinuria is associated with increased mortality.³ Therefore early detection and treatment can prevent morbidity and mortality.

History of proteinuria dates back to 2000 BC in Hindu literature. Hippocrates has described proteinuria as foamy urine. A normal person excretes 150-200mg of protein in urine as result of tubular secretion which

includes less than 30 mg of albumin.^{2,4}

This amount of urinary proteins can be detected by the dipstick testing.³ Proteinuria can be transient following heavy exercise. Persistent proteinuria needs to be investigated. False positive and false negative results are possible in a dipstick test (Table 1). Conditions are as follows:

Proteinuria is classified into microalbuminuria and macroalbuminuria.⁵

Microalbuminuria refers to a subclinical condition with increased urinary albumin excretion. By definition microalbuminuria is the excretion of albumin in urine at rate of 20-200 mcg/min (30-300 mg/day) or albumin to creatinine ratio of 2.5 to 25 mg/mmol in males and 3.5-35mg/mmol in females. National health and nutritional examination survey (NHANES) study revealed that the prevalence of microalbuminuria in age group of 6-80 years is 6.1% in male and 9.7% in females. Prevalence progressively increases with age.^{6,7} Prevalence in hypertension around 4-16%.⁸ Most of them progress to overt proteinuria and end stage renal disease over a period of time. Microalbuminuria is an early maker of nephropathy or ESRD in Diabetes and Hypertension and studies have shown that it is an independent risk factor for atherosclerotic cardiovascular disease.^{3,4} Studies have also shown association of microalbuminuria and increased risk of cardiocascular disease in obese nondiabetic individuals.⁹ Studies like PREVENT (Prevention of renal and vascular end stage diseases), HUNT (nord-trondelag health study) and EPIC (European prospective study) have shown that in persons with microalbuminuria but are nonhypertensive and nondiabetics have increased risk of cardiovascular disease by 40% and 29-50% risk of cardiovascular mortality including stroke.⁵ Glomerular endothelial dysfunction may be cause for microalbuminuria which explains the association with atherosclerosis.¹⁰ Microalbuminuria is also associated with increased risk of stroke.^{5,11}

There are various risk factor for development of proteinuria or microalbuminuria. They are as follows

1. Male sex
2. Advanced age
3. High body mass index
4. Smoking
5. Diabetes mellitus

Table 1:	
False positive	False Negative
Concentrated urine	Diluted urine
PH>7	pH<4
Presence of gross hematuria/WBC/mucous/ semen/vaginal discharge	Protein < 300mg/day
Urease producing bacteria by rising pH	Positively charged proteins like immunoglobulin light chains and beta ₂ microglobulins
Iodinated contrast agent	
Contamination with disinfectant like chlorhexidine	

- 154 6. Hypertension including elevated systolic blood pressure.

Proteinuria is classified as follows

1. Glomerular- Primary and secondary
2. Tubular
3. Tubulointestinal
4. Overflow

Causes of proteinuria are

- A. Benign:
 1. Exercise
 2. Dehydration
 3. Stress
 4. Infections
 5. Orthostatic
 6. Pregnancy
 7. Heat Injury
- B. Organic causes includes various glomerular diseases like Glomerulonephropathies (including IgA nephropathy), diabetes mellitus, hypertension, collagen vascular diseases, malignancy, infections like HIV, hepatitis B etc and drugs and poisoning. tubular diseases like uric acid nephropathy, Fanconi's anemia, heavy metal poisoning and drugs like NSAIDs. Overflow proteinuria conditions are hemoglobinuria, myoglobinuria, multiple myeloma and amyloidosis.³

APPROACH TO DIAGNOSIS

As in any other situation care history and physical examination are mandatory in making the diagnosis and further evaluation. A detailed history can give clue to the use of drugs like NSAIDs and illicit drug abuse and also systemic diseases. Careful examination needs to be carried out to find out the other end organ damages as in diabetes and atherosclerosis. Physical examination may also be useful in collagen vascular diseases and other systemic diseases. Strict glycemic control and blood pressure control can prevent or retard the progression of microalbuminuria to overt proteinuria eventually ESRD and other complications.^{3,4} Urine analysis should be repeated to exclude transient proteinuria. Once the persistent microalbuminuria is established, it needs to be quantified.¹² Quantification can be done using 24 hour urinary protein or timed overnight urine collection. Other methods used for albumin excretion are random urine sampling and spot morning urine sample (first void).⁵ Techniques of quantification are as follows.²

1. Radioimmuno assay by double antibody technique
2. Immunoturbometric method
3. Laser nephrometer
4. ELISA

5. HPCL method

Blood sugar levels, creatinine, electrolyte levels, protein creatinine ratio or albumin creatinine ratio and lipid profile needs evaluation in both type 1 and type 2 diabetes and hypertension. ECG, echocardiography and peripheral arterial doppler studies has to be done to assess the cardiac function as well as to assess atherosclerotic vascular disease. Serological studies to exclude HIV, hepatitis and collagen vascular diseases are to be carried out. urine analysis may reveal red or wbc cast and eosinophils in tubulointestinal nephritis. Electrophoresis may be considered in multiple myeloma and hemoglobinopathies.

TREATMENT

Treatment of microalbuminuria and the condition that has lead to microalbuminuria is atmost important in order to prevent progression to end stage renal disease and also improve cardiovascular morbidity and mortality. Several studies have proven this fact that use of antiproteinuric agents totreat microalbuminuria retards progression to ESRD and better clinical outcome. Angiotensin convertingenzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) are drugs of choice for the treatment of proteinuria or microalbuminuria. ACEI are preferred over ARBs. These agents reduces intraglomerular pressure and preserves integrity of glomerular membrane which inturn reduces proteinuria. ACEI and ARBs not only controls proteinuria but also controls hypertension. Several studies have shown that good blood pressure control retads the progerSSION to ESRD. Dihydropyridine calcium channel blokors should better be avoided. Nondihydropyridine calcium channel blockers and beta blockers are also shown to retard the progression to renal failure. Statins have also shown the beneficial effects in teratment of microalbuminuria as they reduce protein traffic across proximal renal tubular cells. Good glycemic control in all diabetic patients also delays the progression to renal failure.

Apart from antiproteinuric therapy, life style modifications to reduce weight, regular exercise, salt restriction, dietary protein restriction are also required. Smoking cessation, avoiding unnecessary use of NSAIDs and other nephrotoxic drugs helps in preventing progression to renal failure. In patients with heavy proteinuria, severe exertion is to be avoided and supine or recumbent posture is encouraged.^{3,4,8}

CONCLUSION

Proteinuria or microalbuminria is one of earliest and powerful sign of kidney disease and a marker of atherosclerotic cardiovascular disease. Treatment of microalbuminuria and the primary condition which has lead to proteinuria not only retards the progression to renal failure but also reduces morbidity and mortality. Microalbuminuria can be seen commonly in general population, hypertension and diabeic patients. Hence careful investigation in persons with proteinuria in urine analysis and high risk patients can help prevent morbidity and mortality to great extent.

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