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Exercise-induced proteinuria?

Urinalysis reveals an excessive level of protein, but your patient is a runner. How concerned should you be?

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PRACTICE RECOMMENDATIONS

› *Rely on a spot urine microalbumin-to-creatinine or protein-to-creatinine ratio to accurately assess proteinuria.* (B)

› *Repeat testing if routine urinalysis detects proteinuria—especially if the patient reports having exercised in the previous 24 hours.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ As part of a routine physical examination, urinalysis reveals that a patient new to your practice is excreting an excessive level of protein. The patient is physically fit and shared during the history taking that he is an avid runner. The physical examination and other laboratory values were unremarkable. How concerned should you be about the finding of proteinuria?

Exercise-induced proteinuria is generally benign and a function of the intensity—rather than the duration—of exercise.[1] It occurs most often among athletes participating in such sports as running, swimming, rowing, football, or boxing.[2] It's also transient—lasting 24 to 48 hours.[1] Recognizing exercise-induced proteinuria is fairly straightforward—once you know what to look for.

But first, a word about the processes at work.

Diverse processes that work alone—or together

The normal range of protein excretion in healthy individuals is 150 to 200 mg of protein per day, of which albumin constitutes 10 to 20 mg.[3] Individuals with proteinuria persistently higher than this level need further evaluation.

Diverse processes leading to proteinuria—working alone or concomitantly—occur at the level of the nephron.[3]

Glomerular proteinuria results from increased filtration of macromolecules such as albumin across the glomerular capillary barrier. This type of proteinuria can occur with different glomerulopathies, upright posture, or exercise.[4]

Researchers have not identified the mechanisms leading to postexercise proteinuria, but there are several theories. (For more on this, see "Why does exercise increase protein excretion?" on page 25.)

Tubular proteinuria is due to a deranged tubular apparatus with an intact glomerulus. This results in the escape of β2-microglobulin and immunoglobulin light chains from proximal tubular reabsorption. It is often missed on dipstick testing, which detects only albumin. This type of proteinuria

is usually seen in tubulointerstitial diseases or in patients with idiopathic nephrotic syndrome.[5]

Overflow proteinuria occurs when small molecular light chains escape the glomerular filtration barrier and overwhelm the tubular reabsorptive capacity. This type of proteinuria can be seen in multiple myeloma, and is detectable by protein-to-creatinine ratio or urine protein electrophoresis.

The surest means of detecting proteinuria

Albumin excretion >300 mg/d is called macroalbuminuria, overt proteinuria, or dipstick-positive proteinuria. Albumin persistently excreted in the urine between 30 and 300 mg/d is referred to as microalbuminuria.

Because microalbuminuria is not detectable by a standard urine dipstick test, some providers routinely screen for protein with the microalbumin-to-creatinine ratio. A first-voided morning urine specimen is recommended, but random urine samples are an acceptable alternative.[6] The microalbumin-to-creatinine ratio is recommended as a screen for early diabetic nephropathy and other kidney diseases. And a positive test result may also suggest increased risk of cardiovascular disease.[6] Microalbuminuria is defined as persistent albumin excretion between 30 and 300 mg/d.[7]

Exercise-induced proteinuria is a function of the intensity, rather than the duration, of exercise.

When exercise is a factor, here's what to look for

As noted earlier, exercise-induced proteinuria is a function of the intensity of the exercise. Moderate and strenuous (vigorous) exercise are the 2 types of exercise that come into play when discussing proteinuria. Differentiating them is not precise, but is often defined by maximal oxygen consumption (vigorous=60% of VO_2max; moderate <60% VO_2max); metabolic equivalents (vigorous= 6 METS; moderate <6 METS); walking/running speeds (various); and heart rate reserve (vigorous=60% HRR; moderate <60% HRR).[8]

Moderate exercise produces glomerular proteinuria, with an increase in macromolecular (albumin) filtration across the glomerular barrier. Strenuous exercise increases glomerular filtration of low-molecular-weight proteins (β2-microglobulin), which overwhelm the reabsorbing capacity of the tubular apparatus, causing temporary dysfunction and tubular proteinuria.[9] Thus, the pathophysiology is mixed, with a major contribution from glomerular proteinuria.[10]

Strenuous exercise can cause protein excretion to exceed 1.5 mg/min.[11] However, it seldom rises beyond 1 to 2 g/d,[4] and this increase usually reverts to normal physiologic levels within 24 to 48 hours after exercise.[12]

Exercise-induced proteinuria is biphasic.[13] Increased protein excretion occurs 30 minutes after exercise and is related to changes in intraglomerular hemodynamics and the resulting saturation of the renal tubules. Around 24 hours after exercise, oxidative stress on the glomeruli causes another slight elevation in albumin excretion without changes in β2-microglobulin, thereby indicating glomerular proteinuria exclusively.

Even the pros aren't exempt. Exercise-induced proteinuria does not decrease with regular physical training. This was demonstrated in a study of 10 well-trained professional cyclists for whom strenuous exercise increased overnight protein excretion of both tubular and glomerular origin despite ongoing regular physical training.[14]

Creatine supplements do not increase proteinuria. A study of creatine supplementation in animal models noted no changes in 24-hour proteinuria or albumin excretion in both normal and two-thirds-nephrectomized animals.[15] Another study compared creatine use with nonuse in athletes who had been training regularly and strenuously (12-18 h/wk) for 5 to 10 years. They were evaluated for 10 months to 5 years. The groups exhibited equivalent urine excretion rates for albumin and creatinine, with no deleterious effect on kidney function.[16]

What happens when chronic disease is factored into the exercise equation?

Patients with a 2- to 20-year history of insulin-dependent diabetes without chronic kidney disease (CKD) who exhibited normal albumin excretion at baseline were more likely to develop proteinuria after exercise than healthy controls.[17,18] The postulated cause

Why does exercise increase protein excretion?

The root cause of exercise-induced proteinuria is unclear, but the renin-angiotensin system (RAS) and prostaglandins are thought to play a major role. The plasma concentration of angiotensin II increases during exercise, leading to filtration of protein through the glomerular membrane.[30] And angiotensin-converting enzyme (ACE) inhibitors have been shown to significantly diminish exercise-induced proteinuria, thus supporting this theory.[31,32]

Also, strenuous exercise increases sympathetic nervous system activity as well as blood levels of catecholamines, thereby increasing permeability of the glomerular capillary membrane.[33] Furthermore, lactate increases with strenuous exercise and causes conformational changes in serum proteins that, when coupled with glomerular barrier changes, can lead to increased permeability and protein excretion.

was undetected glomerular changes due to diabetes. An exercise-provocation test may one day be useful in predicting future development of nephropathy, but further studies are needed.[19-21]

Exercise increases proteinuria immediately in individuals with metabolic disorders like obesity, through a mechanism different from diabetes mellitus. Proteinuria in the obese population is thought to be glomerular in origin, as opposed to both tubular and glomerular proteinuria in diabetic nephropathy.[22,23]

In CKD, low-intensity exercise long term does not promote proteinuria or lead to rapid progression of CKD. In one study, obese patients (body mass index >30 kg/m^2) with diabetes and CKD stage II to IV who exercised 3 times weekly (aerobic training for 6 weeks, followed by 18 weeks of supervised home exercise) increased their stamina and exhibited slight, statistically insignificant decreases in resting systolic blood pressure and 24-hour proteinuria.[24] A 12-week low-intensity aquatic exercise program for 26 patients with mild to moderate CKD decreased blood pressure and proteinuria and slightly improved glomerular filtration rate (GFR).[25] These results for proteinuria and GFR were shown previously in rats with subtotal nephrectomy.[26]

Elevated urinary albumin excretion with exercise is significantly higher in patients with acromegaly when compared with normal healthy subjects. The underlying pathology is thought to occur at the glomerular filtration barrier with intact tubular function. Somatostatin analog treatment for acromegaly leads to reductions in postexercise albuminuria.[27,28]

How to manage suspected exercise-induced proteinuria

When interpreting the meaning of proteinuria detected on routine urinalysis, keep in mind the temporal relevance between exercise and urine collection. If urine is found to have been collected within 24 hours of intense exercise, repeat testing in the absence of prior exercise on at least one other occasion to differentiate between transient and persistent proteinuria. In confirming transient proteinuria after exercise, reassure the patient that it is a benign condition. This holds true as well for routine microalbumin-to-creatinine urine testing in patients with diabetes who exercise. If the result of a repeat test is high, turn your attention to another possible cause of proteinuria, such as diabetic nephropathy.

Screening for proteinuria during sports preparticipation examinations is not recommended because the diagnostic utility is low.[29] Researchers performed urine dipstick testing for protein, blood, and glucose in preparticipation assessments of 701 students.[29] They detected proteinuria in 40 students and glucosuria in one. Follow-up testing with first-voided morning urine specimens and glucose tolerance testing was normal in all students. JFP

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References

1. Poortmans JR. Exercise and renal function. *Sports Med*. 1984;1:125-153.
2. Gebke KB. Genitourinary system. In: McKeag DB, Moeller JL, eds. *ACSM's Primary Care Sports Medicine*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2007:234.
3. Venkat KK. Proteinuria and microalbuminuria in adults: significance, evaluation, and treatment. *South Med J*. 2004;97:969-979.
4. Rose, BD. *Pathophysiology of Renal Disease*. 2nd ed. New York, NY: McGraw-Hill; 1987:11-16.
5. Sesso R, Santos AP, Nishida SK, et al. Prediction of steroid responsiveness in the idiopathic nephrotic syndrome using urinary retinol-binding protein and beta-2-microglobulin. *Ann Intern Med*. 1992;116:905-909.
6. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137-147.
7. Family Practice Notebook. Urine protein to creatinine ratio. Available at: http://www.fpnotebook.com/urology/lab/urnprtntcrtnrt.htm. Accessed August 9, 2011.
8. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97:141-147.
9. Poortmans JR, Labilloy D. The influence of work intensity on postexercise proteinuria. *Eur J Appl Physiol Occup Physiol*. 1988;57:260-263.
10. Estivi P, Urbino R, Tetta C, et al. Urinary protein excretion induced by exercise: effect of a mountain agonistic footrace in healthy subjects. Renal function and mountain footrace. *J Sports Med Phys Fitness*. 1992;32:196-200.
11. Poortmans JR, Brauman H, Staroukine M, et al. Indirect evidence of glomerular/tubular mixed-type postexercise proteinuria in healthy humans. *Am J Physiol*. 1988;254:F277-F283.
12. Heathcote KL, Wilson MP, Quest DW, et al. Prevalence and duration of exercise induced albuminuria in healthy people. *Clin Invest Med*. 2009;32:E261-E265.
13. Sentürk UK, Kuru O, Koçer G, et al. Biphasic pattern of exercise-induced proteinuria in sedentary and trained men. *Nephron Physiol*. 2007;105:22-32.
14. Clerico A, Giammattei C, Cecchini L, et al. Exercise-induced proteinuria in well-trained athletes. *Clin Chem*. 1990;36:562-564.
15. Taes YE, Delanghe JR, Wuyts B, et al. Creatine supplementation does not affect kidney function in an animal model with pre-existing renal failure. *Nephrol Dial Transplant*. 2003;18:258-264.
16. Poortmans JR, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. *Med Sci Sports Exerc*. 1999;31:1108-1110.
17. Mogensen CE, Vittinghus E, Sølling K. Abnormal albumin excretion after two provocative renal tests in diabetes: physical exercise and lysine injection. *Kidney Int*. 1979;16:385-393.
18. Vittinghus E, Mogensen CE. Albumin excretion during physical exercise in diabetes. Studies on the effect of insulin treatment and of the renal haemodynamic response. *Acta Endocrinol Suppl (Copenh)*. 1981;242:61-62.
19. Watts GF, Williams I, Morris RW, et al. An acceptable exercise test to study microalbuminuria in type 1 diabetes. *Diabet Med*. 1989;6:787-792.
20. Pan X, Wang P, Hu N, et al. A physiologically based pharmacokinetic model characterizing mechanism-based inhibition of CYP1A2 for predicting theophylline/antofloxacin interaction in both rats and humans. *Drug Metab Pharmacokinet*. 2011;26:387-398.
21. O'Brien SF, Watts GF, Powrie JK, et al. Exercise testing as a long-term predictor of the development of microalbuminuria in normoalbuminuric IDDM patients. *Diabetes Care*. 1995;18:1602-1605.
22. Hidaka S, Kaneko O, Shirai M, et al. Do obesity and non-insulin dependent diabetes mellitus aggravate exercise-induced microproteinuria? *Clin Chim Acta*. 1998;275:115-126.
23. Hidaka S, Kakuta S, Okada H, et al. Exercise-induced proteinuria in diseases with metabolic disorders. *Contrib Nephrol*. 1990;83:136-143.
24. Leehey DJ, Moinuddin I, Bast JP, et al. Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. *Cardiovasc Diabetol*. 2009;8:62.
25. Pechter U, Ots M, Mesikepp S, et al. Beneficial effects of water-based exercise in patients with chronic kidney disease. *Int J Rehabil Res*. 2003;26:153-156.
26. Heifets M, Davis TA, Tegtmeyer E, et al. Exercise training ameliorates progressive renal disease in rats with subtotal nephrectomy. *Kidney Int*. 1987;32:815-820.
27. Manelli F, Bossoni S, Burattin A, et al. Exercise-induced microalbuminuria in patients with active acromegaly: acute effects of slow-release lanreotide, a long-acting somatostatin analog. *Metabolism*. 2000;49:634-639.
28. Hoogenberg K, Sluiter WJ, Dullaart RP. Effect of growth hormone and insulin-like growth factor I on urinary albumin excretion: studies in acromegaly and growth hormone deficiency. *Acta Endocrinol (Copenh)*. 1993;129:151-157.
29. Goldberg B, Saraniti A, Witman P, et al. Pre-participation sports assessment—an objective evaluation. *Pediatrics*. 1980;66:736-745.
30. Garrett WE, Kirkendall DT, Squire DL, eds. *Principles and Practice of Primary Care Sports Medicine*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:299-310.
31. Cosenzi A, Carraro M, Sacerdote A, et al. Involvement of the renin angiotensin system in the pathogenesis of postexercise proteinuria. *Scand J Urol Nephrol*. 1993;27:301-304.
32. Székács B, Vajo Z, Dachman W. Effect of ACE inhibition by benazepril, enalapril and captopril on chronic and post exercise proteinuria. *Acta Physiol Hung*. 1996;84:361-367.
33. Poortmans JR, Haggenmacher C, Vanderstraeten J. Postexercise proteinuria in humans and its adrenergic component. *J Sports Med Phys Fitness*. 2001;41:95-100.