On testing for proteinuria: Time for a methodical approach

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FOR MILLENNIA, medical writings have expounded on the color of the urine, its quantity, and sedimentation on standing. Protein in the urine was late to be recognized but proved to be the first reliable diagnostic urine test. Described by Richard Bright in patients with kidney failure in 1817, it remains an important indicator of kidney disease.

See related article, page 535

Now, measuring protein in the urine has become more than just a diagnostic test for kidney disease. Considerable evidence, accrued over the past decade, indicates that:

- Even relatively small increases in protein or albumin in the urine are an early sign of kidney injury and often precede any detectable change in the serum creatinine concentration or glomerular filtration rate
- Protein in the urine is more than a marker: persistently high levels damage the kidney and contribute to progressive loss of kidney function
- In persistent proteinuria, the amount of protein excreted bears a direct correlation to the rate of loss of kidney function
- Interventions that reduce the amount of protein in the urine in persistent proteinuria retard the progression of chronic kidney disease
- 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
- The amount of protein excreted shows a strong and close correlation with the risk of death from cardiovascular disease at all levels of excretion.[1–10]

In this issue of the *Journal*, Kashif and colleagues detail the pathophysiology of proteinuria and why we should look for it in outpatients.[11]

WHY TEST FOR PROTEINURIA?

It is now imperative to test for proteinuria in office practice for several reasons:

- To detect and treat it early, now that therapies are available that can delay the progression of kidney disease[10]
- To identify people at increased risk for cardiovascular events and treat them for coexistent risk factors such as hypertension, hyperglycemia, and smoking, which improves the risk-benefit ratio of interventional strategies[2,5–9]
- To monitor and to evaluate the effectiveness of treatment.

Protein in the urine is more than a marker

GLOMERULAR INJURY VS OTHER CAUSES

The normal rate of protein excretion in healthy adults is less than 150 mg/day. Less than 30 mg of this is albumin, which has a molecular weight just big enough to keep it from passing through the normal, intact glomerular membrane. The rest is composed of different proteins and glycoproteins from tubular epithelial cells.

Albumin, however, accounts for most of the protein in the urine in proteinuria due to glomerular injury, the major pathologic form of proteinuria encountered clinically. Other types of proteinuria, due to decreased tubular reabsorption or increased plasma levels of smaller

proteins (overflow), are less common. Glomerular proteinuria is associated with cardiovascular disease, but the other forms are not.

IS THE PROTEINURIA PERSISTENT?

Glomerular proteinuria is reversibly increased in certain conditions (eg, exercise, fever, sleep apnea). Therefore, testing should be repeated a week or two after proteinuria is first detected to determine if it is persistent.

QUANTIFYING THE PROTEINURIA

It is essential to measure the amount of protein excreted, since it correlates directly with the magnitude of risk, and its reduction constitutes a measure of therapeutic efficacy.

For quantifying proteinuria, there is now convincing evidence that the urine protein-to-creatinine or albumin-to-creatinine ratio in a spot urine sample accurately predicts the level of protein excretion as measured in a 24-hour sample.[12]

The time of day may not matter when collecting a spot sample. First morning specimens minimize the circadian changes in protein excretion and appear to most closely reflect the 24-hour excretion. However, in controlled studies of morning vs random spot urine samples, the differences have been minor and within the expected biologic range of measurements.[13]

A methodical approach to detecting proteinuria can improve renal and cardiovascular outcomes

NEW GUIDELINES

Recent guidelines from the National Kidney Foundation[14] recommend that "all individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk of developing chronic kidney disease, based on clinical and sociodemographic factors" and that "individuals at increased risk of developing chronic kidney disease should undergo testing for markers of kidney damage," specifically for proteinuria.

Patients at increased risk for kidney disease

Clinical risk factors, which should be checked for at routine health encounters, are diabetes, hypertension, autoimmune diseases, urinary tract infection, urinary stones, lower urinary tract obstruction, neoplasia, family history of chronic kidney disease, reduction in kidney mass, exposure to nephrotoxins, and low birth weight.

Sociodemographic risk factors are older age, ethnic minority status (African American, American Indian, Hispanic), exposure to chemical or environmental hazards, and low income or education. Any of these factors place an individual at increased risk and necessitate testing for proteinuria.

Testing for proteinuria

To measure protein, the guidelines recommend that:

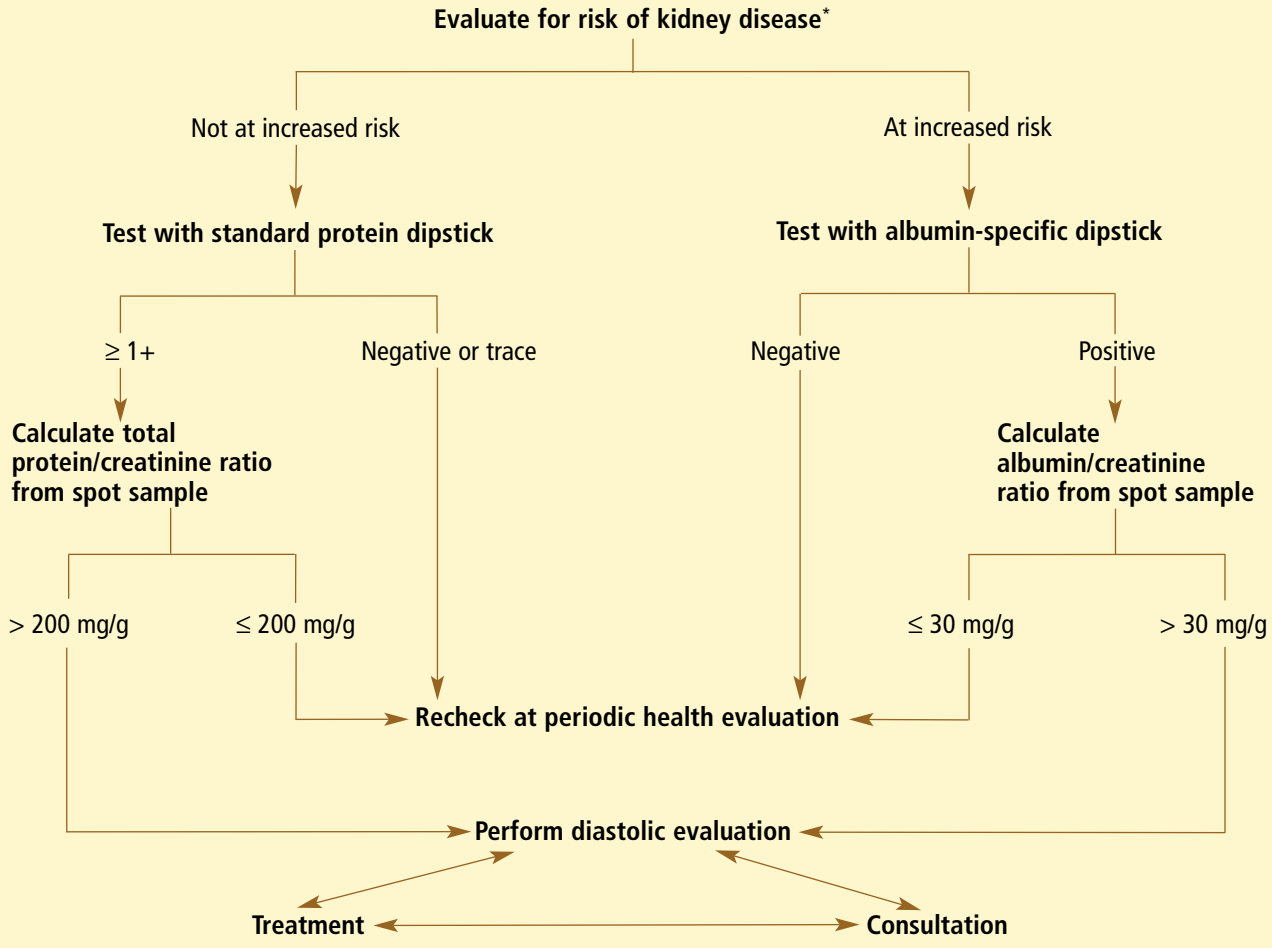
- "Under most circumstances, untimed ('spot') urine samples should be used to detect and monitor proteinuria…It is usually not necessary to obtain a timed urine collection (overnight or 24-hour) for these evaluations"
- "First morning specimens are preferred, but random specimens are acceptable if first morning specimens are not available"
- "In most cases, screening with urine dipsticks is acceptable for detecting proteinuria: standard urine dipsticks are acceptable for detecting increased total urine protein," and "albumin-specific dipsticks are acceptable for detecting albuminuria"
- Patients who test positive should undergo confirmation by a quantitative measurement (protein-to-creatinine or albumin-to-creatinine ratio) within 3 months
- Two or more positive quantitative tests temporally spaced by 1 or 2 weeks should be diagnosed as persistent proteinuria.

An algorithm for testing

The algorithm proposed in these guidelines for detecting and evaluating proteinuria (FIGURE 1) is reasonable and efficient.

The algorithm calls for testing with albumin-specific dipsticks for patients at increased risk of kidney disease (who would be most likely to benefit from early detection and treatment), and for testing with standard protein dipsticks for everyone else. The albumin-specific dipsticks can detect albumin at concentrations as low as 3 to 4 mg/dL (so-called microalbuminuria), while the standard dipsticks detect total protein at concentrations of 10 to 20 mg/dL. Of note: one must specifical-

Office testing for proteinuria



*Clinical risk factors (diabetes, hypertension, autoimmune disease, systemic infection, urinary stone, lower urinary tract obstruction, neoplasia, family history of chronic kidney disease, recovery from acute kidney failure, reduction in kidney mass, exposure to certain drugs, low birth weight) or sociodemographic risk factors (older age, ethnic minorities, exposure to certain chemical or environmental conditions, low income or education)

ADAPTED FROM THE NATIONAL KIDNEY FOUNDATION. K/DOQI CLINICAL PRACTICE GUIDELINES FOR CHRONIC KIDNEY DISEASE: EVALUATION, CLASSIFICATION AND STRATIFICATION. AM J KIDNEY DIS 2002; 39(SUPPL 1):S1–S216.

FIGURE 1

ly ask for the albumin test, as a standard urinalysis does not include it.

If either type of dipstick test is positive, the next step is to quantify total protein excretion from the total protein/creatinine ratio or the albumin/creatinine ratio from a spot sample. This approach circumvents the agony of waiting for results and the added office visit that would be necessary if another dipstick test were repeated at this point. These ratios correlate well with the level of protein excretion, which reflects the level of increased risk, and the information is necessary for the subsequent evaluation of therapy to reduce the amount of proteinuria.

Adopting and implementing such a methodical approach to the detection of proteinuria should allow for early detection and

institution of interventional measures that have been shown to be effective in reducing proteinuria, retarding the progression of kidney disease, and improving cardiovascular mortality and morbidity, with the consequent improvement of outcomes for all individuals at increased risk.

Sir Robert Hutchison (1871–1960) must have had a premonition of things to come, when at the turn of the past century he noted 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?

REFERENCES

1. **Keane WF, Eknoyan G.** Proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). A position paper of the National Kidney Foundation. Am J Kidney Dis 1999; 33:1004–1010.
2. **Grimm RH Jr, Sandsen KH, Kasiske B, Keane WM, Wahi M.** Proteinuria is a risk factor for mortality over 10 years of follow up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int 1997; 63(suppl 63):S10–S14.
3. **Peterson JC, Adler S, Burkart JM, et al.** Blood pressure control, proteinuria and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995; 123:754–762.
4. **Mutner P, He J, Hamm L, Loria C, Whelton P.** Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13:745–753.
5. **Gerstein HC, Mann JF, Yi Q, et al.** Albuminuria and risk of cardiovascular events, death and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286:421–426.
6. **SoRelle R.** Increases in urinary albumin excretion predict risk of death from all causes as well as those from cardiovascular disease. Circulation 2002; 106:e9037–e9038.
7. **Leoncini G, Sacchi G, Viazzi F, et al.** Microalbuminuria identifies overall cardiovascular risk in essential hypertension. J Hypertens 2002; 20:1315–1321.
8. **Hillege HL, Fidler V, Diercks GF, et al.** Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. Circulation 2002; 106:1777–1782.
9. **Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigators.** Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. Ann Intern Med 2001; 134:629–636.
10. **Keane WF.** Proteinuria: Its clinical importance and role in progressive renal disease. Am J Kidney Dis 2000; 35:(suppl 1):S97–S105.
11. **Kashif W, Siddiqi N, Dincer AP, Dincer HE, Hirsch S.** Proteinuria: How to evaluate an important finding. Cleve Clin J Med 2003; 70:535–547.
12. **Schwab SL, Christensen RL, Dougherty K, Klahr S.** Quantification of proteinuria by the use of protein-to-creatinine ratios in single urine samples. Arch Intern Med 1987; 147:943–944.
13. **Chitalia VC, Kothari J, Wells EJ, et al.** Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol 2001; 55:436–447.
14. **National Kidney Foundation.** K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39(suppl 1):S25–S27.

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CORRECTIONS

Osteoporosis in men

(MARCH 2003)

"Osteoporosis in men: Suspect secondary disease first," by Angelo Licata, MD, PhD (Cleve Clin J Med 2003; 70:247–254) contained a typographic error. On page 251 the T-score range for osteopenia was listed as between –1.5 and –2.5. The World Health Organization criteria specify –1.0 to –2.5. We would like to thank Dr. Stefan Monev, of Oshkosh, Wis, for pointing this out.

Preventing kidney failure

(APRIL 2003)

TABLE 2 in "Preventing kidney failure: Primary care physicians must intervene earlier" by Christopher J. Hebert, MD (Cleve Clin J Med 2003; 70:337–344) contained a typographic error. The exponent of the serum albumin concentration should be positive, not negative. The corrected table is shown at right. We would like to thank Dr. Robert Misson, of San Luis Obispo, Cal, for pointing this out.

TABLE 2

Three formulas for calculating the glomerular filtration rate (GFR)

MDRD formula (most accurate – calculator at www.kdoqi.org)

$$GFR = 170 \times \text{serum creatinine concentration}^{-0.999} \times \text{age}^{-0.176} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if race is black)} \times \text{blood urea nitrogen concentration}^{-0.17} \times \text{serum albumin concentration}^{0.318}$$

24-hour creatinine clearance
(intermediate accuracy, least convenient)

$$GFR = \frac{\text{urine creatinine concentration} \times \text{volume in mL}}{\text{serum creatinine concentration} \times \text{time in minutes}}$$

Cockroft-Gault formula (least accurate, most convenient)

$$GFR = \frac{(140 - \text{age}) \times \text{weight in kg} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine concentration}}$$