Resistance Training Enhances the Value of Protein Restriction in the Treatment of Chronic Kidney Disease

Since 1972, when Social Security extended Medicare coverage to patients younger than 65 years of age with end-stage renal disease (ESRD), more than 1 million such patients have entered the program (1). Period prevalence for ESRD in 1998 was 397 971 persons at a cost of $16.74 billion, with 87 534 new beneficiaries of treatment (2). It is projected that by 2010, the number of patients treated for ESRD will be 651 330, at a cost of $28.3 billion (1). Accordingly, a significant effort is now being made to reduce the incidence of ESRD by slowing the rate of progression of chronic kidney disease. An estimated 10.9 million Americans 12 years of age and older have a serum creatinine concentration of 133 μmol/L (1.5 mg/dL) or greater, and 0.8 million have a creatinine concentration of 177 μmol/L (2 mg/dL) or greater (1). These are the at-risk patients who must be targeted for intervention.

Proven methods for slowing progression of chronic kidney disease include therapy with angiotensin-converting enzyme inhibitors (3) and angiotensin receptor blockers (4). Use of a low-protein diet to slow progression is controversial (5–8) but is probably efficacious (7–9), even in patients with nephrotic-range proteinuria (6, 7). Such diets have been shown to diminish uremic symptoms and alleviate some of the complications of chronic kidney disease, including renal osteodystrophy, insulin resistance, and metabolic acidosis (6), all of which may prolong the time to initiation of renal replacement therapy (10). In addition, a recent study has demonstrated synergy in slowing progression of chronic kidney disease with the combination of a low-protein diet and angiotensin II blockade with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (11).

The use of low-protein diets in patients with renal insufficiency is usually not instituted without some concern for safety (12, 13). Loss of lean body mass is common in patients with chronic kidney disease (8) and could be potentiated by dietary protein restriction. It has been emphasized that to prevent protein depletion, adults with uremia must ingest both adequate energy (36 kcal/kg of body weight per day) and 0.57 g of high-biological-value protein per kg per day (13, 14). The Modification of Diet in Renal Disease Study documented lower energy intake in patients who followed a low-protein diet and those who followed a very low-protein diet, which suggests that the quantity of dietary protein or phosphorous prescribed may have influenced patients' energy intake (14). This finding, which was thought to be a cause of the decrease in indices of nutritional status in these patients, underscores the need for a skilled dietitian to assist patients in adhering to the protein restriction while maintaining sufficient energy intake.

Many studies have demonstrated a high prevalence of protein-calorie malnutrition in patients receiving dialysis (14). The prevalence in patients beginning dialysis treatment is similar to that in patients who have received dialysis for months or years (14). This finding, which suggests that malnutrition often becomes established during chronic kidney disease, is important because of the detrimental effect of malnutrition at ESRD onset on subsequent patient survival (15). Indeed, Ikizler and colleagues (12) found that spontaneous dietary protein intake decreases significantly as renal function declines. On the other hand, Coresh and coworkers (16) found that predialysis protein restriction with close clinical monitoring does not worsen and may substantially improve patient survival during the first 2 years of dialysis. Aparicio and associates (10) corroborated Coresh and coworkers' results in a study that used supplemented, very-low-protein diets. The key seems to be close clinical monitoring (10, 13).

Protein-energy malnutrition is a powerful predictor of high morbidity and mortality among dialysis patients. Low serum albumin level is among the nutritional variables that have been independently correlated with 12-month odds ratios for increased mortality (15, 17). However, comorbid conditions that result in elevated inflammatory cytokines may both reduce nutrient intake and cause protein-calorie malnutrition, thereby independently increasing morbidity and mortality. Hypoalbuminemia in these patients may be linked as much to evidence of inflammation as to dietary inadequacy (13). Notwithstanding, due in part to the association between hypoalbuminemia (and presumably nutritional

status) and mortality in patients with ESRD (15, 17), it has been suggested that low-protein diets should be avoided in patients with chronic kidney disease (5, 12).

In this issue, Castaneda and colleagues (18) report the results of a randomized, controlled trial to test the hypothesis that resistance exercise training can preserve lean body mass, nutritional status, and muscle function in patients with moderate chronic kidney disease who are consuming a low-protein diet to slow the progression of renal failure. Their results suggest that resistance training is a safe and effective countermeasure to the negative effects of protein restriction on muscle mass accretion, protein utilization, nutritional status, and muscle function in patients with chronic kidney disease. Low energy intake may have accounted for the decrease in nutritional indices seen in the low-protein-diet control group; however, despite a similar energy intake, persons who followed a low-protein diet plus resistance training had improved nutritional indices because of exercise in almost every measured area after only 12 weeks. These impressive results establish the importance of exercise training to improve the metabolic profile of patients with chronic kidney disease. Resistance training appears to offset any nutritional impact of a low-protein and low-energy diet.

Generalized applicability of Castaneda and colleagues' study methods may be limited. Patients who performed resistance training were supervised by an exercise physiologist who frequently adjusted workload during training to maximize results. In addition, only a small proportion of patients invited to participate in the study consented to the exercise protocol (45 minutes three times per week), and it is unknown how effectively the training regimen would have been sustained beyond the 12-week study period, especially if patients were no longer monitored. Finally, the risks of exercise in this patient population must be considered. The preliminary treadmill stress test that Castaneda and colleagues performed was probably appropriate (19).

The importance of exercise to patients with ESRD has been emphasized (19). A large percentage of such patients fall into groups for which exercise training is specifically recommended. A program of regular physical activity is considered a standard treatment for hypertension, hyperlipidemia, and glucose management, as well as for primary and secondary prevention of coronary artery disease. In addition to mitigating cardiovascular risks, regular physical activity can also positively influence problems of bone deterioration, muscle weakness, and overall deterioration in physical functioning, even in elderly persons and persons with disabilities. Patients with ESRD have a high incidence of these problems, as well as of cardiac risk factors and overt cardiac disease (19).

The study by Castaneda and colleagues extends the value of exercise to patients with chronic kidney disease. Another study also documented improved functional aerobic capacity, muscle strength, and blood pressure in patients with chronic kidney disease who underwent 4 months of exercise training (20). Not only were these same physical improvements demonstrated by Castaneda and colleagues, but combining exercise with a low-protein diet abolished any adverse effects of the latter. Although the safety of a low-protein diet prescribed for whatever reason in patients with chronic kidney disease remains controversial (6–8), the study by Castaneda and colleagues provides a method for improving safety when these diets are used, as well a means for enhancing the overall health of patients with chronic kidney disease.

John B. Copley, MD
Ochsner Clinic Foundation
New Orleans, LA 70121

Current Author Address: John B. Copley, MD, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121.

Ann Intern Med. 2001;135:999-1001.

References

1. **Collins AJ.** End-stage renal disease. Are we ready for an emerging epidemic? [Editorial] Postgrad Med. 2000;108:13-5. [PMID: 10914116]

2. United States Renal Data System (USRDS). USRDS 2000 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2000.

3. **Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al.** Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135:73-87. [PMID: 11453706]

4. **Brenner B, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al.** Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861-9. [PMID: 11565518]

5. **Hakim RM, Lazarus JM.** Initiation of dialysis [Editorial]. J Am Soc Nephrol. 1995;6:1319-28. [PMID: 8589305]

6. **Maroni BJ.** Protein restriction and malnutrition in renal disease: fact or fiction? Miner Electrolyte Metab. 1997;23:225-8. [PMID: 9387122]

7. **Walser M.** Is there a role for protein restriction in the treatment of chronic renal failure? Blood Purif. 2000;18:304-12. [PMID: 10965072]

8. **Mitch WE.** Low-protein diets in the treatment of chronic renal failure. J Am Coll Nutr. 1995;14:311-6. [PMID: 8568106]

9. **Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH.** The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Ann Intern Med. 1996;124:627-32. [PMID: 8607590]

10. **Aparicio M, Chauveau P, De Précigout V, Bouchet JL, Lasseur C, Combe C.** Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. J Am Soc Nephrol. 2000;11:708-16. [PMID: 10752530]

11. **Peters H, Border WA, Noble NA.** Angiotensin II blockade and low-protein diet produce additive therapeutic effects in experimental glomerulonephritis. Kidney Int. 2000;57:1493-501. [PMID: 10760085]

12. **Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM.** Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol. 1995;6:1386-91. [PMID: 8589313]

13. **Mitch WE.** Dietary therapy in uremia: the impact on nutrition and progressive renal failure. Kidney Int Suppl. 2000;57(Suppl 75):S38-43. [PMID: 10828760]

14. **Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, et al.** Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. Kidney Int. 1997;52:778-91. [PMID: 9291200]

15. **Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM.** The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med. 1993;329:1001-6. [PMID: 8366899]

16. **Coresh J, Walser M, Hill S.** Survival on dialysis among chronic renal failure patients treated with a supplemented low-protein diet before dialysis. J Am Soc Nephrol. 1995;6:1379-85. [PMID: 8589312]

17. **Lowrie EG, Lew NL.** Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15:458-82. [PMID: 2333868]

18. **Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, et al.** Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. Ann Intern Med. 2001;135:965-76.

19. **Copley JB, Lindberg JS.** The risks of exercise. Adv Ren Replace Ther. 1999; 6:165-71. [PMID: 10230884]

20. **Boyce ML, Robergs RA, Avasthi PS, Roldan C, Foster A, Montner P, et al.** Exercise training by individuals with predialysis renal failure: cardiorespiratory endurance, hypertension, and renal function. Am J Kid Dis. 1997;30:180-92. [PMID: 9261028]