SECTION VI

Nephrology
Introduction
Examination of urine is one of the most rewarding tests in clinical medicine, as not only it uncovers renal diseases but also it frequently points to a specific diagnosis. Further the quantity and type of proteinuria may help in determining the type of renal disease. Normal daily protein excretion in an adult does not exceed 150 mg. However, benign orthostatic and transient proteinuria should always be excluded before embarking on the detailed investigations for a renal disease. Persistent proteinuria >1.0 g per day, usually indicates renal disease. Proteinuria may be minimal (<1.0 g/day), moderate (1-3 g/day) and heavy (> 3.0 g/day). Spot morning urine protein: creatinine ratio of < 0.2 is normal; 0.2-1 indicates low-grade proteinuria; 1.1 to 3.0 is taken as moderate and >3.0 as heavy proteinuria. Important causes of minimal proteinuria are chronic pyelonephritis, diabetic nephropathy, and inactive glomerular disease, interstitial nephritis and chronic renal failure. Moderate proteinuria is seen in nephritic syndrome and toxic nephropathies; whereas heavy proteinuria indicates active glomerulonephritis (GN).

Path Physiologic Classification of Proteinuria
Barrier to protein filtration is mostly constituted by the glomerular basement membrane and slight damage to it leads to leakage of albumin in the urine. With increase in the damage, besides other proteins, there is leakage of red cells and other types of cells in the urine. The increased urinary protein excretion can result from 4 major mechanisms: (a) altered transglomerular passage of proteins; (b) decreased tubular reabsorption; (c) increased plasma concentration of proteins; (d) addition of proteins to the tubular fluid. Therefore, the most important first step in the clinical evaluation of proteinuria is the classification of proteinuria into (i) glomerular (ii) tubular (iii) overflow proteinuria (iv) other isolated proteinurias.

Glomerular Proteinuria
It is due to alteration of the preselective properties of glomerular capillary wall or due to hemodynamic factors. It is characterized by a disproportionate amount of albumin in urine and the ratio of albumin and B2 micro globulin exceeds 1000 to 1. Normally this ratio ranges from 50 to 1 to 200 to 1. Patients
with glomerular disease may present as asymptomatic proteinuria, nephrotic syndrome or nephritic syndrome. Acute nephritic syndrome associated with oliguria, edema, hypertension, mild proteinuria, active urinary sediments and azotemia is at the top of the clinical pyramid. Mild isolated (fixed) proteinuria <1.5g/day is of little long-term significance and is associated with good outcome. On the other hand, sustained heavy proteinuria suggests a more serious disorder. When proteinuria exceeds 3.5 g/day, it is called nephrotic syndrome (NS) and is associated with hypoproteinemia, hyperlipidemia, edema and lipiduria.

**Tubular Proteinuria**

It is found in both acute and chronic injuries involving the renal tubulo-interstitial region. Tubular proteins do not arise from plasma proteins but are secreted from the cells of different parts of nephron and urinary tract. It usually does not exceed 2.0 g per day. Urinary protein electrophoresis and/immunoelectrophoresis may aid in distinguishing tubular and glomerular proteinuria. The urinary albumin and B2 micro globulin ratio of 10 to 1 suggests the presence of later 1. Further measurement of β2-M lysozyme may help in distinguishing type of UTI besides diagnosis of heavy metals poisoning.5-6

**Overflow Proteinuria**

It is due to filtration by the normal glomerulus of an abnormally large amount of low molecular weight proteins, whose filtration exceeds the capacity of the normal tubules for reabsorption. It is characterized by the presence of abnormal peak or spike on urinary electrophoresis. This is commonly found in cases of multiple myeloma, myoglobinuria, rhabdomyolysis & lymphoproliferative disorders.

**Isolated Proteinuria**

Two forms of proteinuria do not fit into the classification described above. These are benign orthostatic and functional transient proteinuria and are grouped as isolated proteinuria because these are found in the absence of any known disease of kidney.7

**Benign Orthostatic/Postural Proteinuria**

This type of proteinuria does not exceed 2.0g/day and is seen in tall adolescents individuals in upright/ lordotic posture but is not seen in overnight specimen collected immediately on rising and it reappears on ambulation.8 Urinary sediments are normal.

**Functional Transient Proteinuria**

It occurs after fever, a bout of severe exercise or seizure, cardiac failure, or exposure to cold. Usually it is<0.5g/day but may be as heavy as 5.0 g/day (following marathon running). It disappears with the resolution of causative disorder.9

**Clinical Evaluation of Glomerular Proteinuria**

Patients with constant proteinuria require diagnostic scrutiny. Cases with non-nephrotic range proteinuria have better prognosis than with nephrotic range. The first step in its evaluation is to exclude functional/ orthostatic proteinuria and then classify it into glomerular or tubular. Glomerular proteinuria is mainly albumin; where as tubular proteinuria consists of globulins. Further salient difference in glomerular and non-glomerular proteinuria is the presence of hypertension and active urinary sediments in the form of cellular casts in the former. However, sometimes immunoelectrophoresis may be required to differentiate them. Once proteinuria is determined to result from glomerular disease, it is necessary to identify the nature of underlying disease. The etiology of differential diagnosis of such diseases is large (primary/secondary GN) but it can be narrowed down substantially by obtaining a detailed history, physical examination, and appropriate serological testing. Fig. 1 gives the detailed work up in a case of proteinuria.
The History Should Cover the Following Details
Presence of diabetes, deafness, similarly affected family members (Alport’s nephropathy and other familial nephritis), ethnicity (IgA nephropathy more in Asian than black), presence of fever, travel; medication; transfusion; drug abuse; sexual orientation and partners (HIV, hepatitis, syphilis), arthritis, arthralgias, malar or skin rash, oral ulcers, alopecia (systemic lupus erythematosus, other immune and hypersensitivity disorders), hemoptysis (Good Pasture’s disease, Wegener’s granulomatosis, amyloidosis), sinusitis, sterile otitis, neurological deficit, parasthesia (Fabry’s disease) episodes of gross or microscopic hematuria (IgA nephropathy, basement membrane disease), cough, weight loss, breast mass (malignancy, secondary membranous nephropathy), childhood urinary tract infections (reux nephropathy).

Physical Examination
It is directed to establish the presence of systemic diseases and to know whether nephrotic syndrome or its complications are present.

All adults with abnormal proteinuria should have the following investigations
1. X-Ray Chest (Wegener’s granulomatosis, lung diseases causing amyloidosis)
2. Total and differential blood counts
3. 24 hours urinary protein, creatinine & serum as well as urinary electrophoresis
4. Serum chemistry including renal and hepatic function tests, serum albumin and total proteins, lipid gram, blood glucose and calcium levels
5. Ultrasonography for the kidneys
6. Mammography in females more than 50 years of age

Additional Tests May Include
Antinuclear antibodies (Lupus), ANCA (Wegener’s granulomatosis, vasculitis), C3-C4 (endocarditis, post streptococcal GN, lupus, cryoglobulinemia), antihyaluridase, anti-DNase B, ASO (post streptococcal GN), angiotensin converting enzyme (sarcoidosis), antiglomerular basement membrane antibody (Good Pasture’s disease), glycosylated hemoglobin (diabetes), antigen for hepatitis B and C, markers for malignancies and ELISA for HIV.

Rather a thoughtful synthesis of history and physical examination should guide the selection of appropriate tests among those listed (and potentially others not mentioned). Selectivity of urinary protein excretion may also be done because low selectivity indicates injury to podocytes and loss of negative charge of filtration membrane where as high selectivity indicates minimal change disease. Selectivity Index (SI) = IgG clearance/albumin clearance x 100. Protein clearance=Concentration in urine/concentration in plasma. SI<15% means high selectivity and SI >30 means low selectivity. A renal biopsy is done to find out underlying cause of proteinuria, severity of renal disease and to decide the therapy.

Clinical Evaluation of Tubular Proteinuria
A wide range of conditions can cause tubular proteinuria. Therefore an attempt should be made to rule out the important group of diseases responsible for it. A family history of polycystic kidney disease, history of analgesic abuse, frequent childhood urinary tract infections, flank pain or passage of renal stones, signs and symptoms suggestive of collagen vascular disease (vide supra) should always be elucidated. Renal biopsy is infrequently required in tubular proteinuria for the evaluation of diagnosis.

Approach to Therapy
Every effort should be made to identify the causes of glomerulonephritis. The treatment of glomerular disease falls under four categories.

2. Therapy for Specific Glomerular Disease: When a glomerular disease is identified; establishing a specific diagnosis is critical. Patients presenting with nephrotic syndrome without hematuria, infection, collagen vascular disease or malignancy; are likely have idiopathic GN. Renal biopsy is often necessary for the diagnosis of idiopathic GN.
3. Treatment of Underlying Systemic Disease: A complete history, physical examination accompanied by routine blood work uncovers the etiology of NS in 60-70% of cases. Hypertension or diabetes is usually present for more than 10 years before it presents with significant proteinuria. History may reveal exposure to nephrotoxins like analgesics and heavy metals, evidence of systemic diseases like lupus, sickle cell anemia or malignancy. Besides this, in all cases of membranous GN, secondary glomerulopathy (infections, heavy metals, lupus, malignancy) needs to searched and excluded. Similarly histopathologic results may raise suspicion of hepatitis-C (membrano-proliferative GN) plasma cell dyscrasias, oxalosis and amyloidosis. Therefore, tissue examination is often necessary. Chronic GN usually has smaller kidneys. Presences of larger kidneys indicate conditions like amyloidosis, adult polycystic kidney disease, diabetes, multiple
myeloma and chronic obstruction. Rapid deterioration of renal functions with proteinuria can be due to Wegener’s granulomatosis, focal segmental glomerulosclerosis, vasculitis and Good Pasture’s syndrome. For the management of other causes of secondary GN, including malignancies, autoimmune disorders and SLE etc, the treatment of underlying disorder is the key to the therapy. Cases of lupus nephritis with NS should be treated energetically with immunosuppressive therapy. If treatment is started in early part of the disease, when there is no renal dysfunction or it is mild; good results are seen in large majority of cases. The management of NS in primary amyloidosis is unsatisfactory.

4. Prevent or delay progression of glomerular injury: GN is the leading cause of chronic renal failure after diabetes and hypertension. The interval between the onset of proteinuria and end-stage renal disease takes many years in diabetic nephropathy (DN). Therefore, medical intervention is possible only in the early stages of the disease. Since presence of hypertension is the most critical factor in development and progression of DN in these patients as it accelerates the decline in glomerular filtration rate (GFR). Further effective control of hypertension has been shown to decrease albuminuria to 50% and rate of decline in GFR from 0.9 ml/min to 0.29 ml/min. Therefore, there is wide consensus for using anti-hypertensive medication that has most beneficial effect on reducing microalbuminuria and improvement in the glomerular membrane size. This selective property seems to be unique for ACE-I and is independent of systemic blood pressure changes. Therefore anti-hypertensive treatment with ACE-I in DN appears to be protective as it delays progression, if started early at the stage of microalbuminuria even in normotensive individuals. Further, this therapy has also been found to decrease albuminuria in the stage of overt nephropathy. Therefore its use is advocated in all cases of DN with serum creatinine <2.5 mg%. Zellar et al demonstrated a three-fold decline in rate of fall of GFR on a protein-restricted diet (0.6g/kg/day). Long-term consequences of protein restriction are still unknown. Therefore it is logical to prescribe modest dietary protein restriction, which may be increased in the presence of renal failure.

Summary
A dipstick urine test has been used to screen for renal disease, as proteinuria may be the only manifestation of chronic renal injury. However, to define a clinical disease, urine examination for different types of cells, casts and 24 hours protein excretion is required. If proteinuria persists greater than 2+ on repeat examination, clinically significant renal disease may be present. The amount of proteinuria can also differentiate glomerular from non-glomerular proteinuria. However, this should be held as a general rule and should not be considered diagnostic in and of it.

References