



Approach to Proteinuria in Adults and Elderly

Abstract

Proteinuria can create one of the greatest challenges in primary practice, especially in the geriatric population. It is typically detected by dipstick urinalysis, an ordinary, non-invasive test. Proteinuria is frequently a marker of unsuspected kidney disease, progressive atherosclerosis or a systemic disease. There is a strong correlation between urinary protein excretion and progression of renal failure. Furthermore, Proteinuria is a strong and independent predictor of increased risk for cardiovascular disease and death, especially in people with diabetes, hypertension, chronic kidney disease, and the elderly. This article will review the clinical significance of proteinuria in adults, especially in the elderly population, and provide a practical diagnostic approach in addition to a summary of non-specific antiproteinuric therapy.

Keywords: *Proteinuria, Microalbuminuria, Macroalbuminuria, elderly, Risk*



Case

You are seeing a 63-year-old lady with vague clinical symptoms, who was found to have a reading of 2+ proteinuria on urinalysis. She has been previously healthy and does not smoke tobacco or drink alcohol.

- What is the significance of proteinuria?*
- What could be causing the proteinuria?*

- How would you approach this case?*
- How should this be managed now?*
- When should this patient be referred for further investigation?*

Introduction

Proteinuria is a common incidental finding in adult primary care prac-

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Proteinuria - Frothy Urine; adopted with permission³⁴
<http://docfiles.blogspot.com/2007/01/proteinuria-frothy-urine.html>

tice, especially in the elderly population. Proteinuria is often transient and benign, but persistent proteinuria is not only a marker of early kidney disease, but also an independent risk factor for atherosclerotic diseases, such as coronary or cerebrovascular arterial diseases.¹ Individuals with proteinuria are at increased risk of death.²⁻⁴ The incidence of proteinuria in randomly collected urine specimens increases with age and is significantly associated with increased mortality.⁵

Furthermore, persistent proteinuria is directly proportional to the extent of loss of renal function and is also a strong predictor for death related to cardiovascular diseases in the aging population, significantly adding to the already mounting bur-

den from these diseases.⁶

History

Descriptions of the clinical significance of proteinuria appeared in texts of Hindu medicine as early as 2000 B.C.⁷ Moreover, Hippocrates noted the association of foamy urine (a usual effect of excess protein secretion) and kidney disease in his Aphorisms: “When bubbles settle on the surface of the urine, they indicate disease of the kidneys, and that the complaint will be protracted.”⁸⁻⁹

Incidence and Prevalence

Proteinuria on initial dipstick urinalysis testing is found in as many as 17% of selected asymptomatic, otherwise healthy adolescent populations.¹⁰ According to statistics

Table 1: Causes of False Positive and Negative Results for Urine Dipstick Proteinuria¹⁶

False Positive	False Negative
Concentrated urine	Dilute urine
pH >7	pH <4
Presence of gross hematuria, leukocytes, pus, mucus, semen, or vaginal discharge	Protein loss <300 to 500 mg/day (albumin <10–20 mg/day)
Urease-producing bacteria by rising urine pH	Positively charged proteins like: immunoglobulin light chains and beta-2 microglobulin
Iodinated contrast agent	
Contamination with disinfectant like chlorhexidine or benzalkonium	

from the Caring for Australians with Renal Impairment (CARI) Guidelines, about 5% of the general population would develop proteinuria and these individuals are approximately 15 times more likely to develop End-stage Renal Disease (ESRD) than those without proteinuria.¹¹

In a community survey of white adults, aged 20 to 65 years, Winocour et al.¹² reported a 6.3% prevalence of microalbuminuria. In older adults, age 60–74 years, the prevalence rate increases to 13 to 20%.¹³ In octogenarians without diabetes or hypertension, the prevalence rate increases to 18 to 25%, and was not much different from that observed in individuals of the same age with diabetes and/or hypertension.¹⁴ The prevalence of proteinuria increases further with obesity (with a BMI of 20 to 33).¹⁵

Definitions

Normally urine contains less than 150 mg protein per day, with only 20% of it as albumin (less than 30 mg/d or 20 µg/min) and 40% as Tamm-Horsfall mucoproteins, which are secreted by the distal tube.⁹ Proteinuria is defined by the presence of excessive amounts of protein in the urine (>150mg/24 hours). Proteinuria with more than 3500 mg/24 hours is called nephrotic range proteinuria, which usually represents glomerular disease.¹⁶

Microalbuminuria is defined as a urinary excretion of albumin

that is above normal (20ug/min or 30mg/24 hours) but is below the sensitivity of conventional test strips (300mg/24 hours). Microalbuminuria is recognized to be an early marker for nephropathy associated with type 2 diabetes mellitus or hypertension, and also is an independent marker for cardiovascular disease. Albuminuria of more than 300mg/24 hour is called macroalbuminuria.¹⁷

Dipstick testing: The dipstick carries a reagent strip impregnated with a pH indicator, and a buffer. Proteins (especially albumin) bind to the pH indicator dye, which changes color. The sensitivity of reagent strips is only 32% to 46%, with a specificity of 97% to 100%¹⁶, with false positive (22-54%) and false negative (3-13%) results.¹⁸ The dipstick provides a qualitative estimate of the degree of proteinuria since it measures protein concentrations and not absolute amounts. Moreover, the test is able to detect urine protein levels above 300-500 mg/day (albumin > 10-20 mg/day).¹⁶

Quantification: A 24 hour collection is required to quantify the amount of protein (creatinine needs to be measured for accuracy of the collection). This can be cumbersome, costly, and inaccurate especially in the elderly, with some degree of confusion or occasional incontinence.¹⁹

The spot Urine Protein/Creatinine ratio (PCR) or Albumin/Creatinine (ACR):



Key Point

As a common incidental finding, proteinuria is often transient and benign, but persistent proteinuria can be a manifestation of a systemic disease.¹⁶

Table 2: Proposed Definitions of Proteinuria and Albuminuria

	Microalbuminuria	Albuminuria	Proteinuria
Per 24 hours	30–300 mg/d	>300 mg/d	>150–300 mg/d
Dipstick	>3 mg/dL (Albumin specific dipstick)	>20 mg/dL	>30 mg/dL
Random urine	Males >1.9 g/mmol	Males >28 g/mmol	Males >28 g/mmol
ACR or PCR g/mmol	Females >2.8 g/mmol	Females >40 g/mmol	Females >40 g/mmol

Gender specific ranges are from the study by Warram et al (1996) and have been adopted by the K/DOQI guidelines units mentioned only in SI.¹¹

There are sufficient data in the literature to demonstrate a strong correlation between PCR or ACR in a random urine sample and 24-h protein or albumin excretion.^{20–22} A PCR of <23 g/mmol is normal, whereas a PCR of >400 g/mmol indicates nephrotic range proteinuria.^{20–21} (See table 2)

Significance

Proteinuria is one of the most frequent modes of presentation of underlying renal disease, and it is not only an early marker of kidney damage, but also a guide to differential diagnosis, prognosis, and treatment.²³ Ironically, proteinuric patients with kidney damage may remain asymptomatic until advanced stages of renal dysfunction.²⁴ In particular, detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease, and the quantification of proteinuria can be of considerable

value in assessing the effectiveness of therapy and the progression of the disease.^{22,11}

Proteinuria is a powerful predictor of developing hypertension and is associated with a two-fold increase in the risk of developing overt hypertension.²⁵ Furthermore, Proteinuria is a surrogate marker for progressive atherosclerosis, widespread vascular inflammation, and endothelial dysfunction and portends worse cardiovascular and renal outcomes.^{16,24} The degree of microalbuminuria correlates with the magnitude of C-reactive protein elevations and has also been associated with the absence of nocturnal drops in arterial pressure, insulin resistance, as well as abnormal vascular responsiveness.²⁴

A large body of data confirm a strong and continuous association between proteinuria and subsequent risk of coronary heart disease, and suggest that proteinuria should be incorporated into the assessment of an individual's car-



Key Point

Proteinuria is a strong and independent predictor of increased risk for cardiovascular disease and death, especially in people with diabetes, hypertension, or chronic kidney disease and the elderly.⁶

Table 3: Risk Factors for Proteinuria²⁸

Male Sex	Diabetes Mellitus
Advanced age	Hypertension
High Body Mass Index (BMI)	Elevated systolic blood pressure
Smoking	

diovascular risk.²⁶ Furthermore, Proteinuria has been shown to be an independent marker for excessive morbidity and mortality from cardiovascular disease in both diabetic and hypertensive populations.^{17,24} Proteinuria is recognized as an independent risk factor for cardiovascular as well as renal disease and is a predictor of end organ damage.^{11,22}

The increased propensity towards the development of dementia in albuminuric patients suggests a common pathologic mechanism affecting the cerebral and renal microvasculature.²⁷

It is well-known that nephrotic range proteinuria is associated with a wide range of complications, including hypoalbuminemia, edema, hyperlipidemia, and hypercoagulability; faster progression of kidney disease; and premature cardiovascular disease. However, it is now known that sub-nephrotic range proteinuria is also associated with faster progression of kidney disease and development of cardiovascular disease.²³



Key Point

Early detection and treatment of asymptomatic proteinuria in patients with diabetes improves overall survival.¹⁶

Risk Factors

Various risk factors have been identified for proteinuria. Table (3) summarizes them for easy reference.

Mechanisms of Proteinuria

There are four mechanisms of excessive protein excretion in urine:

1. **Glomerular Proteinuria:** Relates to distorted glomerular permeability and causes filtration of plasma proteins (primarily albumin). The quantity of protein can reach above nephrotic range.
2. **Inadequate Tubular Reabsorption:** of normally filtered plasma including albumin, beta-2 microglobulins, immunoglobulin light chains, retinal binding protein, and amino acids. This can be seen commonly in tubulointerstitial diseases.
3. **Increased Tubular Secretion:** of tissue proteins from the epithelial cells of the loop of Henle. This occurs in Tamm-Horsfall proteinuria, reflux nephropathy, obstructive uropathy, and some other tubulointerstitial diseases.¹⁶
4. **Overflow Proteinuria:** of excessively produced and abnormal plasma proteins occur in plasma cell dyscrasias. In this condition tubular cells are not able to reabsorb all of the filtered protein.

Table 4: Different Causes of Proteinuria by Type

Glomerular

Primary

- Minimal change disease
- Idiopathic membranous glomerulonephritis
- Focal segmental glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

Secondary

- Diabetes mellitus
- Collagen vascular disorders (e.g., lupus nephritis)
- Amyloidosis
- Preeclampsia
- Infection (e.g., HIV, hepatitis B and C, poststreptococcal illness, syphilis, malaria and endocarditis)
- Gastrointestinal and lung cancers
- Lymphoma,
- chronic renal transplant rejection
- Glomerulonephropathy associated with the following drugs: Heroin, NSAIDs

Glomerular (continued)

- Gold components
- Penicillamine
- Lithium
- Heavy metals

Tubular

- Hypertensive nephrosclerosis

Tubulointerstitial disease due to:

- Uric acid nephropathy
- Acute hypersensitivity interstitial nephritis
- Fanconi syndrome
- Heavy metals
- Sickle cell disease
- NSAIDs, antibiotics

Overflow

- Hemoglobinuria
- Myoglobinuria
- Multiple myeloma
- Amyloidosis

HIV = human immunodeficiency virus, NSAIDs = nonsteroidal anti-inflammatory drugs. Adapted with permission from Glassrock RJ. Proteinuria. In: Massry SJ, Glassrock RJ, eds. Textbook of Nephrology. 3d ed. Baltimore: William & Wilkins, 1995:602.³³

Etiologies

Intense activity, dehydration, emotional stress, fever, vaginal mucus, urinary tract infection, orthostatic proteinuria (occurs after patient has been upright for some time and is not found in early morning urine, uncommon over age of 30),

pregnancy, heat injury and various inflammatory processes are some of the main causes of benign proteinuria.⁹ Table 4 below provides a comprehensive list of the various disease states that cause proteinuria.

Approach

The first step in the evaluation of

patients with proteinuria should include a comprehensive history and physical examination focusing on the various possible causes (see table 4) as applicable based on the clinical context including drugs, substance abuse, and evidence of systemic diseases. The assessment should also include a search for other cardiovascular risk factors and end-organ damage. (Figure 1)

A repeat urine dipstick examination may be warranted to exclude false positives and transient proteinuria.

Depending on their general medical status, some patients may need periodic follow up.

The next step should be the quantification of proteinuria by PCR (or ACR) in addition to estimated glomerular filtration rate, fasting blood glucose, urine microscopy and specific serologic tests as indicated, e.g. autoantibodies, complement levels, cryoglobulins, hepatitis, HIV serologies, as well as urine and plasma protein electrophoresis. ACR is primarily useful for monitoring certain glomerular diseases like diabetic nephropathy. ACR > 1.9 g/mmol in males and > 2.8 g/mmol in female require close attention.

If proteinuria is considerable (PCR > 28 g/mmol in male and > 40 g/mmol in female), and not transient, then conditions that alter renal hemodynamics like heavy exercise, febrile illness, and congestive heart failure need to be ruled

out. However, PCR > 400 g/mmol (Nephrotic range) requires immediate referral to a nephrologist.

Prognosis

In patients with proteinuria, the prognosis primarily depends on the underlying disease. Being a surrogate for progressive loss of kidney function,²⁹ the renal prognosis is also 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, but patients with persistent proteinuria of more than 1g/day are more likely to progress to end-stage renal insufficiency.¹⁶ Reduction of proteinuria and aggressive blood pressure control resulted in fewer cardiovascular events and halted progression of renal dysfunction.²⁴

Screening

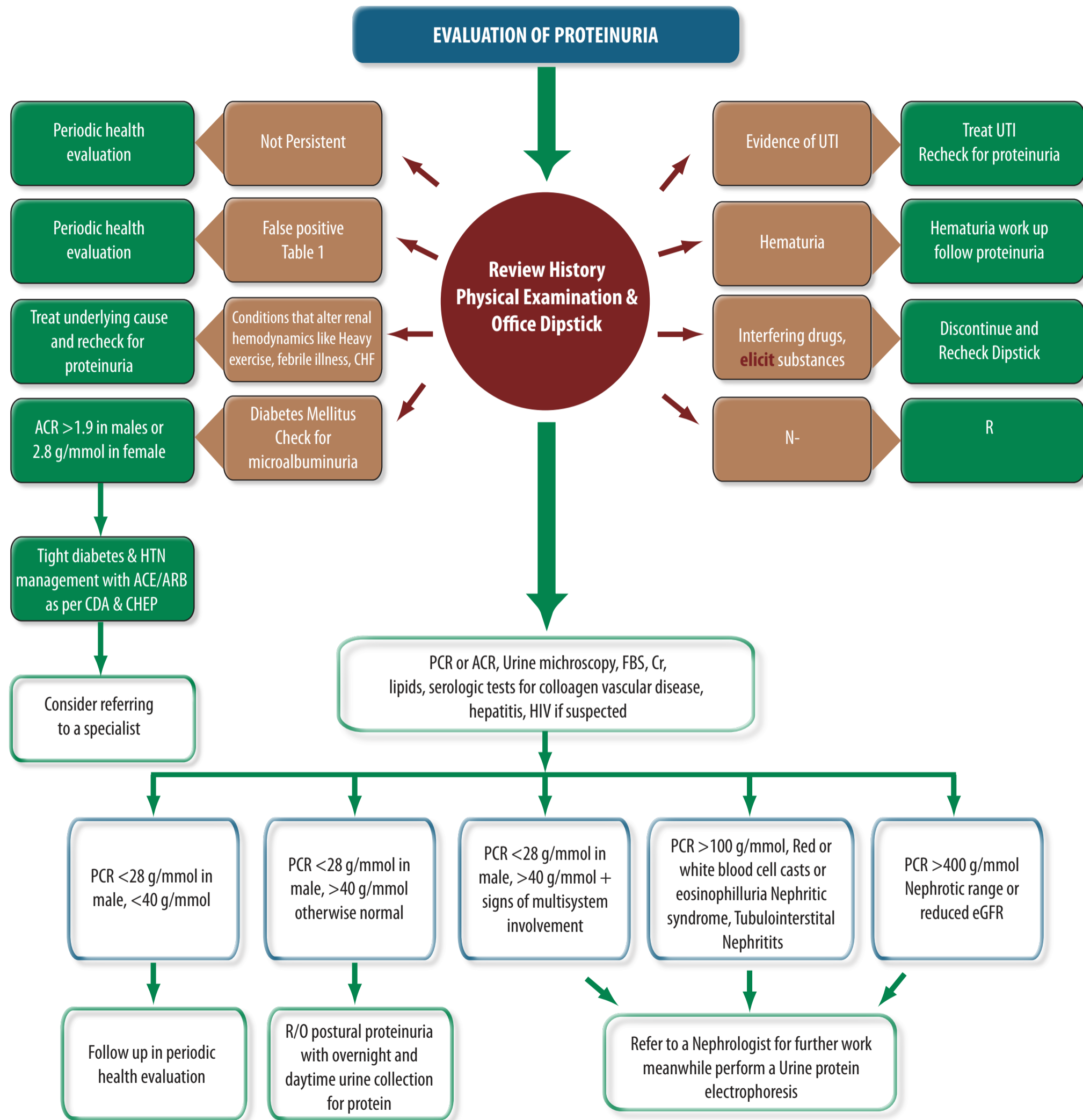
Screening for proteinuria (PCR) is recommended in all subjects who are at high risk of kidney disease (patients with diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate < 60 mL/min/1.73m², or edema, immediate relatives of patients with diabetes, hypertension or renal disease).³⁰ However, in diabetics, Aboriginal and Torres Strait Islanders, annual ACR is preferred as screening modality as it allows detection of early nephropathy.^{11,30} PCR > 100 mg/mmol or



Key Point

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.¹⁶

Figure 1: Approach to Proteinuria



SUMMARY OF KEY POINTS

As a common incidental finding, proteinuria is often transient and benign, but persistent proteinuria can be a manifestation of a systemic disease.¹⁶

Proteinuria is a strong and independent predictor of increased risk for cardiovascular disease and death, especially in people with diabetes, hypertension, or chronic kidney disease and the elderly.⁶

Early detection and treatment of asymptomatic proteinuria in patients with diabetes improves overall survival.¹⁶

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.¹⁶

Patients with hypertension and diabetes mellitus should be regularly screened for proteinuria¹⁶

Reducing proteinuria is of paramount importance in retarding the progression of chronic kidney disease.³²

ACR > 60 mg/mmol should be considered as thresholds to indicate high risk of progression to end-stage renal disease.³⁰

Treatment

Detailed treatment targeting the individualized underlying causes of proteinuria like glomerular diseases is beyond the scope of this review. However, non-specific anti-proteinuric treatments by reducing proteinuria, decrease its complications, retards progression of kidney disease, and improves cardiovascular mortality and morbidity.^{6,27} Clinical trials have consistently

shown that proteinuria reduction was associated with a slower decline in the glomerular filtration rate and led to the recognition that antiproteinuric treatment is instrumental to maximize renoprotection.³⁰⁻³¹ There is also mounting evidence that decreasing proteinuria is associated with improving renal outcome regardless of the underlying disease process.³²

Antiproteinuric agents preserve the integrity of the glomerular membrane and limit proteinuria by reducing intraglomerular pressure. The benefit of antihypertensive therapy, especially with angiotensin-converting

Clinical Pearls

Sir Robert Hutchison (1871–1960) must have had a premonition of things to come, when he stated that: *“The ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigation. They ask us, why did you not test my urine?”*⁶

enzyme inhibitors (ACEIs), to slow the progression of kidney disease is greater in patients with higher levels of proteinuria compared to patients with lower levels of proteinuria.²³

Antiproteinuric Therapies

ACEI or ARB Therapy or a Combination: Blocking the renin-angiotensin system has been shown to improve vascular compliance and increase adiponectin levels, factors that may contribute to the antiproteinuric effect of ACEI and ARB.²⁴ Thus ACEI and ARBs delay the progression of proteinuric nephropathies toward terminal failure, and they are extremely important in proteinuric patients, especially diabetic patients with microalbuminuria.

ACEI, rather than ARB, is the initial choice. ACEI therapy reduces proteinuria by about one third. At maximum recommended doses, ACEI may be more antiproteinuric than ARB. ARB is recommended in ACEI-intolerant patients (due to cough, angioedema, or allergy). There is now clear evidence that combina-

tion of ACEI/ARB therapy is more antiproteinuric than ACEI or ARB alone. The optimum antiproteinuric strategy appears to be addition of ARB to maximum ACEI in those who fail to achieve their proteinuria goal on ACEI alone.³²

Blood pressure management

Blood pressure control with ACEI, ARB, beta-blockers, non-dihydropyridine calcium channel blocker, or aldosterone antagonists is also extremely important in reducing proteinuria and delaying the progression to renal failure, especially in hypertensive and diabetic nephropathy. Dihydropyridine Calcium channel blocker should be avoided unless it is really needed for blood pressure control.³²

Control of blood Lipid levels

Statins may reduce protein traffic across proximal tubular cells by two mechanisms: 1- decreasing protein filtration at the glomerulus directly (as suggested by Douglas and colleagues), 2- by blocking receptor-mediated endocytosis of the filtered protein through inhibition of G protein prenylation. 3- In addition, statins may mitigate the damage induced by residual protein traffic by inhibiting the ensuing inflammatory response. Since proteinuria is a potential surrogate for progressive loss of kidney function, a confirmed beneficial effect of statins on proteinuria would support the hypothesis that these



Key Point

*Patients with hypertension and diabetes mellitus should be regularly screened for proteinuria.*¹⁶

medications also reduce the risk of kidney failure.²⁹

Other non-specific antiproteinuric therapy includes weight reduction in overweight patients, lifestyle modification like regular exercise, dietary protein restriction (protein-controlled diet consisting of 0.75–1.0 g/kg/day), salt restriction, smoking cessation, glucose control in diabetic patients, stop taking NSAIDs/nephrotoxic/over the counter medications that might be associated with proteinuria, and avoiding estrogen/progestin replacement therapy in postmenopausal women with kidney disease. In heavy proteinuria, a supine or recumbent posture is encouraged, and severe exertion is discouraged.^{30,32}

Case Discussion

A careful examination of the patient's history revealed two months of back pain and constipation. Her repeat urine dipstick was still positive for 2+ protein. Her PCR was 710g/mmol. Her urine protein electrophoresis showed a monoclonal band. Bone marrow aspirates showed more than 30% plasma cell infiltration. Her X-ray revealed multiple osteolytic lesions consistent with multiple myeloma.

Conclusion

Proteinuria is a common diagnostic challenge in practice and a growing

body of evidence emphasizes the value of proteinuria in the pathogenesis of renal diseases, vasculopathy and dementia. Proteinuria is a surrogate marker for progressive atherosclerosis, and a marker of widespread vascular inflammation, and endothelial dysfunction. Considering the mounting burden of diabetes, hypertension, and vascular disease in the aging population, using our simple diagnostic algorithm will guide a primary care provider to more effectively categorize, investigate, and refer proteinuric patients to a specialist. Furthermore, reducing proteinuria by utilizing non-specific antiproteinuric modalities has paramount importance.

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Key Point

Reducing proteinuria is of paramount importance in retarding the progression of chronic kidney disease.³²

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