REVIEW

WAQAR KASHIF, MD
Department of Medicine, Medical College of Wisconsin, Milwaukee

NAUMAN SIDDIQI, MD
Department of Medicine, Medical College of Wisconsin, Milwaukee

AYSE P. DINCER, MD
Department of Medicine, Medical College of Wisconsin, Milwaukee

H. ERHAN DINCER, MD
Department of Medicine, Medical College of Wisconsin, Milwaukee

SHELDON HIRSCH, MD
Chief, Division of Nephrology, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago

Proteinuria: How to evaluate an important finding

ABSTRACT

Proteinuria is a common laboratory finding in outpatients and should not be discounted. When it is due to a glomerular disease, early diagnosis is important to prevent further renal damage. Proteinuria may also be a marker for progressive atherosclerosis.

KEY POINTS

The most widely used method to detect proteinuria is the urine dipstick test. Although the dipstick test is cost-effective and simple, its sensitivity is not always high enough.

The finding of proteinuria should merit at least a cursory look for causes of false-positive results; if these are absent, the proteinuria should be confirmed by a repeat test.

If proteinuria is persistent, systemic diseases should be ruled out, and the proteinuria should be carefully evaluated to determine its potential to progress to renal insufficiency. Close follow-up, extensive workup, and timely nephrology referral may be necessary.

Early detection and treatment of asymptomatic proteinuria in patients with diabetes improves overall survival.

PROTEINURIA should be taken seriously, even in outpatients without symptoms.

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A common incidental finding, proteinuria is often transient and benign, but persistent proteinuria can be a manifestation of a systemic disease. It can represent the early stages of chronic kidney disease, which can progress to kidney failure. It is also a marker of and probably an independent risk factor for atherosclerotic diseases, such as coronary artery disease or stroke. People with proteinuria have an increased risk of death.[1–3]

This article reviews the mechanisms of proteinuria, its clinical importance, and our approach to screening and diagnosis.

MECHANISMS OF PROTEINURIA

There are four mechanisms of excessive protein excretion: increased glomerular filtration, inadequate tubular reabsorption, overflow, and increased tubular secretion.

- **Increased glomerular filtration** of normal plasma proteins is due to altered glomerular permeability.

Albumin is normally a minor component of urinary protein (TABLE 1), but it is elevated in glomerular diseases. Both the size and the charge of the protein molecule determine whether it can be filtered through the glomerulus.[4–7] The glomerular capillary walls contain functional pores through the glomerular basement membrane, which block large molecules but allow smaller ones to pass.

In addition, both capillary endothelial cells and the glomerular basement membrane

TABLE 1

Normal values for protein excretion

CATEGORY	VALUE (MG/24 HOURS)
Total protein excretion	
Normal value in adults	< 150
Proteinuria	≥ 150
Nephrotic-range proteinuria	> 3,500
Albumin excretion	
Normal albumin excretion	2–30
Microalbuminuria	30–300
Macroalbuminuria	> 300

have a net negative charge due to polyanions such as heparan sulfate proteoglycans. This negative charge creates a barrier for anions like albumin.[6,7]

Proteinuria usually reflects an increase in glomerular permeability, but small amounts of protein in the urine may be the result of tubular disease (see below).

- **Inadequate tubular reabsorption** of the small amounts of normally filtered proteins occurs in tubulointerstitial diseases.

Smaller proteins such as beta-2 microglobulins, immunoglobulin light chains, retinal binding protein, and amino acids pass across the glomerular membrane, but are normally reabsorbed from the proximal tubule. In tubulointerstitial diseases, normally filtered proteins are lost in the urine owing to a defect in tubular epithelial cells, resulting in nonnephrotic–range proteinuria.

- **Overflow** of elevated normal or abnormal plasma proteins occurs in plasma cell dyscrasias.

Overflow proteinuria occurs when there is an excessive amount of protein and the tubular cells cannot reabsorb all that is filtered. If this condition persists, the tubular cells may be damaged by precipitation of microproteins, leading to further proteinuria.

- **Increased secretion** of tissue proteins from the epithelial cells of the loop of Henle occurs in Tamm-Horsfall proteinuria.

Tamm-Horsfall protein is a mucoprotein formed by the cells of the ascending thick limb and the distal convoluted tubule, and it is normally restricted largely to renal tubular cells.[8] It forms the backbone of urine casts as it takes the shape of the tubule and traps other components such as red blood cells, white blood cells, and epithelial cells.

Tamm-Horsfall protein has been shown to leak into the interstitium in human and experimental reflux nephropathy, obstructive uropathy, and some other tubulointerstitial disorders.[9,10] It has a high affinity for Bence-Jones proteins, and the aggregation of these light chains on Tamm-Horsfall proteins form the basis of cast nephropathy in myeloma kidneys.

TESTS TO DETECT AND MEASURE PROTEINURIA

Dipstick testing

Urine dipstick testing is the most commonly used test for proteinuria.

The dipstick carries a reagent strip impregnated with a pH indicator, usually tetrabromophenol, and a buffer to maintain a pH of 3.0. Proteins (especially albumin) bind to the pH indicator dye, which changes color. This change is independent of the urine pH.[11–14]

Urine dipstick testing is usually highly specific, although it can give false-positive results in some situations (FIGURE 1). On the other hand, it is not as sensitive as quantitative methods. Using 20 to 25 mg/dL of total protein as the limit of detection in clinical specimens, the sensitivity of reagent strips is only 32% to 46%, with a specificity of 97% to 100%.[15,16]

False-negative results can occur if the urine is dilute and protein loss is mild, as the method detects protein concentrations and not absolute amounts. Therefore, dipstick testing is useful only when urinary protein exceeds 300 to 500 mg/day (or albumin > 10–20 mg/day).

Moreover, the dipstick is essentially specific for albumin, which is negatively charged, so it may miss other, positively charged proteins. It is insensitive for detecting low-molecular weight proteins such as immunoglobulin light chains and beta-2 microglobulin.

Dipsticks are useful only for urinary protein > 300 to 500 mg/day

Approach to a patient with proteinuria

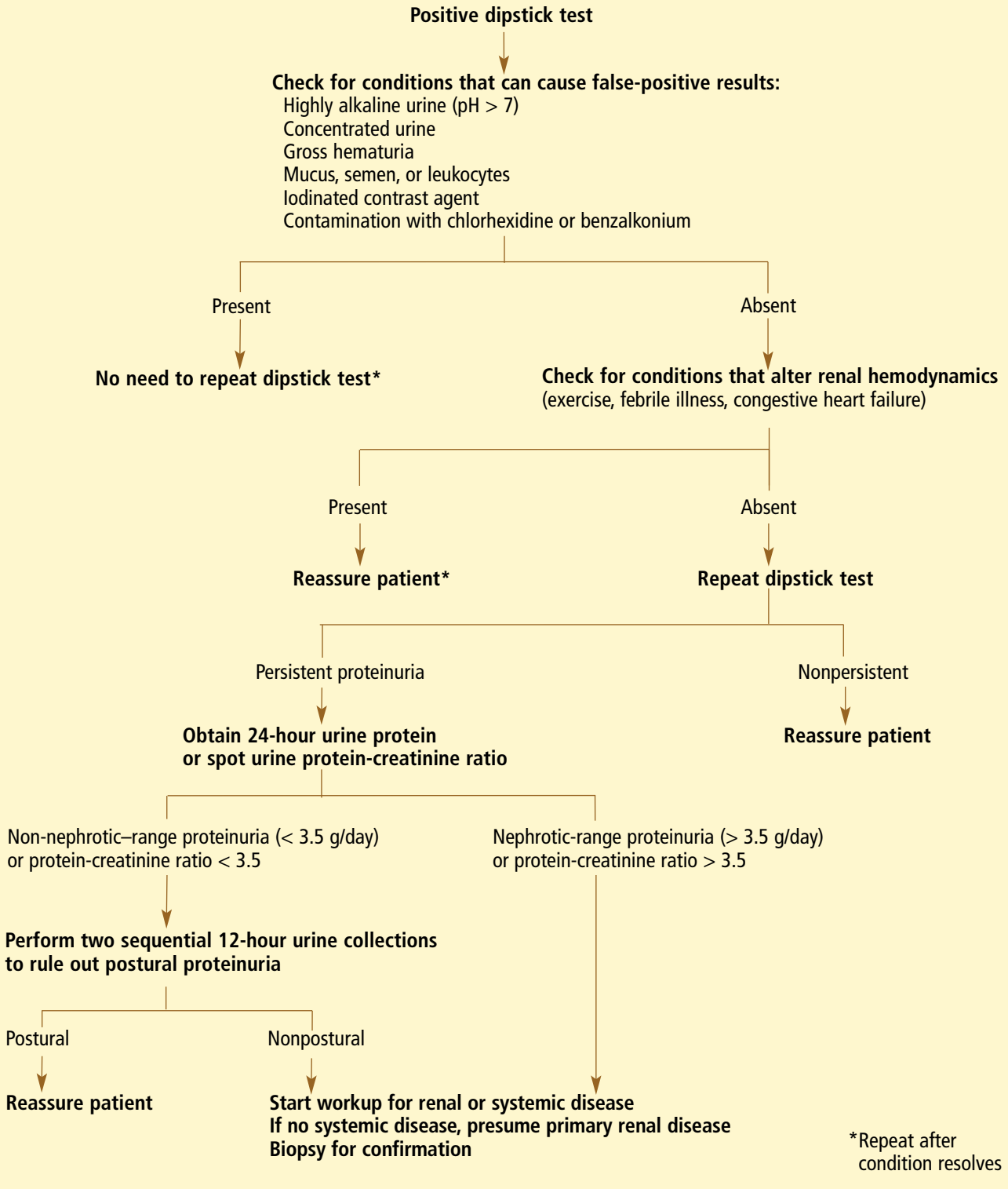

FIGURE 1

Turbidometric tests

If you suspect that a protein other than albumin is present in elevated amounts in the urine, a turbidometric test should be done. The two most commonly used are the sulfosalicylic acid test and the heat (Putnam) test.

The sulfosalicylic acid test detects both large and small protein molecules.[17] Eight drops of 20% solution of sulfosalicylic acid are added to 10 mL of the urine. The results range from "clear" to "flocculent precipitate," suggesting protein levels of 0 to greater than 500 mg/dL, respectively.

This test can give false-positive results in the presence of gross hematuria, highly concentrated urine, iodinated contrast agent, tolbutamide metabolites, high levels of cephalosporin or penicillin analogs, or sulfonamide metabolites. The test can be falsely negative with highly alkaline urine.

The heat test. In this test, 5 mL of urine is centrifuged, 2 mL of acetate buffer is added to the supernatant, and this solution is incubated at 56°C for 15 minutes. A precipitate indicates Bence-Jones proteins. These can be dissolved by heating the mixture to 100°C for 3 minutes. This test is not widely used.

Radiocontrast agents can cause false-positive results in both dipstick testing and the sulfosalicylic acid test[18]; therefore, testing should not be done until 24 hours after a contrast study.[19]

24-Hour protein measurement

It is essential to know how much protein is being excreted to predict long-term prognosis. Quantitative measurement of protein in a 24-hour urine collection remains the gold standard, especially since protein excretion may vary with the circadian rhythm.[20]

Patients should be told to begin the collection at a fixed time by voiding into the toilet and then saving all of the urine they pass thereafter, including urine collected 24 hours later at the same time.

One must also measure the creatinine in the collected urine to assess whether the collection is complete. Men usually excrete 19 to 26 mg of creatinine/kg/day, and women excrete 14 to 21 mg/kg/day. Creatinine excretion increases with muscle mass and weight. It decreases in old age.

Spot urine sampling

Spot urine sampling is another reliable method of screening for proteinuria and does not have the compliance problems associated with 24-hour urine collection. The protein and creatinine concentrations should be measured, and the protein-creatinine ratio calculated.

The spot protein-creatinine ratio correlates well with the amount of protein excreted in a 24-hour sample ($r^2 = 0.97$).[21] A milligram-per-milligram protein-to-creatinine ratio of 0.2 or less is normal, whereas a ratio of 3.5 or greater is in the nephrotic range.

The albumin-creatinine ratio likewise correlates well with 24-hour albumin excretion. On a milligram-per-gram basis, an albumin-creatinine ratio of less than 30 is normal, 30 to 300 is considered microalbuminuria, and greater than 300 is overt nephropathy.[22]

Derhaschnig et al[23] measured albumin concentrations and albumin-creatinine ratios in 264 hypertensive patients and compared these values with 24-hour albumin measurements. The finding of microalbuminuria in a spot sample had a sensitivity of 91%, specificity 84%, positive predictive value 44.2%, and negative predictive value 97.9% for predicting microalbuminuria in a 24-hour sample. For the protein-creatinine ratio the sensitivity was 87.8%, specificity 89.3%, positive predictive value 29.3%, and negative predictive value 96.2%.

Excretion of protein is highly variable throughout the day, especially in pregnant patients with hypertension. Therefore, a 24-hour urine protein collection is recommended to obtain more reliable results, especially in pregnancy.[20]

Protein: creatinine ratio: Normal: ≤ 0.2 Nephrotic-range proteinuria: ≥ 3.5

Urine protein electrophoresis

Qualitative evaluation of proteinuria can be done using immunoelectrophoresis. In Bence-Jones proteinuria there is a monoclonal peak in the gamma region, whereas a broad heterogeneous peak in the gamma region indicates tubular proteinuria, in which the protein molecules are usually smaller than albumin.

WHO SHOULD BE SCREENED?

Patients with hypertension and diabetes mellitus should be regularly screened for proteinuria, which is well documented to portend a worse prognosis in these patients.[24–26] On the other hand, the cost-effectiveness and benefit of screening people without symptoms or relevant associated diseases is debatable and is being argued in nephrology circles.

CONSIDER FACTORS THAT AFFECT PROTEIN EXCRETION

When screening for proteinuria, one should consider the many factors that can influence urinary protein excretion.

Factors that can transiently increase protein excretion include exercise, congestive heart failure, urinary tract infection, and acute febrile illnesses. Nonsteroidal anti-inflammatory drugs (NSAIDs) and occasionally angiotensin-converting enzyme (ACE) inhibitors can cause proteinuria that is reversible, but they sometimes cause persistent proteinuria secondary to tubulointerstitial nephritis.

Proteinuria > 3.5 g/day usually indicates glomerular disease

On the other hand, NSAIDs, ACE inhibitors, and angiotensin-receptor blockers (ARBs) can also *decrease* the amount of protein in the urine. NSAIDs reduce proteinuria by reducing renal prostaglandin synthesis.[27] The reduction in proteinuria by NSAIDs is associated with a reduced glomerular filtration rate (GFR), which is presumed to reflect reduced glomerular hydrostatic pressure due to afferent vasoconstriction. In contrast, ACE inhibitors and ARBs decrease intraglomerular hydrostatic pressure by causing efferent vasodilatation.

Proteinuria is also associated with obesity, especially the central type.[28–30] Several mechanisms have been proposed, including insulin resistance, elevated glucagon levels, and glomerular hyperfiltration,[31] and it may not be related to blood pressure control.[32] Typical renal histologic features include glomerular hypertrophy, focal segmental glomerulosclerosis, increased mesangial matrix and cellularity, relative preservation of foot process morphology, and absence of evidence of inflammatory or immune-mediated pathogenesis.[33,34]

Obesity-associated proteinuria responds well to a weight-reduction diet and ACE inhibitors.[35,36]

IS THE PROTEINURIA TRANSIENT OR PERSISTENT?

Transient proteinuria is common, benign, and usually mild (< 1 g/day). In most patients, it is discovered incidentally. It may be seen in patients with a recent history of fever, cold exposure, emotional stress, or strenuous exercise (FIGURE 1).

This type of proteinuria usually resolves within several days after the precipitating factor disappears. Patients with transient proteinuria have normal urinary sediment and do not progress to renal failure.[37,38]

Orthostatic (postural) proteinuria occurs only in the upright position.[39–42] It is persistent but benign, and it completely normalizes in the recumbent position. It is seen primarily in young adults, usually is less than 1 g/24 hours, and is thought to be due to an alteration in glomerular hemodynamics. The renal histology is generally normal or nonspecific, and the long-term prognosis is excellent.[38,41,43]

Persistent proteinuria is defined as being present on two or more occasions. It is believed to reflect structural renal disease and may progress to chronic renal insufficiency.

Persistent proteinuria can also be a part of a systemic disease. While non-nephrotic proteinuria (< 3.5 g/day) is seen in tubulointerstitial diseases and in mild degrees of glomerulopathies, nephrotic-range proteinuria (> 3.5 g/day) usually indicates glomerular disease.

Once systemic diseases that cause nephrotic syndrome, such as diabetes mellitus, heavy metal poisoning, collagen vascular disease, nephrotoxic drugs, amyloidosis, and plasma cell dyscrasia have been excluded, the likely cause is primary glomerular disease (TABLE 2).

APPROACH TO PROTEINURIA

When proteinuria is detected, one should make sure that it is not a false-positive result and the patient is not on medications that

may alter renal hemodynamics and protein excretion. It is also important to exclude conditions in which mild proteinuria may occur, such as a urinary tract infection, acute febrile illnesses, massive hematuria, or recent strenuous exercise (FIGURE 1).[44,45]

If proteinuria is persistent, ie, present on two occasions, a 24-hour urine collection for proteins or a random total protein-to-creatinine ratio should be obtained.[46] A careful history and physical examination should identify any preexisting systemic diseases (FIGURE 1).

Laboratory workup

A laboratory workup is required in nearly all patients with persistent proteinuria. First, one should determine the degree of proteinuria and examine the urinary sediment to determine whether severe renal disease is present.

Urine microscopy. We cannot overemphasize the importance of examining a freshly spun urine sample under the microscope. Glomerular disease usually presents with abnormal urinary findings such as red blood cell casts and dysmorphic red blood cells. White blood cell casts may indicate glomerular or interstitial disease. Oval fat bodies are usually seen in nephrotic-range proteinuria.

Blood tests. The serum creatinine concentration, a chemistry profile, and blood counts should be obtained in all patients. The serum creatinine level is proportional to the muscle mass, which is affected by age, sex, and nutritional status. Moreover, slight changes in GFR, as in early stages of renal disease, may not be reflected in serum creatinine levels. Therefore, a more comprehensive evaluation of GFR using a 24-hour urine creatinine and urea might be needed.

Immune system tests. In the absence of an obvious cause of proteinuria such as diabetes, the workup should also include measurements of antinuclear antibody, antineutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), complement levels, and the erythrocyte sedimentation rate to evaluate for rheumatologic diseases (eg, systemic lupus erythematosus, Wegener granulomatosis, Goodpasture syndrome, cryoglobulinemia), lymphoproliferative diseases, and solid organ cancers.

Screening for infections such as human immunodeficiency virus, hepatitis B and C, and syphilis should also be performed.

Urinary protein immune electrophoresis should be ordered if there is a suspicion of multiple myeloma or if there is discrepancy between the urine dipstick test and the sulfosalicylic acid test.

TABLE 2

Classification of causes of proteinuria

Isolated
- Transient
  - Functional
- Persistent
  - Postural

Disease-related (renal or systemic)
- Non-nephrotic–range proteinuria (< 3.5 g/24 hours)
  - Mild glomerular disease
  - Tubulointerstitial disease
  - Acute tubular necrosis
  - Hypertension
  - Collagen vascular diseases
  - Multiple myeloma
  - Bacterial endocarditis
- Nephrotic-range proteinuria (> 3.5 g/24 hours)
  - Primary glomerulopathies
    - Minimal change disease
    - Membranous glomerulonephritis
    - Focal-segmental glomerulonephritis
    - Immunoglobulin A nephropathy
    - Membranoproliferative glomerulonephritis
  - Secondary glomerulopathies
    - Acute poststreptococcal glomerulonephritis
    - Malignancy
    - Drugs (gold, nonsteroidal anti-inflammatory drugs, heroin, penicillamine)
    - Infections (human immunodeficiency virus; hepatitis A, B, C)
    - Obesity
    - Reflux nephropathy

Ultrasonography of the kidney

It is important to rule out structural urinary lesions. Renal ultrasonography should be done, as it provides information on renal size, scarring, and possible obstruction. It also helps in planning for biopsy, as biopsy of a small, scarred kidney might not be useful and might cause bleeding. Similarly, the presence of a solitary kidney may also be a contraindication for performing a biopsy.

After this initial workup, referral to a

nephrologist is appropriate for definitive diagnosis and further management.

Biopsy

Whether to perform a biopsy or not is always an important question. Cohen et al,[47] Turner et al,[48] and Shah et al[49] reported that information gained directly from the biopsy influenced physicians' judgments regarding diagnosis, prognosis, and treatment in more than half of cases of diverse types of renal disease. Likewise, Richards et al[50] conducted a prospective study of 276 biopsies and found that biopsy altered management in 42% of cases.

Renal biopsy is indicated in all cases of nephrotic-range proteinuria except in obvious diabetic nephropathy or drug-induced proteinuria that resolves when the drug is stopped.[51,52] Renal biopsy is usually not indicated in mild proteinuria (< 1 g/day) with normal renal function and negative urine sediment.[53]

The decision to perform a biopsy should not be delayed, since the prognosis depends on the histology and early treatment in certain cases. The common types of glomerular pathology are listed in TABLE 2.

Patients with hypertension and diabetes mellitus should be regularly screened for proteinuria

CLINICAL IMPORTANCE AND PROGNOSIS

The prognosis of patients with proteinuria is related to the quantity of protein excreted. Non-nephrotic proteinuria is associated with a lower risk of progression to renal insufficiency than nephrotic-range proteinuria. Patients with persistent proteinuria of more than 1 g/day are more likely to progress to renal insufficiency.

Further workup and management are not warranted for patients with transient proteinuria, because the chance of progression to chronic renal insufficiency is extremely low. However, the diagnosis should be accurate before deciding not to perform any further workup. This patient population is heterogeneous and if there is a suspicion of comorbid disease, closer follow-up would be wise. In patients with postural proteinuria, no further evaluation is needed once the diagnosis has been established.

Patients with persistent proteinuria are almost invariably considered to have structural renal disease, although the data conflict about their prognosis.[54–58] Patients with persistent proteinuria should be referred to a nephrologist as early as possible and may need a renal biopsy as mentioned above.

In most cases, progressive glomerular disease is accompanied by tubulointerstitial damage, the extent of which is closely linked to an adverse renal outcome. It has been postulated that certain proteins, such as albumin, transferrin, and lipoproteins can lead to tubulointerstitial injury.[59,60]

Proteinuria and cardiovascular disease

Proteinuria may be a surrogate marker for progressive atherosclerosis, and it is important to check for proteinuria in diabetic patients who are undergoing coronary artery bypass surgery to determine prognosis.[60] The association of proteinuria as a risk factor for cardiovascular disease, cardiovascular mortality, and all-cause mortality has been extensively studied.[1–3,61–65] It has been reported that macroalbuminuria predicts mortality in young hypertensive men.[66,67]

Microalbuminuria occurs in 5% to 40% of patients with hypertension without renal failure or diabetes mellitus.[68] It is also more common in African American patients in association with systolic hypertension, high pulse pressure, and with the loss of diurnal variation in blood pressure.[69,70] This indicates that renal dysfunction occurs earlier in hypertension than has been recognized and is greater with severe hypertension.

Coronary artery disease occurs in 31% of patients with microalbuminuria vs 22% of patients without microalbuminuria.[71] Myocardial infarction is more common as well: 7% vs 4%.[71] Left ventricular mass and concentric left ventricular hypertrophy have been reported to be higher in patients with microalbuminuria independent of blood pressure. Carotid artery intimal and medial wall thickness is also increased along with a higher prevalence of retinopathy.[71–74]

Proteinuria is associated with higher mortality rates in most studies.[75–79] The cardiovascular mortality rate in elderly people with microalbuminuria is reported to be as high as 2.94 times that in nonmicroalbuminuric controls.[3] It is increased even further in people

with diabetes and microalbuminuria (odds ratio 24.3).

Insulin sensitivity and lipid levels are also adversely affected in patients with microalbuminuria. This relation raises the question of whether we need to screen patients who have or are at risk for cardiovascular disease or stroke, including patients with dyslipidemia or a positive family history and smokers.

The mechanism of the association between proteinuria and cardiovascular disease is poorly understood[79] although several mechanisms have been proposed. Albuminuria is thought to be a reflection of a generalized endothelial cell disturbance and dysfunction.[78]

Furthermore, albuminuria has been shown to be related to increased extravascular coagulation, which may lead to increased release of von Willebrand factor, contributing to the formation of microthromboses.[80] Plasma levels of von Willebrand factor and urinary albumin excretion rates are highly correlated.[81] Whether the microalbuminuria is a result of the atherosclerosis or an independent marker is not clear at this time. At present there is no consensus on screening these patients.

TREATMENT

Treatment of glomerular diseases is beyond the scope of this review.

Antiproteinuric agents preserve the integrity of the glomerular membrane and limit proteinuria by lowering intraglomerular pressure. Thus ACE inhibitors and ARBs delay the progression of proteinuric nephropathies toward terminal failure,[25] and they are extremely important in proteinuric patients, especially diabetic patients with microalbuminuria.

Control of hypertension is also extremely important in reducing proteinuria and delaying the progression to renal failure, especially in hypertensive and diabetic nephropathy.

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ADDRESS: *Nauman Siddiqi, MD, Department of Medicine, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.*