CME Topic

Proteinuria and Microalbuminuria in Adults: Significance, Evaluation, and Treatment

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Abstract: This paper reviews current concepts regarding the pathophysiology, diagnostic evaluation, and treatment of microalbuminuria and proteinuria in adults. Microalbuminuria (in diabetics) and proteinuria are early markers for potentially serious renal disease, and are associated with increased risk of atherosclerotic cardiovascular disease. Proteinuria also contributes to renal scarring, and accelerates the progression of chronic kidney disease to end-stage renal failure. Screening of diabetics for microalbuminuria, and the initial workup of proteinuria, should occur in the primary care setting. Reduction of microalbuminuria in diabetics may retard its progression to overt diabetic nephropathy. Therapy of renal diseases should aim for optimal blood pressure control and the maximum possible reduction in urinary protein excretion. Angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) therapy is the most effective measure to achieve this. These drugs also provide protection against the cardiovascular problems that are highly prevalent in this patient population.

Key Words: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, chronic kidney disease, microalbuminuria, proteinuria

Proteinuria is a well-known marker for renal disease.[1] The association of heavy proteinuria (nephrotic syndrome) with edema, hypoalbuminemia, hyperlipidemia, hypercoagulability/thromboembolism, and susceptibility to infection is also well recognized.[2] Over the past two decades, evidence for a direct adverse impact by proteinuria on the progression of chronic kidney disease to end-stage renal failure has accumulated.[3,4] Proteinuria and microalbuminuria are also associated with increased risk of atherosclerotic cardiovascular disease.[5,6] There are approximately 19 million Americans with chronic kidney disease,[7] and the vast majority of them will have proteinuria as a manifestation of renal disease. Thus, proteinuria is commonly encountered in the primary care setting.

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Definitions

Normal adults excrete less than 150 to 200 mg/d of protein in the urine.[8–10] Very little of this protein is albumin (less than 10–20 mg/d). Albumin excretion in the range of 30 to 300 mg/d or, as is more commonly reported, 30 to 300 mg/g of urinary creatinine, is referred to as microalbuminuria. At these levels, standard dipsticks do not detect albumin in the urine, and specific measurement of albumin using highly albumin-sensitive techniques is required. Although gender-specific limits for normal urinary albumin excretion have been suggested (17 mg/g of creatinine for men and 25 mg/g in women),[11] for clinical purposes, using the same cut-off value for both sexes is sufficient.

Key Points

- Persistent microalbuminuria (in diabetics) and overt proteinuria are important markers for the subsequent development of progressive chronic kidney disease, and are also associated with a high risk of cardiovascular disease.
- The total daily urinary excretion of albumin or protein is reliably quantitated by the ratio of their concentration to the concentration of creatinine in a random urine sample. Testing a random sample of urine has largely replaced the cumbersome 24-hour urine collection in clinical practice.
- Reduction of microalbuminuria in diabetics and overt proteinuria irrespective of etiology, together with strict blood pressure control, is helpful in ameliorating the progression of chronic kidney disease.
- Identifying and correcting cardiovascular risk factors are key aspects of managing microalbuminuric and overtly proteinuric patients.
- The use of an angiotensin-converting enzyme inhibitor (ACE-I) and/or an angiotensin-receptor blocker (ARB) is the most effective way of ameliorating these urinary abnormalities.
- Screening for microalbuminuria and overt proteinuria, and timely referral for nephrology evaluation of these patients in the primary care setting, is critically important.

The terms "proteinuria" and "albuminuria" are often used synonymously in the medical literature. This is generally acceptable, since in general the most abundant urinary protein in patients with renal disease is albumin. However, it should be remembered that the standard dipstick is almost exclusively sensitive to albumin. Strictly speaking, a positive dipstick test should therefore be referred to as albuminuria (or macroalbuminuria, to differentiate it from microalbuminuria) rather than proteinuria, since other proteins in the urine, such as globulins, light chains, and glycoproteins are not detected by dipstick testing. Besides macroalbuminuria, other terms used to refer to standard dipstick-positive proteinuria are "overt" proteinuria and "clinical" proteinuria. In the rest of this article, the term overt proteinuria will be used to refer to a positive standard dipstick test. National Health and Nutritional Examination Survey III data reveal a prevalence of microalbuminuria of 10.6% and overt proteinuria of 1.1% in the US adult population.[7]

Renal Barriers to Protein Excretion, and Mechanisms of Abnormal Proteinuria

In the normal kidney, the negatively charged glomerular capillary wall repels negatively charged albumin and prevents its filtration (charge-barrier).[9] The slit-pores between the podocytes in the glomerular capillary wall are small enough to exclude larger proteins such as globulins from the glomerular filtrate (size-barrier). The role of structural proteins, such as nephrin, podocin, and α-actinin, normally present in the slit-pores in preventing protein filtration has recently come to be recognized.[12] Inherited abnormalities in these proteins result in hereditary forms of nephrotic syndrome.

Glomerular charge and size barriers allow the passage into the glomerular filtrate of only small, positively charged proteins such as β-2 microglobulin and immunoglobulin light chains, and small amounts of albumin. The proximal tubular epithelium reabsorbs and catabolizes most of the proteins that escape the glomerular barriers.[9] Glomerular filtration of protein, therefore, contributes minimally to normal urine protein content. Most of the protein in normal urine is the Tamm–Horsfall glycoprotein secreted by the renal tubules.[8–10] Table 1 shows the pathophysiologic mechanisms that underlie increased urinary protein excretion in various disorders.

Qualitative Tests for Urinary Protein

Dipsticks or tablets that can detect microalbuminuria are available for qualitative screening of the urine (Micral dipstick [Boehringer Mannheim Diagnostics, Indianapolis, IN], Microbumintest tablet [Ames Miles Laboratories, Elkhart, IN]). However, the definitive diagnosis of microalbuminuria requires quan-

Table 1. Pathophysiologic mechanisms in proteinuria

Mechanism	Causes
"Overflow" proteinuria	
High blood levels of positively charged small molecular weight light chains escape glomerular charge and size barriers and overwhelm tubular capacity to reabsorb and catabolize them.[9,10]	Multiple myeloma; other paraproteinemic states.
Glomerular proteinuria	
Selective—loss of only the glomerular charge-barrier, albumin excreted predominantly.[2]	Minimal change disease.
Non-selective—loss of both the charge and size-barrier with excretion of albumin and larger molecular weight proteins (such as IgG).[2]	Glomerulopathies other than minimal change disease.
Tubular proteinuria	
Albumin and larger proteins restricted by intact glomerular barriers. Small molecular weight proteins normally freely filtered at the glomerulus (such as β-2 microglobulin) escape reabsorption/catabolism because of renal tubular damage.[9,10]	Early stages of various tubulointerstitial disorders. "Secondary" glomerular pathologic changes developing in the later stages may cause glomerular proteinuria in patients with tubulointerstitial disorders.
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.[9,10,13]	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 g. If the random urine 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.

titation of albumin excretion by enzyme-linked immunoassay (ELISA)/radioimmunoassay/nephelometry techniques.[8]

As stated above, standard dipsticks detect predominantly albumin, and are not sensitive to other proteins such as globulins, glycoproteins, and immunoglobulin light chains.[8] The less commonly used sulfosalicylic acid test (Bumintest) detects albumin and other proteins in the urine. Thus, a strongly positive sulfosalicylic acid test, with a weak or negative dipstick test, implies the presence of proteins other than albumin (such as immunoglobulin light chains), and suggests the diagnosis of disorders such as multiple myeloma.[8] False positive results may occur with both dipstick and sulfosalicylic acid tests, but are rare.[8] Qualitative testing of urine needs to be repeated to confirm persistence of overt proteinuria before a work-up is undertaken.

Quantitation of Microalbuminuria and Overt Proteinuria

In patients with a negative standard dipstick test, the magnitude of microalbuminuria can be determined by measuring the concentration of albumin in either a random ("spot") sample or a timed collection (usually 24 hours) of urine. Random sampling of the urine is the preferred method, because it avoids the need for the cumbersome 24-hour urine collection. The most commonly used method of expressing the result of the microalbuminuria test is milligrams of albumin/gram of creatinine in the random sample of urine. If timed urine collection is used, the results are expressed as milligrams of albumin/24 hours or micrograms of albumin/min. Normal values for albumin excretion and levels that define microalbuminuria have been discussed earlier.

The quantity of overt proteinuria revealed by dipstick testing is affected by the concentration of the urine sample.[8,10] Dilute urine might result in a weakly positive test, despite the presence of large amounts of protein, and the reverse occurs in highly concentrated urine. Twenty-four hour urine collection, the time-honored method for quantitation of overt proteinuria, is cumbersome and often inaccurate due to collection errors. When renal function (whether normal or impaired) is stable, the ratio of the concentration of urine protein (mg/dL) to urine creatinine (mg/dL) (urine protein /urine creatinine ratio) in a random sample correlates well with the 24-hour urinary protein excretion, because the daily excretion of creatinine in the urine is fixed.[13,14] Creatinine is a product of skeletal muscle metabolism. Daily generation of creatinine depends on the muscle mass of the individual, and, therefore, varies with age and gender. Adults with average muscle mass excrete approximately 1,000 mg/d of urinary creatinine. Thus, a random urine protein/urine creatinine ratio of <0.2 indicates a normal 24-hour urinary protein excretion of less than <0.2 g, a ratio between 0.2 and 3.5 indicates a daily excretion of greater than 0.2 g but less than 3.5 g, and values greater than 3.5 indicate a daily protein excretion of more than 3.5 g.[10,13]

There may be significant day-to-day variations of up to 15 to 40% in daily total urinary protein excretion both in normal subjects and those with renal disease. This is due to the effects on urinary protein excretion of variables such as physical activity, dietary salt and fluid intake, and blood pressure. There is also diurnal variation in urinary protein excretion (highest between 6 AM and noon). Hence the recommendation to check the second voided morning specimen to measure the microalbumin or protein to creatinine ratio. However, for the purposes of clinical practice, the time of the day at which the random urine sample is obtained is generally not important.

It should be noted that in subjects with above- or below-average muscle mass, the random urine protein/urine creatinine ratio may not correspond numerically to the total 24-hour excretion of protein. For example, in a person with less than average muscle mass excreting only 600 mg/d of urinary creatinine, a random urine protein/urine creatinine ratio of 3.0 represents daily protein excretion of 1.8 g, whereas in a very muscular individual excreting 1,500 mg/d of creatinine, the same ratio of 3.0 will indicate daily protein excretion of 4.5 g. The main value of the easily measured random urine protein/urine creatinine ratio is to classify patients based on the magnitude of proteinuria, and consider in the differential diagnosis renal disorders characterized by these different levels of urinary protein excretion. The ratio is also an easy way of following the trend in proteinuria over time in individual patients.

"Benign" Postural Proteinuria

Elevated urinary protein excretion in samples obtained in the upright posture (day or ambulatory samples) with normal protein excretion in samples obtained in recumbency (night samples) is referred to as postural proteinuria.[15] The random urine protein/urine creatinine ratio in a sample obtained in the upright posture can not be compared with that obtained after overnight recumbency to make the diagnosis of this condition because of diurnal variations in the glomerular filtration rate resulting in moment-to-moment variations in the excretion of urinary protein and creatinine.[10] Separate collection of the total volume of urine excreted during the day and night is required to identify postural proteinuria. Almost exclusively seen in patients less than 30 years of age (because postural proteinuria frequently disappears in older patients), this condition is characterized by normal renal function, blood pressure, and urinary sediment, and daily urinary protein excretion usually of less than a gram (random urine protein/urine creatinine ratio <1.0).[15] Most of these patients do not develop progressive renal disease on prolonged observation, and hence the epithet "benign." Occasionally, postural proteinuria may be the initial presentation of more serious renal

disease. Periodic monitoring of the renal status of patients with postural proteinuria is, therefore, warranted.

Subnephrotic Proteinuria and Nephrotic Syndrome

Patients with subnephrotic proteinuria (>0.2 g and <3.5 g/d, or random urine protein/urine creatinine ratio of >0.2 and <3.5) may have either nonglomerular renal disease (tubulointerstitial, vascular, or cystic disorders) or a glomerulopathy.[10] Early or mild glomerular damage, severe reduction in the glomerular filtration rate or marked reduction in serum protein level can result in subnephrotic proteinuria in patients with glomerulopathies. Even patients with initially subnephrotic proteinuria may eventually progress to end-stage renal disease. Thus the magnitude of proteinuria alone cannot be used to assess the severity of kidney disease.

Nephrotic syndrome is defined as proteinuria of >3.5 g/d (random urine protein/urine creatinine ratio >3.5) and is only caused by glomerular disease.[2,10] Other features of the nephrotic syndrome, such as edema, hypoalbuminemia, hyperlipidemia, thromboembolism, and increased susceptibility to infection, are not always present. Classification of overt proteinuria on the basis of the quantity and type of protein, and the causes of different levels of proteinuria, are shown in Table 2.

Contribution of Proteinuria to Progressive Renal Damage

The loss of a critical number of nephrons, irrespective of the initial cause, results in self-perpetuating and progressive renal scarring. Elevated glomerular filtration rate, sustained by increased intraglomerular pressure and glomerular hypertrophy (both mediated by angiotensin II) in the initially undamaged nephrons, are implicated in the inexorably progressive renal damage.[3,16–20] Hyperfiltration in intact remnant glomeruli can compensate for the loss of function in the initially damaged nephrons, but is eventually maladaptive. Elevated intraglomerular pressure and glomerular hypertrophy lead to progressive glomerulosclerosis, thus accelerating the loss of renal function. Other factors contributing to the self-perpetuating loss of renal function include systemic hypertension, high dietary protein intake, anemia, hyperlipidemia, elevated calcium-phosphate product resulting from renal failure, intercurrent renal insults (eg, the use of nephrotoxic drugs [nonsteroidal antiinflammatory drugs, iodinated radiologic contrast, aminoglycosides], pyelonephritis, obstructive uropathy), and cigarette smoking.[16–19,21]

Over the past two decades proteinuria itself has been implicated as a cause of progressive renal damage.[3,4] Several large human trials have shown that the greater the magnitude of baseline proteinuria, the faster the progression of renal failure. Furthermore, the decrease in proteinuria during therapy in these trials correlated strongly with slower progression of chronic kidney disease, independent of the degree of blood pressure control.[22–34] These observations suggest a pathogenic role for proteinuria in progressive renal injury. Therapy is generally more effective in slowing the progression of chronic renal failure in patients with heavy baseline proteinuria. However, a beneficial effect has also been shown in patients with lesser levels of proteinuria.[35]

In experimental studies, increased protein filtration across the glomerular capillary wall and tubular reabsorption/catabolism of larger than normal amount of filtered protein have been shown to induce the production of pro-inflammatory and

Table 2. Classification of proteinuria based on quantity of protein excreted

Quantity of urinary protein	Causes
Normoalbuminuria/normal urinary protein	
Less than 200 mg/d of total protein with less than 10–20 mg of albumin/d (random urine protein/urine creatinine ratio <0.2).	Normal individuals.
Microalbuminuria	
Albumin excretion of 30–300 mg/day or 30–300 mg/g of urinary creatinine or >20 mcg/minute. At these levels, dipstick testing does not detect albuminuria. Measuring the albumin/creatinine ratio (mg/g) in a random/"spot," urine sample is the preferred method.	Early, "subclinical" diabetic nephropathy. Not enough studies to determine the value of microalbuminuria screening in the early stages of other glomerular diseases, hypertensives and metabolic syndrome patients.
Overt proteinuria—subnephrotic range	
Albumin excretion of >300 mg/d or >300 mg/g of urinary creatinine or >200 mcg/minute. Total daily protein excretion >300 mg and <3.5 g (random urine protein/urine creatinine ratio >0.2–<3.5). Dipstick positive for albuminuria.	Tubulointerstitial, vascular and cystic diseases of the kidney. Glomerular diseases in their early/milder stage or in the setting of marked reduction in glomerular filtration rate or serum protein levels. Proteinuria of >2 g/d (random urine protein/urine creatinine ratio >2.0) is rare in tubulointerstitial/vascular/cystic diseases and is very suggestive of glomerular disease.
Nephrotic range proteinuria	
Excretion of >3.5 g/d of protein (random urine protein/urine creatinine ratio >3.5)	Various glomerular diseases.

fibrogenic cytokines, and increase the expression of adhesion molecules and chemoattractants.[36–39] The induction of these molecules by proteinuria contributes to progressive glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular sclerosis, and thus accelerates the loss of renal function. Reduction in urinary protein excretion is now recognized as an important therapeutic goal in chronic kidney disease.[16–19,21]

Importance of the Early Detection and Evaluation of Microalbuminuria and Overt Proteinuria

Even if the glomerular filtration rate is normal, detection of microalbuminuria is important for two reasons. It is an early marker for the subsequent development of nephropathy in diabetics.[40,41] Strict glycemic[42] and blood pressure control, especially with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB) may minimize the risk of progression of microalbuminuria to overt proteinuria and clinical diabetic nephropathy.[43–45] However, the value of microalbuminuria as a predictor of the subsequent development of overt diabetic nephropathy has been questioned. A recent study showed a 58% incidence of regression of microalbuminuria unrelated to ACE-I use.[46] It has been suggested that screening for microalbuminuria may be valuable in hypertensives and in patients with the metabolic syndrome (syndrome X),[47,48] but this has not yet become an established clinical practice guideline.

End-stage renal disease has become a major worldwide public health problem. In the United States, over 350,000 patients are currently sustained by dialysis or renal transplantation, at a cost of over $15 billion to the taxpayer.[49] The incidence and prevalence of end-stage renal disease is expected to double over the next decade due to the increasing life-expectancy of the population, and the increased incidence of predisposing diseases, such as type-2 diabetes and hypertension.[50,51] The National Kidney Foundation has classified chronic kidney disease into 5 stages (Table 3).[11] Overt proteinuria is usually the initial manifestation of chronic kidney disease. As already discussed, reducing urinary protein excretion may help to slow the progression of chronic kidney disease of any etiology[16–19,21] and help to delay the need for renal replacement therapy (dialysis or transplantation). The importance of timely screening for and evaluation of microalbuminuria and overt proteinuria in the primary care setting, followed, if indicated, by early nephrology referral cannot be overemphasized.

Microalbuminuria is also a marker for generalized endothelial dysfunction and predicts increased risk of atherosclerotic cardiovascular disease.[5,6] This risk increases markedly and progressively with increasing overt proteinuria and decreasing glomerular filtration rate.[52] Diligent search for and aggressive correction of all cardiovascular risk factors is warranted in this patient population.[5,6,52,53]

Table 3. Stages of chronic kidney disease[a]

Stage	Glomerular filtration rate (mL/min/1.73 m^2)	Comments
1	>90	Normal renal function but markers for kidney disease present: abnormal urinalysis, microalbuminuria, overt proteinuria, diabetes mellitus, hypertension or abnormal renal imaging studies. Institute renoprotective and cardioprotective measures.
2	60–89	Mild renal dysfunction. Institute or continue renoprotective and cardioprotective measures.
3	30–59	Moderate renal dysfunction. Institute or continue renoprotective and cardioprotective measures.
4	15–29	Advanced renal failure. Prepare for dialysis or transplantation. Institute or continue cardioprotective measures.
5	<15	End-stage renal disease. Initiate dialysis or perform transplant. Institute or continue cardioprotective measures.

[a]Proposed by the National Kidney Foundation.[11]

Diagnostic Evaluation of Microalbuminuria and Overt Proteinuria

Microalbuminuria

Annual screening for microalbuminuria (if standard dipstick testing is negative) starting 5 years after the diagnosis of type 1, and at the time of diagnosis of type 2 diabetes mellitus (because it is difficult to time its onset) is recommended.[54,55] Albumin excretion can vary on a day-to-day basis depending on factors such as vigorous physical activity. Thus, persistence of microalbuminuria needs to be confirmed by retesting within 1 to 3 months before interventions to correct it are undertaken.

Overt proteinuria

In healthy adults, periodic urinalysis to detect overt proteinuria is not recommended as a health-maintenance measure.[56] However, in the presence of risk factors for kidney disease, such as diabetes mellitus and severe hypertension, annual testing by dipstick for overt proteinuria is important.[1,11] A positive dipstick test indicates the presence of albumin in the urine, because it detects albumin almost exclusively, and obviates the need for ordering tests for microalbuminuria. In overtly proteinuric patients, monitoring the excretion of total proteins in the urine rather than albumin specifically is preferable.[21] Measuring albumin specifically is

Table 4. Laboratory studies in the evaluation of proteinuria: tests for assessing severity of the causative renal disease

Type of test	Value of the test
Urinalysis including microscopy	
Even in patients with normal renal function, urinalysis should be performed periodically if risk factors for kidney disease (hypertension, diabetes mellitus and other indicators of stage 1 kidney disease) are present.[11]	Detection of proteinuria. Proteinuria with microscopic hematuria ("active" urinary sediment) generally suggests more severe glomerular damage.
Tests for microalbuminuria	
Not required if dipstick is positive for albumin. For initial screening, albumin-sensitive dipstick or tablet can be used (Micral, Microbumintest). For confirmation, random/"spot" urine albumin/creatinine ratio (mg of albumin/g of creatinine) is the preferred method.	Detection of early diabetic nephropathy. Predictor of increased cardiovascular risk. Value of this test to detect early stages of other glomerulopathies, and in patients with hypertension or metabolic syndrome (syndrome X) not yet fully established.
Quantitation of Overt Proteinuria	
Random/"spot" urine protein/urine creatinine ratio is the preferred method. Avoids the need for cumbersome 24 hr urine collection.	Differential diagnosis of various renal diseases depending on amount of protein excreted (see Table 2) and assessing the severity of renal disease.
Separate day time (upright) and night time (recumbent) collection of urine for protein measurement	Ruling out postural proteinuria. Random urine protein/urine creatinine ratio of day and night samples can not be used to diagnose postural proteinuria.[10]
Serum creatinine/calculated glomerular filtration rate	
Since the serum creatinine level is proportional to the muscle mass of the individual, even a serum creatinine level in the "normal" range might indicate impaired renal function in nonmuscular individuals. Thus, the glomerular filtration rate should always be calculated using the serum creatinine value.[57,58]	Assessing severity of renal disease. Serum creatinine level $\geq$1.2 mg/dL in an adult female and $\geq$1.4 mg/dL in an adult male, or a calculated creatinine clearance <90 mL/min should be considered as renal failure.
Serum total protein, albumin, and lipoproteins	Assessing the effects of proteinuria on the level of proteins and lipids in the blood.

more expensive and might miss the presence of other proteins such as globulins, light chains, and protein markers of tubular damage (β-2 microglobulin). In addition, since a portion of the filtered albumin is broken down into unmeasured metabolites, specific albumin tests may underestimate the magnitude of albuminuria. Tables 4 and 5 show the tests used to evaluate proteinuric patients.

Occasionally, carcinomas and lymphomas may present initially with overt proteinuria.[59] However, the yield of cancer screening in the evaluation of overt proteinuria is low and only age-appropriate annual cancer screening is warranted.

Indications for Nephrology Consultation in Overtly Proteinuric Patients

Nephrology evaluation is indicated in overtly proteinuric patients with a random urine protein/urine creatinine ratio >1, and (even if the ratio is between 0.2 and 1.0) those with glomerular filtration rate <60 mL/min (or serum creatinine $\geq$1.2 in women and $\geq$1.4 mg/dL in men), hypertension, history of systemic diseases (eg, diabetes mellitus, systemic lupus erythematosus), use of medications or illicit drugs known to cause proteinuria (gold, penicillamine, captopril, chronic use of nonsteroidal antiinflammatory drugs, heroin), family history of renal disease or, if required for insurance/employment purposes. The nephrology consultant can help to decide if renal biopsy and immunosuppressive therapy are indicated. Measures to reduce the magnitude of proteinuria and slowing the progression of renal failure are best undertaken with the input of a nephrologist. Even if it is determined that there is no immediate indication for nephrology referral, periodic monitoring of the blood pressure, serum creatinine and the random urine protein/urine creatinine ratio at least annually is warranted. If any of these parameters worsen, nephrology evaluation is indicated.

Treatment of Proteinuria

There are three aspects to the treatment of the proteinuric patient: corticosteroid and immunosuppressive therapy of the causative renal disorder, correcting the clinical effects of proteinuria, and measures to reduce the quantity of urinary protein.

Table 5. Laboratory studies in the evaluation of proteinuria: tests for identifying etiology of causative renal disease[a]

Type of test	Purpose of the test
Blood glucose; glycosylated hemoglobin	Detection of diabetes mellitus, the most common cause of overt proteinuria and chronic kidney disease.
Serum immunoelectrophoresis and monoclonal protein evaluation; urine immunoelectrophoresis and light chain typing	Detection of multiple myeloma and other paraproteinemic states. To be included in evaluation of patients >45 years old.
Tests for autoimmune disorders: Antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA),[b] anti-glomerular basement membrane antibody,[b] rheumatoid factor/cryoglobulins,[b] serum C3 and C4 complements	Detection of systemic lupus erythematosus, vasculitides, systemic sclerosis, Sjögren syndrome, antiglomerular basement membrane antibody disease, cryoglobulinemia, hypocomplementemic renal diseases (lupus nephritis; membranoproliferative, post-infectious and cryoglobulinemic glomerulonephritis).
Tests for infectious disorders: Hepatitis B surface antigen, Hepatitis C antibody, Human Immunodeficiency Virus (HIV) antibody, antistreptolysin antibody,[b] VDRL test	Detection of Hepatitis-B, Hepatitis-C or HIV-associated renal disease, poststreptococcal glomerulonephritis, glomerulopathy in secondary syphilis.

[a] *VDRL, Veneral Disease Research Laboratory.*

[b] *Indicated in patients with "nephritic" urine sediment (presence red blood cells ± red blood cell casts).*

Immunosuppressive therapy of the causative renal disorder

Therapy aimed at the immunologic mechanisms causing proteinuric renal disorders is not discussed further here because it is usually undertaken with the assistance of a nephrologist. Evidence-based recommendations on this subject have been published.[60,61]

Treatment of the clinical effects of proteinuria

This addresses the problems of edema, hyperlipidemia, thromboembolism, and infection associated with heavy proteinuria.[2] Edema requires dietary sodium restriction and the use of diuretics. Hyperlipidemia associated with nephrotic syndrome warrants treatment with a statin for hypercholesterolemia or fibrate for hypertriglyceridemia. In addition to its cardiovascular benefits, such therapy may also slow the loss of renal function.[19,21,62] Nephrologists differ in their approach to the treatment of the hypercoagulability associated with heavy proteinuria: prophylactic anticoagulation in all patients with a serum albumin level <2.5 g/dL, versus all markedly hypoalbuminemic patients with membranous nephropathy (the glomerulopathy with the highest risk of thromboembolism), versus anticoagulation therapy only after the occurrence of a thromboembolic event.[2] Once initiated, anticoagulation needs to be continued as long as heavy proteinuria persists.

Measures to reduce microalbuminuria and overt proteinuria

Reduction of microalbuminuria with an ACE-I or ARB may decrease the subsequent development of overt proteinuria and clinical diabetic nephropathy.[43–45] In fact, the "prophylactic" treatment of even normoalbuminuric diabetics with drugs blocking the renin-angiotensin system has been suggested.[63,64]

In overtly proteinuric patients, measures to reduce proteinuria are worthwhile even in the absence of the clinical features of the nephrotic syndrome, because reduction of proteinuria retards the rate of progression of chronic renal failure.[16–19,21] Dietary protein restriction[65–67] and ACE-I and/or ARB therapy[22–35] have been shown to reduce proteinuria. While there are no controlled studies in patients with renal disease, intuitively, pharmacologic blockade of the renin-angiotensin system may also be protective against the cardiovascular problems highly prevalent in patients with chronic kidney disease.

Most long-term trials in type 1 diabetic nephropathy and nondiabetic renal diseases have been with ACE-Is, and with ARBs in type 2 diabetic nephropathy. Based on these studies, it has been recommended that patients with type 1 diabetic nephropathy and nondiabetic renal diseases are best treated with an ACE-I and type 2 diabetics with an ARB. However, several short-term and a few long-term comparative studies have shown these two classes of drugs to have equal efficacy in patients with chronic kidney disease.[30,68–70] The decision to select an ACE-I versus an ARB for initial therapy is influenced by a number of factors besides the type of renal disease. In patients with ACE-I-induced cough or angioedema, only an ARB can be used because these side effects are extremely rare with the latter. Captopril, enalapril, and lisinopril are available in generic form, and cost considerations may dictate the use of a generic drug. ARBs appear to increase the serum potassium less than the ACE-Is,[71] but the utility of substituting the former for the latter drug when

hyperkalemia limits therapy has not been established. The benefits of both these groups of drugs in chronic kidney disease is probably a class-effect since the different ACE-Is used in the landmark trials were equally renoprotective,[22–24,30] and irbesartan and losartan have produced similar results in type 2 diabetic nephropathy.[27,28] In general, a drug permitting once-a-day dosing should be chosen to improve compliance. Table 6 outlines the selection/adjustment of antihypertensive drugs to reduce proteinuria. Measures to deal with the adverse effects of drugs blocking the renin-angiotensin system are shown in Table 7.

The relative importance of blood pressure control (which might by itself reduce proteinuria) and proteinuria reduction in affording renoprotection continues to be debated.[92,93] Proteinuria targets may not always be achieved despite maximal therapy. In such patients, it should be ensured that at least the blood pressure goals are achieved. The control of both systolic and diastolic blood pressure to recommended levels is important. Besides blood pressure control and reduction of proteinuria, other measures also help to ameliorate the progression of renal failure: dietary protein restriction, optimal diabetes control, correction of calcium/phosphorous levels, treatment of hyperlipidemia, correction of anemia, smoking cessation, and avoidance of nephrotoxic agents (nonsteroidal antiinflammatory agents, cyclooxygenase-2 inhibitors, aminoglycosides, radio-contrast).[11,19,21]

Renin-angiotensin system blockade may not be unique in conferring renoprotection. A large study showed that a β-blocker and an ACE-I were equally effective in diabetic nephropathy.[94] In the African-American Study of Kidney Disease, the amlodipine arm was terminated early because it was inferior to ramipril in slowing the progression of renal failure, but the double-blind comparison of ramipril to a β-blocker is continuing.[29]

Table 6. Use of different groups of antihypertensive medications for blood pressure control, and reduction of microalbuminuria or overt proteinuria

Goals:

a) Normoalbuminuria or at least 50% reduction in albuminuria in microalbuminuric patients.

b) Daily protein excretion of <500–1000 mg or random urine protein/urine creatinine ratio of <0.5–1.0 in patients with overt proteinuria, or at least a 50% reduction of baseline proteinuria.[18,19,21]

c) Blood pressure: Systolic <130 and diastolic <80 mm Hg (Joint National Commission-7 recommendation[72,73] and <125 systolic and diastolic <75 mm Hg (National Kidney Foundation recommendation).[11]

Initial Therapy:

i) Initiate therapy with an angiotensin-converting enzyme inhibitor (ACE-I) in patients with type 1 diabetic nephropathy or nondiabetic renal disease, and an angiotensin-receptor blocker (ARB) in patients with type 2 diabetes (see text for criteria for selection of a drug from one of the two classes).

ii) Dietary salt restriction and/or addition of a diuretic: potentiates antiproteinuric and antihypertensive effects of renin-angiotensin system blocking drugs.[74]

iii) Monthly increase of the dose of these medications until blood pressure and proteinuria goals achieved (watching for symptomatic hypotension) or maximal recommended antihypertensive dose is reached.

If blood pressure and/or proteinuria goals not achieved despite maximal doses of ACE-I or ARB, in combination with a diuretic:

i) Addition of nondihydropyridine calcium channel blockers (diltiazem or verapamil) and/or beta-blocker may decrease proteinuria in addition to improving blood pressure control. Dihydropyridine-calcium channel blockers (nifidepine, amlodipine) may increase proteinuria,[75,76] but may be needed to achieve control of blood pressure.

ii) In severely hypertensive patients (systolic ≥160 and/or diastolic ≥90 mm Hg), this step-wise approach is inappropriate and combination therapy with a drug from each of the above-mentioned groups might be required right at the start. Most patients will require the combined use of 3 to 4 classes of drugs to achieve blood pressure and proteinuria control.[77]

iii) Other options to reduce proteinuria include using an ACE-I or ARB in higher than the maximum doses recommended for blood pressure control,[78,79] combination therapy with these two classes of drugs,[30,80–87] addition of spironolactone[88] or a nonsteroidal antiinflammatory drug.[2] Such therapies greatly increase the risk of acute elevations of serum potassium,[89] and creatinine,[90] and require very close monitoring of these levels.

Conclusion

Microalbuminuria and overt proteinuria persisting on retesting the urine should be regarded as potentially serious abnormalities. The quantity of protein excreted per day, the serum creatinine level, and the calculated glomerular filtration rate determine the severity of the underlying renal disorder. Patients with overt proteinuria, >1 g/d (or random urine protein/urine creatinine ratio > 1.0) or associated with reduced renal function will benefit from evaluation by a nephrologist. Even with normal renal function and overt proteinuria of 0.2 to 1 g/d, nephrology consultation is indicated if hypertension, systemic diseases which commonly involve the kidneys (eg, diabetes mellitus, systemic lupus erythematosus), a history of use of medications or illicit drugs known to cause proteinuria, or a family history of renal disease is present. Type 1 diabetes of more than 5 years' duration, and type 2 diabetes irrespective of known duration, are indications for annual testing for microalbuminuria. Importantly, therapy in microalbuminuric or overtly proteinuric patients should aim for blood pressure control to a level <130 to 125 mm Hg systolic, and diastolic <80 to 75 mm Hg, and the maximum possible reduction of microalbuminuria and overt proteinuria to retard the development/progression of chronic kidney disease. Microalbuminuric and overtly proteinuric patients have a high risk of developing cardiovascular disease. In addition to focusing on renal disease, close attention should be paid to correcting all risk factors for cardiovascular disease in this patient population. The cornerstone of such renal and cardiovascular protective therapy is the use of ACE-Is and/or ARBs.

Table 7. Common problems encountered during the use of ACE-Is ARBs in patients with chronic kidney disease[a]

Problem	Monitoring and therapy
Hyperkalemia	
Caused by decreased aldosterone levels resulting from blockade of the renin-angiotensin system. This leads to decreased urinary and colonic excretion of potassium.	Monitor serum potassium levels closely during initial 3–4 weeks of therapy and after each dose increase. Aim for serum potassium <5.5 mEq/L. Instruct patient about the need for dietary potassium restriction and avoidance of potassium-containing salt substitutes. Avoid potassium supplements/potassium-sparing diuretics. Addition of a loop-diuretic to increase urinary potassium excretion. Value of changing from ACE-I to ARB to reduce hyperkalemia[71] has not been established. Daily doses of a cation-exchange resin (sodium polystyrene sulfonate).
Increase in serum creatinine level	
Caused by decreased glomerular filtration rate due to decreased intraglomerular hydrostatic pressure resulting from glomerular efferent arteriolar dilatation when angiotensin II level is decreased or angiotensin II action is blocked by these two groups of drugs. Usually occurs within 2 to 3 weeks of starting therapy.[90]	Monitor serum creatinine level closely during initial 3–4 weeks of therapy and after each dose increase. Up to a 30% increase is expected. Stop therapy only if >30% increase of serum creatinine occurs.[90]
ACE-I-induced cough (10–15% of patients) or angioedema (<5% of patients)	
Due to elevated kinin levels resulting from inhibition of the converting enzyme which catabolizes kinins into inactive metabolites.	Caution patient to watch out for these symptoms. Switch to an ARB. These side effects are very rare with ARBs.
Worsening anemia of chronic kidney disease	
Due to decreased erythropoietin level or effect on bone marrow.[91]	Initiate erythropoietin therapy if hemoglobin level <11 g/dL.

[a]*ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.*

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