Decoding the Modification of Diet in Renal Disease study

The long-awaited Modification of Diet in Renal Disease (MDRD) study emerged with a whimper rather than a roar. Mandated by Congress and sponsored by the National Institutes of Health, the multicenter MDRD study was originally designed to test the hypothesis that low-protein, low-phosphate diets could slow the rate of progression of chronic renal disease of diverse etiologies. The investigators implicitly assumed that chronic renal diseases, characterized by reductions in glomerular filtration rate (GFR), progress inexorably through common mechanisms and that these mechanisms might respond to generic rather than disease-specific interventions. In simplest terms, the MDRD study failed to demonstrate any clinical benefit of protein-restricted diets on the progression of chronic renal disease, although it did show some potentially beneficial biologic effects.[1]

Was this a true-negative observation (ie, low-protein diets really do not work), or were important positive effects diluted by the inclusion of unresponsive subsets? The MDRD study is so complex in its origins, implementation, and interpretation that its full and appropriate influence on the practice of nephrology will need time to develop. Nevertheless, the comments and background that follow might help place the MDRD study in perspective.

ALL TYPES OF RENAL DISEASE INCLUDED

The full-scale MDRD study randomized 840 patients to different diet and blood pressure goals and measured their rates of decline in GFR by iodine-125-iothalamate clearance for an average of 2.2 years (range 0 to 3.7 years). Approximately one fourth of the patients had polycystic kidney disease, another fourth had various glomerular diseases, and the remaining half had other renal diseases, mainly chronic tubulointerstitial processes such as nephrosclerosis. Patients who required insulin were excluded, and only 3% had diabetes mellitus.

TWO STUDIES IN PARALLEL

The MDRD was actually two studies in parallel. Study 1 involved 585 patients who had GFRs of 25 to 55 mL/min/1.73 m^2; they were randomized to either a normal diet (1.3 g of protein per kg per day) or a low-protein diet (0.58 g of protein per kg per day). Study 2 involved 255 patients with GFRs of 13 to 24 mL/min/1.73 m^2 who were randomized to either a low-protein diet or a very-low-protein diet (0.28 g of protein per kg per day, supplemented with a mixture of essential amino acids and their deaminated ketoacids).

Study 2 had two major justifications. First, the investigators rightfully felt that patients with low GFRs could not ethically be randomized to normal protein intake because of protein's potential to aggravate azotemia and precipitate uremic symptoms. Indeed, the current standard of practice for patients with GFR values less than 25 mL/min/1.73 m^2 is some degree of reduction in protein intake, probably to approximately 0.7 to 0.8 g/kg/day. The second justification for study 2 was to test whether ketoacids of essential amino acids have unique beneficial effects on the progression of chronic renal disease, as some had strongly contended.[2,3] Because ketoacids taste unpleasant and need to be taken in bulky amounts, it seemed likely that only patients with low GFRs, who were at imminent risk for dialysis, would be sufficiently motivated to take them for

an extended time. Study 2 was mainly a pharmacologic study of ketoacid supplementation compared with restriction of dietary protein.

KETOACID THERAPY UNSUCCESSFUL

Although the patients adhered commendably to the prescribed ketoacid regimen, ketoacid supplements did not slow the rate of decline in GFR or progression to dialysis.[1] Ketoacid supplements were so unsuccessful in delaying progression to dialysis that this purpose was de-emphasized in the final results, and their role has been described mainly as a means to safely achieve more severe restriction in dietary protein. A clear but understated outcome of the MDRD study was to quiet enthusiasm for ketoacid therapy for chronic renal disease.

PROTEIN RESTRICTION

The primary results of the MDRD study were reported on an intention-to-treat basis, ie, according to assigned rather than achieved treatments. Intention-to-treat approximates clinical practice, especially when complicated interventions such as diets are involved, but it may beg the question of efficacy if the treatment is not fully delivered. Patients assigned to the low-protein diet actually consumed an average of 0.73 g of protein per kg per day; the prescribed amount was 0.58 g/kg/day. To achieve this sustained protein restriction (and to maintain normal protein intake in the control group), specially trained dieticians met monthly with each patient for extended periods of time, an intensity of service not likely to be met or affordable in clinical practice. Therefore, in practical terms, the study revealed that with near-maximal resources, the most protein restriction that can be achieved and maintained is approximately 0.7 g/kg/day.

The major complexity of the MDRD study was the lack of linearity in rates of change in GFR observed in patients assigned to either the low-protein or low-blood-pressure goals. In patients in study 1 assigned to low-protein or low-blood-pressure goals, GFR declined *faster* for the first 2 to 4 months than in patients assigned to normal-protein or usual-blood-pressure goals (1.1 mL/min/month vs 0.3 mL/min/month). This initial brisk decline was followed by a slower decline that averaged 0.2 mL/min/month. The basis for the initial short-term decline is unknown but is presumably (and vaguely) hemodynamic. Thereafter, GFR declined significantly slower in patients randomized to protein restriction regardless of blood pressure goal. Thus, there were some definite but counterbalancing effects of protein restriction and blood pressure control on the tempo of progression.

If we integrate and extrapolate these compound results over 36 months of observation, there is no detectable difference in the overall rate of decline in GFR: a mean loss of 12.1 mL/min in 3 years (95% confidence interval 10.5 to 13.8) for the normal-protein group vs 10.9 mL/min (95% confidence interval 9.2 to 12.6) for the low-protein group. After 3 years, the treatment and control groups reached statistically indistinguishable GFR values, although they arrived there by different sequences. This leaves open the possibility that protein restriction achieved some useful biologic effect that was lost over the intermediate term of 3 years because of early deleterious effects. Although an overall benefit might conceivably have been demonstrable over a longer period of time, this is speculative and the projected gains would be clinically small.

The biphasic pattern was not observed in patients with initial GFRs between 13 and 25 mL/min/1.73 m^2 (study 2). In these patients, the decline in GFR was linear over time and not statistically affected by either the dietary or the blood pressure interventions. Because assignment to study 1 or study 2 was based on an arbitrary GFR value, the lack of internal consistency between this result and that observed in study 1 tends to erode confidence in the optimistic interpretation of a favorable effect of protein restriction. On the other hand, patients in study 2 who were assigned to the very-low-protein diet had an overall mean rate of decline in GFR that was 0.8 mL/min/year slower than in those assigned to the low-protein diet ($P = .07$). Although not statistically significant by traditional P values, P values of .07 may indicate a type 2 error or false-negative result.

The GFRs of patients who started at a GFR of 20 mL/min/1.73 m^2 declined by 4.4 mL/min/year with a low-protein diet and by 3.6 mL/min/year with a very-low-protein diet. In practical terms, such patients would require dialysis (when their GFRs decline to 10 mL/min/1.73 m^2) in 2.27 years with a low-protein diet or in 2.78 years with a very-low-protein diet. This 6-month difference is an arguable gain, at best.

POLYCYSTIC KIDNEY DISEASE

The low-protein diet was convincingly ineffective in patients with polycystic kidney disease, a subset of 200 patients with declines in GFR that were brisk (0.5 mL/min/month), linear, and statistically inseparable between treatment and control groups.[4] Was it a mistake to include these patients in the original design of the MDRD study? Is there something unique about this disease that makes it unresponsive to generic interventions such as protein restriction and aggressive blood pressure control?

These questions were anticipated in the design phase, and the exclusion of patients with polycystic kidney disease was rejected for both theoretic and practical reasons. In 1984, current theory held that all forms of chronic renal disease progressed by common mechanisms. In practical terms, it would have been imprudent and impolitic to categorically exclude such a large and readily identifiable group of patients with clearly progressive disease, especially in anticipation of the patient recruitment difficulties that did indeed materialize.

Nevertheless, there is understandable concern that the inclusion of this large, unique, and unresponsive group of patients may have diluted the power of the MDRD study to detect clinically meaningful benefits in patients with chronic renal diseases other than polycystic kidney disease. This concern can be addressed in part by analyzing the other subsets, but these analyses will be weakened by a reduced number of patients.

BLOOD PRESSURE

The MDRD study could be more correctly entitled the Modification of Diet *and Blood Pressure* in Renal Disease study. Studies 1 and 2 had 2 × 2 factorial designs that allowed evaluation of GFR outcomes according to mean arterial pressure goals independent of diet. The blood pressure component was not represented in the original design of the MDRD study. It emerged in the very late stages because of two observations from the feasibility studies that preceded the full-scale trial. First, blood pressure control in the 90 patients in the feasibility trial had not been very successful, presumably because of emphasis on the dietary intervention. Second, the feasibility trial showed a strong inverse correlation between mean arterial pressures and preservation of GFR, including significant regression within the traditionally normal range.[5]

The final design was therefore adjusted to accommodate an important newer hypothesis: that treatment to a lower-than-usual blood pressure goal might safely and effectively slow the rate of decline in GFR. There was no opportunity, however, to test the ability to achieve the two specific blood pressure goals, nor was hypertension added as an inclusion criterion. Approximately 15% of the study patients were not hypertensive, and some had spontaneous blood pressures lower than those to which they were randomized. Moreover, at least in retrospect, there was insufficient systematization in the selection and constancy of antihypertensive agents, although the notion of agent-specific renoprotective benefits that is so strong now[6] was unestablished when the full-scale MDRD study was designed in 1986.

Lack of systematic control of blood pressure was a problem in at least one previous study that purported to show beneficial effects of low-protein diets.[7] Although uncontrolled hypertension was not a problem in the MDRD study, there was only limited success in achieving the 15-mm Hg difference in mean arterial pressure designated in the original design, something that had not been attempted previously. This lapse occurred because patients assigned to the higher mean arterial pressure goal of 107 mm Hg achieved average blood pressures lower than designed, while those assigned to the lower-than-usual goal of 92 mm Hg were right on target. Notably, the average mean arterial pressure on entry was 98 ± 11 (standard deviation) mm Hg; thus, most patients assigned to the higher mean arterial pressure goal needed to increase their blood pressure. Some investigators were understandably reluctant to rush to achieve this. Nevertheless, the main goals were achieved: overall blood pressure was tightly controlled to traditionally normal values, and a small but statistically significant separation of 4.7 mm Hg occurred between the low- and usual-mean-arterial-pressure groups.

Reappraising blood pressure goals

Amid these potential weaknesses, a major positive observation that emerges from the MDRD study is the powerful effect of blood pressure goals on rates of decline in GFR in patients who have protenuric forms of chronic renal disease. In both study 1 and study 2, patients with protein excretion rates greater than 1 g/day at baseline benefitted significantly from randomization to the lower blood

pressure goal. The achieved mean arterial pressure averaged 92.6 mm Hg (approximately 128/75 mm Hg) in this group vs 97.6 mm Hg (approximately 138/78 mm Hg) in the usual-mean-arterial-pressure group. A low mean arterial pressure goal slowed the rate of decline in GFR by about 30% in patients whose protein excretion rates exceeded 3 g/day and was intermediate but significant in those with rates between 1 and 3 g/day. The extent of this blood pressure effect is so dramatic as to force a reappraisal of blood pressure goals in patients with proteinuric forms of chronic renal disease and to redirect our attention to the protein excretion rate as an important marker (or perhaps risk factor) in patients with chronic renal disease, regardless of attributed etiology.

THE MESSAGES FOR CLINICAL PRACTICE

How should the MDRD study results affect clinical practice? In scientific and clinical terms, the MDRD study failed to demonstrate that protein restriction to a prescribed goal of 0.58 g/kg/day or an achieved goal of 0.73 g/kg/day effectively retards the overall progression of chronic renal disease of diverse etiologies. Unfortunately, failure to detect benefits does not exclude their possible presence to some degree beyond the sensitivity of the study, or in some limited subsets that might emerge from secondary analyses. With this understanding, the following interim conclusions seem reasonable.

Low-protein diets have no demonstrable benefit in patients with moderate degrees of chronic renal failure (GFRs greater than 25 mL/min/1.73 m^2), and these patients should receive the standard minimum protein allowance of 0.8 g/kg/day. Patients with GFRs less than 25 mL/min/1.73 m^2 may benefit slightly from very low protein intake, but this is difficult to achieve and requires monthly monitoring of nutritional safety, including measurement of body weight and serum albumin and transferrin concentrations. Ketoacid therapy is not effective. Patients with polycystic kidney disease whose GFRs have declined to the ranges examined in the MDRD study do not benefit from low-protein diets or lower-than-usual blood pressure goals.

Protein excretion rates represent an important characterization of chronic renal disease regardless of attributed etiology; patients with chronic renal disease characterized by protein excretion rates of more than 1 g/day should maintain mean arterial blood pressures less than 98 mm Hg (135/80 mm Hg), and those excreting more than 3 g/day should achieve 92 mm Hg (125/75 mm Hg), if this is not otherwise undesirable.

Finally, nutritional safety must not be jeopardized in efforts to achieve ephemeral gains in renal preservation. Safety is not a trivial restriction. The MDRD experience supports the safety of low-protein diets only within the achieved levels (which averaged 0.73 g/kg/day for the low-protein group) rather than the prescribed levels, and only for the limited duration that averaged 2.2 years. Formidable evidence now accumulating links clinical markers of protein malnourishment with excess mortality in patients with end-stage renal disease,[8] an ultimate phase for most patients with chronic renal disease.

In summary, the MDRD study failed to provide a definite answer to the fundamental question that it was designed to address, but it succeeded in focusing attention on more potentially productive strategies.

VINCENT W. DENNIS, MD
Department of Nephrology and Hypertension
The Cleveland Clinic Foundation
Investigator, MDRD study

REFERENCES

1. **Klahr S, Levey AS, Beck GJ, et al.** The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994; **330**:877–884.
2. **Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, Tungsanga K.** The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. N Engl J Med 1984; **311**:623–629.
3. **Walser M, Hill S, Ward L.** Progression of chronic renal failure on substituting a ketoacid supplement for an amino acid supplement. J Am Soc Nephrol 1992; **2**:1178–1185.
4. **Klahr S, Beck G, Breyer J, et al.** Dietary protein restriction and reduced blood pressure goal in adults with polycystic kidney disease. J Am Soc Nephrol 1994; **4**:263.
5. Modification of Diet in Renal Disease Study: design, methods, and results from the feasibility study. Am J Kidney Dis 1992: **20**:18–33.
6. **Lewis EJ, Hunsicker LG, Bain RP, Rohde RD.** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; **329**:1456–1462.
7. **Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR.** Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991; **324**:78–84.
8. **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**:1001–1006.