

Long-Term High Intake of Whole Proteins Results in Renal Damage in Pigs¹⁻³

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Abstract

Despite evidence of potential antiobesity effects of high-protein (HP) diets, the impact of consuming diets with protein levels at the upper limit of the acceptable macronutrient distribution range (AMDR) on kidney health is unknown. To test whether HP diets affect renal health, whole plant and animal proteins in proportions that mimicked human diets were given to pigs, because their kidneys have a similar anatomy and function to those of humans. Adult female pigs received either normal-protein (NP) or HP (15 or 35% of energy from protein, respectively) isocaloric diets for either 4 or 8 mo. The higher protein in the HP diet was achieved by increasing egg and dairy proteins. Although there were initial differences in body weight and composition, after 8 mo these were similar in pigs consuming the NP and HP diets. The HP compared with NP diet, however, resulted in enlarged kidneys at both 4 and 8 mo. Renal and glomerular volumes were 60–70% higher by the end of the study. These enlarged kidneys had greater evidence of histological damage, with 55% more fibrosis and 30% more glomerulosclerosis. Renal monocyte chemoattractant protein-1 levels also were 22% higher in pigs given the HP diet. Plasma homocysteine levels were higher in the HP pigs at 4 mo and continued to be elevated by 35% at 8 mo of feeding. These findings suggest that long-term intakes of protein at the upper limit of the AMDR from whole protein sources may compromise renal health. *J. Nutr.* 140: 1646–1652, 2010.

Introduction

Although the acceptable macronutrient distribution range (AMDR)⁸ for protein has been set at 10–35% of energy, the Institute of Medicine (IOM) Committee for the Reference Intakes for Macronutrients indicates that there is insufficient data on the long-term safety of the upper limit of this range (1). Despite this, high-protein (HP) diets are increasingly being recommended as one of the management strategies for weight control in overweight and obese individuals (2,3). HP diets appear to be effective with respect to reductions in appetite, body mass, fat mass, and retention of lean mass, at least in the short term (4,5). However, in view of the high prevalence of obesity, type 2 diabetes, and metabolic syndrome (6,7), it is important to understand the effect of high levels of dietary protein on health. This is particularly important for the kidney, because these populations are characterized by renal hyperfiltration and increased risk of kidney disease (8–10).

Consumption of HP diets in the short term leads to hemodynamic changes, increased renal workload, and an increase in glomerular filtration rate (GFR) (11–13). However, to our knowledge, there are no reports of long-term effects of HP diets at the upper end of the AMDR on human kidneys, and the effects of moderately HP diets on GFR in normal kidneys are unclear. Brandle et al. (14) examined individuals who had been consuming elevated protein diets for at least 4 mo and reported that protein intake was correlated to creatinine clearance. However, creatinine clearance does not necessarily reflect GFR, as demonstrated in a 2-wk HP intervention study in which the HP diet increased creatinine clearance but not inulin clearance (15). In overweight individuals consuming moderately HP diets (25% of energy) for 6 mo, GFR was higher compared with those consuming a reduced protein diet but not compared with controls who maintained their normal protein intake (16). Whether the adverse effect of dietary protein levels at the upper end of the AMDR (35% of energy) on GFR persists in the long term is not known.

Because changes in renal pathology take place before changes in renal function occur, evidence of dietary HP effects on renal pathology is limited to studies in rodents. These studies have provided evidence for adverse effects of HP diets on the normal kidney in the long term. Rats and mice exposed to HP diets have a greater prevalence of developing nephropathy, including glomerular hypertrophy, glomerulosclerosis, tubulo-interstitial

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³ Supplemental Table 1 and Figures 1–3 are available with the online posting of this paper at jn.nutrition.org.

⁸ Abbreviations used: AMDR, acceptable macronutrient distribution range; GFR, glomerular filtration rate; HP, high protein; IOM, Institute of Medicine; MCP-1, monocyte chemoattractant protein-1; NP, normal protein.

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fibrosis, tubule regeneration, and chronic inflammatory cell infiltration (17–20). However, one of the reasons that the IOM rejected these data as a basis for setting the AMDR for protein was the belief that evidence from rodent models was not applicable to human health. Furthermore, most of these studies have used a single source of purified protein, which do not reflect the human diet and may have unique effects on pathological changes in the kidney. Specific protein sources and amino acids

TABLE 1 Composition of experimental diets

Ingredient	NP	HP
	g/kg diet	
Wheat ¹	304	304
Barley ¹	76	76
Low ash poultry meal ²	44	44