Effect of a Low- Versus Moderate-Protein Diet on Progression of CKD: Follow-up of a Randomized Controlled Trial

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Background: Whether low-protein-diet (LPD) as opposed to moderate-protein-diet (MPD) regimens improve the long-term survival of patients with chronic kidney disease (CKD) or induce protein-caloric malnutrition is unknown.

Study Design: Intention-to-treat analysis of follow-up data from a randomized controlled trial.

Setting & Participants: 423 patients with CKD (stages 4-5) were randomly assigned between January 1999 and January 2003 and followed up until December 2006 or death. The first phase of follow up was from January 1999 to June 2004; additional follow-up was from July 2004 to December 2006.

Intervention: LPD versus MPD (protein intake, 0.55 vs 0.80 g/kg/d).

Outcomes: Protein-caloric malnutrition (defined as the occurrence of 1 of the following: loss of body weight $>$ 5% in 1 month or 7.5% in 3 months or body mass index $<$ 20 kg/m^2 with serum albumin level $<$ 3.2 g/dL and normal C-reactive protein level [$<$0.5 mg/dL]), dialysis, death, or the composite outcome of dialysis and death.

Results: Baseline mean age was 61 years, estimated glomerular filtration rate was 16 mL/min/1.73 m^2, proteinuria had protein excretion of 1.67 g/d, body mass index was 27.1 kg/m^2, protein intake was 0.95 g/kg/d, and there were 57% men. Duration of follow-up was 32 months (median, 30 months; 25th-75th percentiles, 21-39). Average protein intakes were 0.73 $\pm$ 0.04 g/kg/d for the LPD and 0.9 $\pm$ 0.06 g/kg/d for the MPD. 3 patients (0.7%) met criteria for protein-caloric malnutrition. 48 patients died (11%), 83 initiated dialysis therapy (20%), and 113 (27%) reached the composite outcome. In unadjusted Cox survival analyses, effects of the LPD on these outcomes were 1.01 (95% CI, 0.57-1.79), 0.96 (95% CI, 0.62-1.48), and 0.98 (95% CI, 0.68-1.42), respectively.

Limitations: Low event rates for dialysis therapy initiation and death.

Conclusions: Most patients, who were regularly followed up in CKD clinics, were acceptably adherent to the prescribed dietary protein intake restrictions; the LPD and MPD did not lead to protein wasting; and the LPD did not decrease the risk of death or dialysis therapy initiation compared with the MPD.

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INDEX WORDS: Chronic kidney disease; low-protein diet; outcomes.

The effect of dietary protein restriction on the survival of patients with chronic kidney disease (CKD) is unknown. The rationale for such an effect is based on the ability of protein restriction to control several mechanisms of disease that are believed to be responsible for the high morbidity and mortality of patients with failing kidneys. Decreased protein, sodium, and phosphate intake is able to reduce the accumulation of nitrogenous compounds; optimize serum levels of bicarbonate, potassium, and phosphate[1-4]; prevent the development of severe secondary hyperparathyroidism[5,6] and resistant hypertension[7,8]; and reduce proteinuria[9,10] and the degree of anemia.[11]

A large body of evidence indicates that advanced stages of CKD, including end-stage renal disease requiring renal replacement therapies, are characterized by high rates of adverse outcomes.[12] However, it still is uncertain whether achievement of the clinical and metabolic goals indicated by international guidelines with dietary interventions decreases the risk of dialysis therapy and death in patients with CKD.

Only recently, the Modification of Diet in Renal Disease (MDRD) Study Group has inves-

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tigated the effects of a low-protein diet (LPD) on the onset of kidney failure and mortality through extended follow-up after trial completion.[13] This study explored whether assignment to an LPD (0.58 g/kg/d) compared with the usual-protein diet (1.3 g/kg/d) influenced the risk of reaching end-stage renal disease and the composite outcome of kidney failure requiring dialysis therapy and all-cause mortality. However, the major limitation of this study is the absence of clinical follow-up and dietary information after trial completion.

We have recently reported data from a randomized controlled trial of patients with CKD stages 4-5 (estimated glomerular filtration rate [eGFR] $<$ 30 mL/min/1.73 m^2) of the metabolic effects of 2 diet regimens based on different protein content: 0.55 and 0.80 g/kg/d.[4] In the present study, we report results of a 48-month follow-up phase of the initial trial. This study sought to determine: (1) whether the risk of malnutrition, the major drawback of an LPD, is considerable and increases as protein intake decreases; (2) the extent to which patients adhere to the prescribed diet regimen over time; and (3) whether patient outcomes are affected by diet prescriptions and nutritional status through improved metabolic control and achievement of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) target goals for 7 main cardiovascular risk factors.[14-17] The design of the study allowed us to test whether dietary prescription had a carryover effect after dialysis therapy was started.

METHODS

Study Design

The study was conducted at the CKD Clinic of the University Federico II of Naples, Italy, where 753 consecutive patients (CKD stages 2-5) were screened from January 1999 to January 2003. Details of the study have been described previously.[4] The study was approved by the local medical ethics committee. Briefly, the following enrollment criteria were used: aged 18 years and stable kidney function with basal eGFR $<$ 30 mL/min/1.73 m^2. After a monthly check of eGFR for 3 months (run-in), patients with stable kidney function (eGFR variability $<$ 15%) were deemed eligible for the study. During this period, patients maintained their previous diet. Renal function was expressed as eGFR calculated using the 6-variable MDRD Study equation.[18]

At baseline, 423 patients were enrolled in the study (Fig 1) and randomly assigned to 1 of the 2 test diets: 0.55 g of

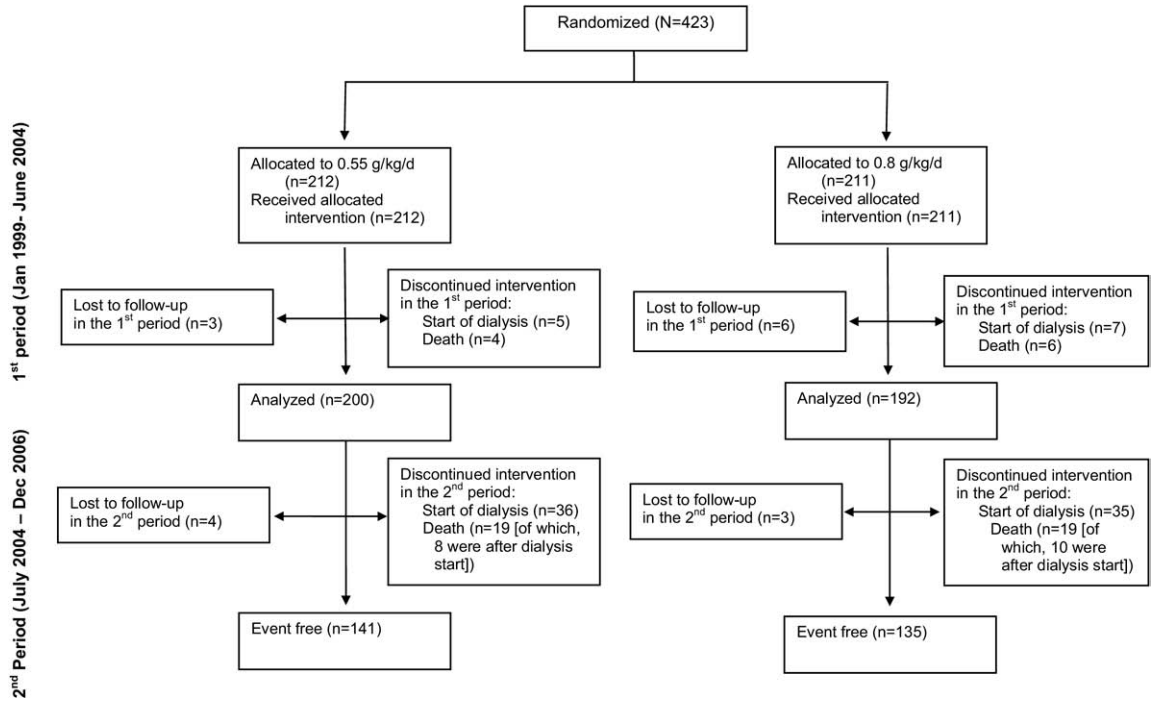

Figure 1. Patient flow diagram shows selection and discontinuation according to groups. The 1st period (January 1999-June 2004) corresponds to the duration of the randomized controlled trial, and the 2nd period (July 2004-December 2006) corresponds to long-term follow-up.