

Effects of Dietary Protein Intake on Renal Functions*

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The effects of proteins on renal functions have been studied extensively in several mam-

malian species. Early observations (1928) identified harmful effects of protein ingestion on the kidneys of the male gender of a strain of rats predisposed to naturally occurring renal failure.¹ Other early observations (1932) focused on acute renal hemodynamic changes in normal dogs associated with ingestion of meals varying in protein content.²

Research conducted between these early studies and the present time has resulted in considerable advancement in our knowledge of protein effects on the kidneys, but many aspects remain controversial or unknown. One caveat to consider in interpretation of results of many of the dietary studies has been failure to control variables other than protein intake. In particular, effects attributed to protein have not always been differentiated from effects of calories, lipids, or inorganic constituents of diets.

Protein Effects: Normal Kidney Acute Effects after a Single Meal

Smith³ cites work by Moustgaard and others that demonstrated that a single high protein meal (30 to 60 g casein/kg body weight) given to a dog caused an increase in glomerular filtration rate (GFR), which reached a maximum at 3 to 6 hours and returned to normal after 24 hours. When protein was administered at intervals of 10 to 12 hours, fasting GFR did not return to baseline values but stabilized after 3 days of feeding. When a low protein intake was resumed, GFR returned to initial values in 4 to 5 days. The increase in GFR associated with meat feeding is paralleled by an increase in renal plasma flow (RPF).

These early studies in dogs have been duplicated in several other mammalian species with qualitatively similar results.

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However, species vary in the magnitude of the response.

Chronic Effects of High Protein Diets

Increase in kidney size in rats placed on a high protein diet was reported in 1932.⁴ The same effect has been noted in numerous other species, including dogs. The number of nephrons is fixed near the time of birth, so the increased size is due to changes in existing nephrons. Hypertrophy predominates as the mechanism regardless of age, although in immature rats some hyperplasia occurs. Although all segments of the nephron increase in size following protein-induced hypertrophy, studies in rats indicate that a preferential degree of hypertrophy occurs in the thick ascending limb of the loops of Henle.⁵ Recent attention on progression of renal disease has focused on glomerular hypertrophy, despite generalized hypertrophy of all segments of the nephron.

Mechanisms of Protein Effects: Normal Kidneys

Although both acute hemodynamic effects and chronic hypertrophy effects of protein ingestion are well documented, mechanisms involved in each and their potential interrelationships are only partially defined. Acute hemodynamic changes can be induced by direct injection of amino acids into the renal artery, and such experiments have led to the theory of an intrarenal tubuloglomerular feedback mechanism as a basis for the increase in RPF and GFR.⁶ An effect is achieved when amino acids are given orally as well. These positive effects from amino acids indicate that the process of digestion of protein is not essential for renal hemodynamic effects. Not all amino acids are equipotent, but a variety of both essential and nonessential amino acids have effects in dogs.⁷

Other studies demonstrate a role for polysystemic mediation of the renal changes, and a case has been made for glucagon as a significant player in this mediation. Some studies support a polysystemic pathogenesis but suggest that glucagon is not the only factor involved.^{8,9}

More recent studies demonstrate the presence of many growth factors in association with the process of hypertrophy. However, the triggering mechanisms and the orchestration of the event still require substantial definition. Hypertrophy has been investigated mostly with stimuli other than protein intake (such as reduction in renal mass), and it is not clear whether all stimuli operate to cause hypertrophy by the same pathway. An old and still popular theory of the genesis of hypertrophy is the “work” theory. With a postprandial increase in GFR, the filtered load of solute is increased and increased tubular resorption of many components must be performed to maintain homeostasis. The active transport processes constitute tubular “work,” stimulating hypertrophy.¹⁰ The “work” theory would tie acute renal effects of protein ingestion to chronic effects, but a direct relationship between the two has never been proven.

Another theory of the mechanism of hypertrophy states that total renal mass is governed by perception of total body mass through an organ-specific feedback system that is independent of renal “work.” This theory is supported by studies such as one utilizing diversion of urine from one kidney into the postcava; renal hypertrophy did not occur despite an increase of 50% in the renal excretory “work” by the anatomically intact kidney.¹¹

The Self-Perpetuation Theory of Progression of Renal Failure

Micropuncture techniques have been used to investigate renal hemodynamics in a strain of inbred rats (Munich Wistar rats) in which surface glomeruli are accessible to puncture.¹² In a series of studies, it was found that a 5/6 reduction of renal mass led to an increase in intraglomerular capillary pressure in residual nephrons. Subsequent to reduction of renal mass glomerulosclerosis and mesangial matrix accumulation were observed. A cause-effect relationship between glomerular hypertension and morphologic deterioration of the kidney was postulated, and the self-perpetuation theory of renal damage was born. According

to this theory, once functional renal mass is reduced to some critical level, the glomerular capillary hypertension that develops causes progressive renal injury, even if the original disease that caused reduction of renal mass is no longer present. The reduction of renal mass by surgical ablation of renal tissue is commonly referred to as the “remnant kidney” model of renal failure. The progression of renal lesions and decline in renal dysfunction in rats with “remnant kidneys” led to the question of whether the same changes occurred in other species.

Micropuncture studies on “remnant kidneys” of both dogs and cats have demonstrated that single nephron GFR, glomerular capillary pressure, and glomerular size are increased.^{13,14} The surgical reduction of renal mass results in development of histologic lesions in the “remnant kidney” of both dogs and cats.¹⁵⁻¹⁷ In both species, GFR increases after renal ablation in association with com-

pensatory hypertrophy, and in dogs studied for 2 years or more after 15/16 reduction in renal mass a decline in GFR and development of terminal uremia is common.^{18,19} A decline in GFR has not been noted in cats with “remnant kidneys,” but follow-up studies in these cats have been limited to 1 year in duration.²⁰⁻²²

Role of Protein in Progression of Renal Injury

Previous to the self-perpetuation theory of renal failure, dietary protein restriction was advocated for extrarenal benefits. Clinical observation revealed that protein restriction alleviated some of the clinical signs of uremia, presumably because “toxins” generated during protein catabolism were produced in smaller amounts if less protein was available for catabolism. This rationale for protein restriction obviates a need for protein restriction until signs of uremia appear. On the other hand, if dietary protein intake influences the rate at which renal disease progresses, then imposing protein restriction before the onset of development of signs of uremia would be rational. Studies demonstrated that in “remnant kidney” rats, dietary protein restriction was beneficial, reducing intraglomerular hypertension and decreasing the severity of renal lesions.²³ This benefit, which corroborated observations made some 40 years earlier on protein effects on rats, led to the advocacy of protein restriction as a renoprotective maneuver for species other

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than rats. In addition to glomerular hypertension, other factors associated with reduction of renal mass also have been incriminated in progression of renal disease. These include renal hypertrophy,²⁴ which also is influenced by protein intake.

Although the data are convincing for an effect of dietary protein on progressive renal injury in rats, data from other species are not. It would appear that two points should be considered:

- Is glomerular hypertension/hypertrophy injurious to all species or are rats particularly vulnerable?
- Is modulation of protein intake effective in reducing glomerular hypertension/hypertrophy in species other than rats?

Studies in “remnant kidney” dogs document that GFR and renal hypertrophy are influenced by dietary protein intake.²⁵⁻²⁷ However, these whole animal studies do not distinguish between a change in GFR due to increased glomerular capillary pressure or increased filtration surface (glomerular hypertrophy). Only one micropuncture study has been reported from “remnant kidney” dogs in which effects of dietary protein intake were examined. In this study, effects of a 16% and a 32% protein diet were compared. Results indicated that single nephron GFR was greater in dogs on the 32% protein diet but glomerular capillary pressure was not higher in this group.²⁸ On the other hand, glomerular volume was greater in dogs receiving the 32% protein diet than in dogs receiving the 16% protein diet. The greater glomerular volume provided a greater surface area for filtration, explaining a higher single nephron GFR with the 32% protein diet.

Dogs with Renal Dysfunction: Feeding Experiments

Several studies have addressed the issue of effects of protein intake on renal function and morphology in dogs with reduced renal mass. Most of these studies have treated the kidneys as a “black box” and determined the extent of morphologic and functional changes rather than investigating presumed mechanisms of their occurrence. These “black box” studies have served a very useful purpose because current theories concerning the pathogenesis of progression of renal

failure are not restricted to glomerular hypertension and hypertrophy. Mechanisms not yet even postulated may also exist. Should mechanisms other than glomerular hypertension and hypertrophy play a role, they would presumably be uncovered by such “black box” studies.

A few studies have compared diets in dogs with naturally occurring renal diseases.²⁹⁻³² In all instances diets varied in several components other than protein. Since dogs were managed clinically, they sometimes received nondietary treatments that could have affected disease outcome. The unknown etiology of the naturally occurring disease also provided potential for considerable variation between dogs in the rate of progression of disease by mechanisms unrelated to diet. These studies have provided some information to veterinarians on clinical responses to various commercially available foods, but they have not been able to define the role of dietary protein intake on progressive renal injury.

Several studies have examined effects of diet in dogs with “remnant kidneys.”^{17,18,26,33-35} This model has the advantage of normal renal morphology in the “remnant kidney” at the onset of dietary manipulations. Subsequent changes in renal morphology can then be attributed to the reduction of renal mass as modified by the diet or other variables being studied. Some of these studies have been conducted using commercially available diets that varied in amounts of several components including protein. When differences between diet effects were found in these studies, effects could not be attributed specifically to protein.

Other studies have used diets that were formulated so that protein was the only variable (except for carbohydrate sources to maintain the diets isocaloric); results from these studies are more revealing regarding protein effects. Table 1 provides a summary of experiments done to determine diet effects on dogs with reduced renal mass. When attention is focused on those experiments in which protein has been isolated as the only variable, the data are overwhelmingly indicative of a failure to demonstrate a protein effect on the functional or morphologic deterioration of kidneys of “remnant kidney” dogs.

It remains possible, however, that some forms of naturally occurring renal disease in dogs may be responsive to protein restriction. “Remnant kidney” dogs have a mild but not a marked systemic hypertension.^{36,37} Data on systemic

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TABLE 1
Summary of Experiments on Dogs with Reduced Renal Mass that Examined Renal Effects of Diet

Model	Diets Compared	Duration	Conclusions, Comments	Ref.
3/4 NX	Three commercial diets varying in many components; protein levels of 44%, 14%, and 7% of metabolizable energy (ME)	Up to 48 months	No evidence of adverse effect of diets on renal function. Histologic trend towards more severe lesions in the highest protein diet. No diet effects demonstrated by electron microscopy. Dogs were nonazotemic for most of the study.	33,34
11/12 NX	Three commercial diets varying in many components; protein levels of 44%, 14%, and 7% of ME	40 weeks	No evidence of functional deterioration on any diet; no morphologic assessment of kidneys was reported.	26
11/12 NX	Three commercial diets varying in many components; two levels of protein; 41% and 15%–16% ME	8 weeks	Renal lesions developed; severity of lesions was related to decrements in GFR but not to diet.	17
15/16 NX	Two experimental diets designed to vary only in protein levels; 31% and 16% ME	24 months	No differences between groups in deterioration of renal function or in severity of renal lesions.	18
11/12 NX	Two experimental diets designed to vary only in protein levels; % ME unclear; diets were 40% and 14% protein	100 weeks	No functional deterioration with time with either diet; no difference in severity of renal lesions between diets.	35
½ NX Geriatric dogs	Two experimental diets designed to vary only in protein levels; protein levels of 31% and 16% ME	48 months	No functional deterioration with time with either diet; no difference in severity of renal lesions between diets.	42
½ NX Geriatric dogs	Three experimental diets; 30%, 34%, 20% ME; fat content of 30% diet 2× others	48 months	No functional deterioration with time with any diet; no difference in severity of renal lesions between diets.	43

NX = nephrectomy.

blood pressure in dogs with naturally occurring renal disease are somewhat controversial, due in part to the inconsistency in results obtained by indirect methods of blood pressure measurement. One comprehensive study of blood pressure in dogs with naturally occurring renal failure suggests that systemic hypertension usually is mild.³⁸ Primary glomerular diseases with marked proteinuria make up a minority of cases of naturally occurring renal failure in dogs. Samoyed dogs with severe proteinuria due to a sex-linked hereditary defect in glomerular basement membrane formation were fed two commercial diets that differed in the quantity of many components including protein. The diet restricted in nutrients delayed the onset of glomerular deterioration and azotemia.³⁹ Further study will be required to

establish if minority subpopulations of dogs with renal failure due to diseases such as Samoyed dogs derive any benefit from dietary protein restriction.

Progressive loss of renal mass by a variety of mechanisms eventually leads to a common clinical entity (uremia) with common pathophysiologic responses employed to strive for homeostasis. Morphologic characteristics of kidneys can vary initially depending on etiology but also evolve to a common character referred to as “end stage” kidneys. Studies of kidney tissue from humans with naturally occurring renal diseases have revealed that progression of tubulointerstitial lesions is a better predictor of progression of renal disease than is progression of glomerular lesions.⁴⁰ A “hypoxia theory” postulates that even when the

inciting disease is glomerular, delivery of blood via efferent arterioles to the tubulointerstitium becomes compromised, leading to tubulointerstitial injury.⁴¹ In dogs the most common form of renal disease is one in which tubulointerstitial lesions predominate. The similarity between morphologic changes in the “remnant kidney” and those encountered in dogs with the prevalent form of naturally occurring renal disease is striking, such that it is doubtful that the two forms could be differentiated from each other by a veterinary pathologist. Until data are provided to disprove the “remnant kidney” model as representative of the common form of chronic renal disease occurring naturally in dogs, results obtained using this model provide the best basis for drawing conclusions about protein effects on the progression of renal disease in dogs.

Older dogs have a higher incidence of chronic renal disease than young dogs, and restricting protein intake in these dogs has been advocated as a renoprotective maneuver. In a study designed to test this hypothesis, experimental dogs 7 to 8 years of age were divided into two groups. Dogs in both groups had uninephrectomy performed to increase vulnerability of the remaining kidney to any protein effects. One group was fed a low protein diet, and the other group received a high protein diet for the subsequent 4 years.⁴² Results of this study indicated that there were no adverse effects of the high protein diet (Table 1), and mortality was actually higher in the low protein group. A similar study was conducted in another laboratory, and, likewise, no adverse effect of high protein diets was detected.⁴³ In the latter study, however, increased mortality in dogs receiving the low protein diet did not occur.

Cats with Renal Dysfunction: Feeding Trials

Two studies have examined effects of dietary protein intake on the kidneys of cats with reduced renal mass, but results of the studies were markedly different. In the first study,^{21,44} two diets were formulated that differed in protein content (20% and 38% ME from protein), were high in fat content (36% dry weight), but were nearly identical in other noncarbohydrate components. “Remnant kidney” cats were divided into two groups, and each group received one of the diets for 12 months. The low protein diet was less palatable,

and thus the group receiving this diet had reduced intake of calories and other nutrients in addition to protein. At the conclusion of the study the group fed the protein/calorie-restricted diet had a much lower score for glomerular lesions than the group fed the other diet. Other differences between groups that were associated with diet included transient development of hypokalemia and a large weight gain in the protein/calorie-replete group and development of hypoalbuminemia in the protein/calorie-restricted group. Diets for both groups used pork liver and casein as protein sources.

Studies in rats have demonstrated that restriction of calories could be as effective as protein restriction in slowing progression of renal disease.⁴⁵ A second study in cats was patterned after the first with the objective of distinguishing protein effects from calorie effects.²² In the second study, four diets were formulated to represent the combinations of low protein–low calorie, low protein–high calorie, high protein–low calorie, and high protein–high calorie diets. Soy and casein protein sources predominated in the diets. Cats were fed to duplicate caloric intake of cats in the previous study, but more protein was delivered to avoid protein malnutrition in the low protein groups. At the conclusion of 1 year of feeding trials, there was no effect of either protein or calories on the severity of glomerular lesions and the lesions were mild in all groups. Diets replete in calories were associated with higher scores for tubulointerstitial lesions, but these lesions also were mild.

The reason for a diet effect on glomerular lesions in the first study is not apparent. Speculation includes adverse effects of transient hypokalemia, protein source, metabolic differences associated with marked weight gain, other nutrient differences between diets, or an interaction of these factors. The conflicting results from the two studies of cats will require further study for resolution. The negative re-

sults from the second study indicate that protein restriction in cats with renal disease remains to be proven as an effective maneuver for ameliorating progression of renal disease.

At the conclusion of 1 year of feeding trials, there was no effect of either protein or calories on the severity of glomerular lesions and the lesions were mild in all groups.

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