Proteinuria: Harbinger of Serious Clinical Consequence?

Iris Lee, MD, and Alden M. Doyle, MD, MS, MPH

Proteinuria can be a harbinger of significant renal disease and is now recognized as an independent risk factor for cardiovascular (CV) events [1–4]. As the significance of proteinuria and its potential pathogenic role are better appreciated, the identification and interpretation of proteinuria in primary care practice has become increasingly important. Appropriate diagnosis and treatment hold promise to have an important impact on both the incidence and progression of renal disease as well as CV mortality. In this paper, we discuss the classification and clinical implications of proteinuria, review methods of detection and quantification of proteinuria, and provide a framework for understanding the different treatment options that are available.

Definitions
The composition of normal as well as abnormal urine is derived from both plasma and renal proteins. About 40% of normally excreted protein consists of plasma albumin, another 40% consists of Tamm-Horsfall mucoproteins secreted by the renal tubules, and about 20% consists of plasma immunoglobulins. In healthy individuals, the normal rate of protein excretion is 80 ± 24 mg per day. The classic definition of proteinuria is urinary protein excretion of greater than 150 mg per day. Urinary protein excretion greater than 500 mg per day is termed overt proteinuria. Microalbuminuria (MA) is defined as urinary albumin excretion of 30 to 300 mg per day or an albumin/creatinine ratio of 30 to 300 mg/g.

Mechanisms of Proteinuria
There are 3 primary mechanisms of proteinuria: glomerular, tubular, and overflow. The glomerulus represents the first normal barrier to protein filtration because of its unique selective permeability based on protein size and charge. Proteins with a molecular weight of less than 20,000 Daltons (immunoglobulins) are filtered freely and reabsorbed by the proximal tubule. Larger proteins such as albumin, with a molecular weight of more than 65,000 Daltons, are restricted by the glomerulus under normal conditions. Glomerular damage from any cause can alter the permeability of the glomerular basement membrane, usually leading to large protein losses. Glomerular disease is usually present when the quantity of proteinuria is greater than 2 g per day, although smaller quantities do not necessarily rule out glomerular causes.

In proteinuria of less than 2 g per day, one should also consider nonglomerular sources, including tubular and overflow mechanisms. Tubular proteinuria is caused by tubulointerstitial disease, when damage to the proximal tubule impairs its normal ability to reabsorb proteins filtered by the glomerulus. Overflow proteinuria occurs when increased plasma concentration of proteins overwhelms the normal capacity of the proximal tubules to reabsorb protein.

Detection and Evaluation of Proteinuria
Dipstick urinalysis is commonly used in the outpatient setting to semi-quantitatively measure urine protein concentration. Standard dipsticks (eg, Chemstrips) principally detect negatively charged proteins such as albumin; the test may fail to detect positively charged proteins such as some immunoglobulin light chains. False-positive results on conventional dipstick testing occur with alkaline urine (pH > 7.5), with highly concentrated urine, and with gross hematuria. False-negative results usually occur with dilute urine and when the urinary proteins are nonalbumin proteins. Measurements should be avoided in situations known to produce proteinuria, such as heavy exercise, heart failure, acute febrile illnesses, and urinary tract infections.

The sulfosalicylic acid (SSA) test can be a useful adjunct to the dipstick test as it is sensitive to both anionic and cationic proteins and can therefore reveal the presence of (cationic) immunoglobulin proteins not detected by the standard dipstick. An SSA test that reveals significantly more proteinuria than is detected by the dipstick method should lead to a direct assessment of immunoglobulin production and excretion by urine and serum protein electrophoresis. The detection of monoclonal immunoglobulins may suggest the presence of diseases such as multiple myeloma, which can cause renal injury, and should prompt an evaluation by an oncologist.

A positive (1+ or greater) dipstick test for proteinuria should be confirmed by repeat testing on a morning urine
An initial urinalysis that reveals even small amounts of proteinuria should undergo quantitative testing with the protein/creatinine ratio [5,6]. An initial urinalysis that reveals small amounts of persistent proteinuria is considered persistent. Patients with persistent proteinuria should undergo quantitative testing with either a 24-hour urine collection for protein or a spot urine protein/creatinine ratio [5,6]. An initial urinalysis that reveals even smaller amounts of proteinuria is considered transient and the diagnosis should be confirmed by obtaining a specimen on at least 2 occasions over the next month. If both of these are negative, proteinuria is considered transient and no specific follow-up is indicated. If both are positive, then the proteinuria is considered persistent. Patients with persistent proteinuria should undergo quantitative testing with either a 24-hour urine collection for protein or a spot urine protein/creatinine ratio [5,6].

The 24-hour measurement of urinary protein has long been the gold standard method for quantifying proteinuria, but it can be difficult to obtain and time-consuming in the outpatient setting. The spot urine protein/creatinine ratio has emerged as a more practical alternative as it is less expensive and is more easily obtained in outpatients. It has been found in multiple studies to correlate well with the 24-hour collection (correlation coefficient, 1.1) [5,6].

A microscopic analysis of the urine should be performed at the time of initial quantification because the findings may be helpful in determining the pathologic process leading to proteinuria. Findings such as dysmorphic erythrocytes, erythrocyte casts, or fatty or granular casts suggest underlying renal injury. These findings may warrant renal biopsy or serologic testing for systemic diseases associated with renal disease and proteinuria such as lupus, HIV, and hepatitis B and C. Additionally, these patients should have a thorough review of systems and drug history taken, as these elements may suggest the presence of other systemic factors that may contribute to the development of renal disease.

Detection of Microalbuminuria

Screening for MA is a well-established test for early renal disease in diabetic patients. The conventional dipstick is insensitive to MA, as it does not detect levels of urinary albumin under 30 mg/dL. Quantitative and semiquantitative methods are available to measure MA. The American Diabetes Association (ADA) [7] recommends using 1 of 3 quantitative methods: 24-hour urinary albumin excretion, timed collections, or un timed random albumin/creatinine ratio. To reduce the number of false-positives, the ADA recommends repeat testing, with at least 2 or 3 tests being positive over a 3- to 6-month period, before designating a patient as microalbuminuric. However, implementing this in clinical practice may be difficult and has been reported to not improve diagnostic accuracy [8].

Semi quantitative methods for detecting MA include Micro-Bumin test, Micral test, and AlbuScreen. Although semi quantitative methods of measuring MA are not advocated by the ADA, these methods are often used in practice because of their increased convenience and lower cost. Some investigators have reported that these tests often correlate poorly with more quantitative urine protein determinations [5,9]. However, a pooled analysis of 10 studies demonstrated a high sensitivity and specificity for the Micral test (92.3% sensitivity and 83.2% specificity) [8]. Quantitative tests for MA have reported sensitivities from 56% to 100% and specificities from 81% to 98%, whereas semiquantitative tests for MA have reported sensitivities from 51% to 100% and specificities from 21% to 100% [8]. Although semiquantitative testing may yield higher false-positive results, testing may be useful in simply ruling out MA. In one study, the combination of SSA testing and routine urine dipsticks provided equivalent efficacy and lower cost than the Micral test in ruling out MA. Using both Chemstrip MA and SSA testing had a negative predictive value of 99%, the same as the Micral test. However, the false-positive rates of all 3 screening tests were high [10]. There has been some suggestion that semiquantitative MA tests could at least substitute for the first quantitative test [8]. Once MA is confirmed, an attempt to quantify the amount of albumin that is excreted in the urine should follow, using either a spot urine albumin/creatinine ratio or a 24-hour urine collection [6].

Classification of Proteinuria

Proteinuria may be classified as 1 of 5 types: transient, orthostatic, persistent, isolated, or nephrotic. Prognosis for each type of proteinuria classification differs substantially. Transient proteinuria was previously defined (≤ 1+ proteinuria but subsequent dipsticks negative) and is benign. Orthostatic proteinuria, described in younger persons, has been found to be associated with maintenance of normal renal function on long-term follow-up. It is defined as urinary protein excretion of less than 2 g per day in individuals younger than 30 years who are free of other chronic disease. These patients characteristically have increased protein excretion in the upright position, so split urine collections are recommended to confirm this diagnosis.

Persistent proteinuria can be secondary to underlying systemic or renal disease or due to other causes. The prognosis and treatment varies widely depending on the cause and is beyond the scope of this paper. Patients who have persistent proteinuria in the setting of a normal creatinine clearance, normal urinary sediment, urinary excretion of greater than 2 g per day of protein, and no obvious underlying cause are said to have isolated proteinuria. These patients have a 20% risk for renal insufficiency after 10 years and should be followed with a urinalysis and creatinine clearance every 6 months [5]. Patients with either persistent or isolated proteinuria, or those with proteinuria associated with renal insufficiency, should be referred to a nephrologist to aid in further work up and management.

Nephrotic-range proteinuria (> 3.5 g per day) carries the worst prognosis, and is always associated with serious renal
or systemic disease. It is often a part of the full-blown nephrotic syndrome, which is defined as nephrotic-range proteinuria, hypoalbuminemia, edema, and hyperlipidemia. These cases warrant immediate attention, including a referral to a nephrologist.

**Clinical Significance of Proteinuria**

**Proteinuria and Progression of Renal Disease**

Proteinuria plays a crucial role in the development of renal pathology. Experimental findings in animals show that proteinuria causes direct cellular injury to mesangial and tubular epithelial cells. This promotes increased recruitment of inflammatory cells, some of which have fibrosis-promoting effects. Clinical studies also confirm that the amount of proteinuria matters, with patients with more proteinuria having worse renal outcomes and faster progression to end-stage renal disease (ESRD) [11–15].

Overt proteinuria is a strong independent predictor of ESRD in diabetic as well as nondiabetic patients. In nondiabetic patients, it is the strongest predictor for developing ESRD. The Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) study [14] evaluated patients from the Ramipril Efficacy in Nephropathy (REIN) trial [16]; patients were nondiabetic with chronic nephropathy and mild to moderate renal insufficiency (creatinine clearances ranging from 20 to 70 mL/min) and proteinuria greater than 1 g per 24 hours. The study found that higher proteinuria was the only baseline predictor of shorter kidney survival, and its predictive value was independent of underlying renal disease, blood pressure control, and treatment randomization during follow-up. The Modification of Diet in Renal Disease (MDRD) study [17], in similar fashion, examined nondiabetic patients with renal disease and found the rate of decline of glomerular filtration rate (GFR) was greatest in patients with urinary protein excretions of greater than 1 g per 24 hours and that GFR decline increased progressively with each incremental gram of proteinuria.

Even proteinuria levels in the microalbuminuric range have been determined to be an independent risk factor for the development of overt nephropathy and subsequent loss of renal function. This has been found to be true in type 1 and type 2 diabetics as well as nondiabetic hypertensives [4,18–20]. In a prospective study that looked at the natural course of MA in type 1 diabetes over 10 years, the median duration from onset of MA to the development of nephropathy was 7 years [18]. The role that MA has on the development of renal disease in type 2 diabetes is not as clear. The rate of decline in GFR was found to be similar in normoalbuminuric and microalbuminuric patients with type 2 diabetes in a 3.4-year follow-up study [21]. A small but longer follow-up study in type 2 diabetes patients with and without MA found that 46.8% of patients with MA had died compared with 21.3% of patients without MA. Five out of 8 patients remaining in the MA group had developed nephropathy compared with 1 patient in the normalalbuminuric group. Despite conflicting reports, biopsy studies show that the majority of type 2 diabetes patients with MA have histopathologic changes in the kidney consistent with diabetic kidney disease [9,22].

**Proteinuria and Cardiovascular Risk**

Proteinuria (including MA) has been found to be an independent risk factor for CV morbidity and mortality [2-4,6,11]. It is not well understood if proteinuria functions solely as a surrogate marker of vascular dysfunction or directly contributes to the underlying pathologic processes of vascular disease. It has, however, been noted that the presence of albuminuria is often linked to other characteristics such as insulin resistance, salt-sensitive hypertension, endothelial dysfunction, dyslipidemia, and obesity [1,2,23]. Following these observations, it has been postulated that the onset of MA may reflect the presence of a developing atherogenic environment and is perhaps a renal manifestation of diffuse endothelial pathology.

In one study of nondiabetic hypertensive patients, those with MA were more likely to have coronary artery disease, stroke, myocardial infarction (MI), peripheral vascular disease, and left ventricular hypertrophy than those without MA [24]. A more recent study [2] demonstrated that any degree of albuminuria confers risk, even levels lower than the accepted cutoff for MA. Nondiabetic and diabetic patients from the HOPE investigation were studied to see whether MA and levels lower than the microalbuminuric threshold increased risk for MI, stroke, congestive heart failure (CHF), or all-cause death. The study excluded patients with dipstick-positive proteinuria and patients with significant renal disease. Patients with MA at baseline had an adjusted relative risk of 1.83 for major CV events, 2.09 for all-cause mortality, and 3.23 for hospitalization for heart failure. Similar results were found in diabetic and nondiabetic patients, and all outcomes were significant after controlling for other CV risk factors. Albumin/creatinine ratio (ACR) was shown to be a continuous CV risk factor: for every 0.4 mg/mmol increase in ACR, the hazard of the primary outcome (CV death, MI, stroke) increased by 5.9%, all-cause mortality by 3.9%, all-cause death by 6.8%, and CHF hospitalization by 10.6% [2].

**Interventions that Reduce Proteinuria**

The National Kidney Foundation’s (NKF’s) position paper, Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE) [6], recommends the following therapeutic interventions to reduce proteinuria and renal disease progression in all patients with detectable MA or any greater degree of albuminuria: (1) a blood pressure goal below 130/85 mm Hg (although below 125/75 is preferable),
(2) therapy with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), (3) dietary salt restriction, and (4) dietary protein restriction (0.8 g/kg body weight). Patients with persistent proteinuria despite these measures should be referred to a nephrologist and should receive regular (every 3 to 4 months) follow-up to include monitoring of proteinuria, blood pressure, and dietary compliance and measurement of serum albumin and cholesterol. In addition, risk reduction management of other known CV risks should be implemented.

Over the last decade, a large body of research has developed that strongly supports the clinical benefits of ACE inhibitor therapy in patients with proteinuria. ACE inhibitor therapy has been shown to delay the progression to overt nephropathy in diabetic patients with MA and is a well-accepted standard of care in diabetes. The 2002 ADA guidelines include a strong recommendation for the use of ACE inhibitors or ARBs in all diabetic patients with either MA or advanced nephropathy. In a meta-analysis of 9 randomized placebo-controlled trials of subjects with diabetic nephropathy and MA, the relative risk for developing macroalbuminuria or overt proteinuria in patients treated with an ACE inhibitor compared with placebo was 0.35 [25]. All patients had an estimated GFR within the normal range, and the degree of MA in both placebo and treatment groups at baseline were similar. ARB therapy can be especially useful for patients who cannot tolerate the side effects of ACE inhibitors, such as cough and angioedema. Some physicians have advocated using a combination of ACE inhibitors and ARBs, using the rationale that these agents block different steps in the angiotensin/aldosterone cascade and that some patients on long-term ACE inhibition show some “escape.”

There is also evidence that ACE inhibitor therapy slows the progression of nondiabetic renal disease. A meta-analysis of 7 randomized placebo-controlled trials involved subjects with overt proteinuria and renal insufficiency from various causes. In this study, the relative risk for a doubling of the creatinine or developing ESRD was 0.60 for patients treated with an ACE inhibitor compared with placebo [25]. In another meta-analysis of 11 randomized placebo-controlled trials of nondiabetic renal disease, ACE inhibitor therapy was more effective than non–ACE inhibitor therapy in slowing nondiabetic renal disease progression [26]. In this analysis, proteinuria was the only baseline factor that significantly modified the ACE inhibitor effect. Moreover, the risks for renal disease progression increased as level of proteinuria increased in stepwise fashion, and the renoprotective effects of ACE inhibitors were most pronounced at the higher levels of proteinuria. Proteinuria in nondiabetics, therefore, presents an independent and graded risk for development and worsening of renal disease, and the more proteinuria is present the more advantage patients will reap from the use of ACE inhibitors.

Taken together, these and other data strongly support the use of ACE inhibitors or ARBs in all patients with persistent proteinuria. For one, this intervention has been shown to lower urinary protein excretion rates dramatically. Second, these agents have been demonstrated to slow the progression of renal disease in both diabetics and nondiabetics. Finally, proteinuria confers CV risk regardless of whether diabetes is present [2,4]. As proteinuria per se becomes accepted as a marker for global CV risk (and even, perhaps, vascular dysfunction), more consideration should be given to treating patients with overt proteinuria with agents to attenuate the risk of heart attack and stroke.

**Screening Recommendations**

As the role of urinary protein excretion in disease is better appreciated, the target population for proteinuria screening is expected to grow. Although there are no universally agreed upon screening guidelines, there is widespread agreement on screening for MA in patients with diabetes. Guidelines by the ADA and National Kidney Foundation recommend that patients be screened for MA at diagnosis and receive annual screening for MA thereafter. Although there are no controlled trials that show that MA screening prevents progression to nephropathy in diabetics [8], there is good evidence that this degree of proteinuria responds to treatment and that, in general, treatment of proteinuria does improve renal outcomes.

Although it is not known whether MA in hypertensives predicts progression to renal failure, higher blood pressure compounds the risk that proteinuria conveys on progression to renal failure. Although no specific guidelines exist that address screening for MA among hypertensives, office-based screening could at least potentially identify nondiabetic hypertensive patients at high risk of developing CV disease [2,24].

Other clinical situations in which albuminuria may be associated with increased CV and renal events include obesity or a family history of CV or renal disease [6]. Detecting the presence of MA may help identify those individuals that require more intensive therapy and closer follow-up. It is not clear how screening for MA and implementing treatment for MA impact on long-term CV outcomes. These areas remain the focus of ongoing investigation. Some studies indicate that identifying and screening patients who have first-degree relatives with hypertension, diabetes, or kidney disease may be beneficial [27]. New NKF guidelines [28] recommend screening all patients who have an elevated risk of developing kidney disease. Besides patients with diabetes and hypertension, these would include patients with the following risk factors:

- family history of kidney disease
- autoimmune diseases such as lupus
• heightened exposure to drugs such as analgesics that can cause loss of kidney function
• systemic infections such as HIV or hepatitis
• age greater than 60 years
• high-risk ethnic backgrounds (black, Hispanic, American Indian)
• history of acute renal disease

A strategy for screening the healthy population at large has not yet been well defined. The prevalence of dipstick-positive proteinuria in large population-based studies ranges from 1% to 5%, and the positive predictive value of an abnormal screening test in asymptomatic individuals is very low (0 to 1.4%) [29]. There remains, therefore, a significant debate about the utility of screening asymptomatic individuals without any other risk factors for CV or renal disease. So, until further study clarifies the role of urine protein detection in these asymptomatic individuals, screening should be directed towards those patients with risk factors such as diabetes, hypertension, dyslipidemia, cardio/cerebro/peripheral vascular disease, or those with pre-existing renal insufficiency.

Summary
Proteinuria is an important independent risk factor for both renal and CV disease. The negative impact of proteinuria potentially holds true for all individuals, not just those with clinically significant renal disease or diabetes. Although the long-term impact of MA screening has not been well defined in controlled studies, a growing body of evidence strongly suggests a benefit from screening on outcomes. This evolving dataset will aid in further defining effective standards of screening for at-risk patients, and will ultimately improve the ability of physicians to reduce morbidity and mortality in the large group of patients who are at risk for CV and renal disease.

Corresponding author: Alden M. Doyle, MD, MS, MPH, Renal-Electrolyte and Hypertension Div., Univ. of PA, 700 CRB, 421 Curie Blvd., Phila., PA 19104.

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