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EFFECTS OF PROTEIN INTAKE ON THE PROGRESSION OF RENAL DISEASE

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CONTENTS

In the past decade there has been considerable interest in the role of protein intake on the progression of chronic renal disease (43, 45). This article reviews the evidence that protein restriction ameliorates the progression of renal disease in experimental animals and humans. It considers the potential mechanisms by which dietary protein modifies renal function and influences

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the progression of renal disease. It also addresses the potential impact of changes in protein intake on the measurements used to assess renal function and hence the progression of renal disease. I first describe how the progression of renal disease is assessed and the potential mechanisms responsible for its relentless course. Subsequent discussion focuses on the effects of dietary protein on kidney function and on the progression of renal disease.

ASSESSING THE PROGRESSION OF RENAL DISEASE

Chronic renal failure is characterized by a progressive and usually irreversible decline in glomerular filtration rate (GFR). It is caused by numerous diseases. Three major mechanisms have been proposed to explain the progressive course of renal disease (46): (*a*) persistent injury due to the initial pathogenic insult, (*b*) secondary glomerular injury either due to adaptive changes in initially normal or minimally affected glomeruli or to intraglomerular coagulation, and (*c*) secondary injury due to compensatory changes or to abnormalities in tubular and interstitial function. Distinguishing glomerular from tubular or interstitial abnormalities is sometimes difficult.

Measurements of GFR are used to estimate the mass of functional renal tissue or the number of functioning nephrons. The ideal markers of GFR are substances that are freely filtered across the glomerular capillaries, not secreted, reabsorbed, catabolized, or synthesized by the kidney. The substance should be harmless, be easy to administer, and measure accurately. Several exogenous compounds fulfill these requirements, but no endogenous substance is ideal to assess GFR. Clinically, however, the clearance of endogenous creatinine is used to assess GFR (50).

The concentrations of blood urea nitrogen (BUN) and serum creatinine have been used as indicators of the level of GFR. Urea is the final product of protein catabolism. It has a molecular weight of 60 and is freely filtered at the glomerulus. Subsequently about half of it diffuses back into the blood as the filtrate passes down the tubules. At low urine flow rates, tubular reabsorption of urea is enhanced, which leads to an increase in BUN. Increased protein intake and/or catabolism also increases BUN concentrations. Therefore, at any level of GFR, the BUN values may be affected by changes in urine flow and protein catabolism and/or protein intake.

Creatinine is produced from endogenous creatine and phosphocreatine in muscle (50). The quantity produced and excreted depends on muscle mass and, in a given individual, is relatively constant from day to day. Serum creatinine concentration is not affected by changes in protein catabolism but is affected by variations in protein intake, particularly meat. Most of the creatinine excreted in the urine is filtered, but one component depends on tubular secretion. In general serum creatinine concentration rises when GFR falls.

Changes in serum creatinine concentrations, particularly with decrements in GFR between 60 and 90% of normal, may be relatively small, however, and values may remain within the accepted limits for serum creatinine levels in a normal population (50). Although creatinine clearance accurately measures GFR in individuals with normal renal function, with progressive renal disease the creatinine clearance exceeds GFR. The ratio of creatinine clearance to true GFR increases progressively as GFR decreases because of an increasing contribution of creatinine secreted to the total amount of creatinine excreted in the urine (50).

Some researchers have proposed (58, 88) that in a particular patient, regardless of the etiology of the renal disease, a plot of the reciprocal of the serum creatinine concentration (1/serum creatinine) versus time is a linear function and that a change in the slope of this relationship indicates a change in the rate of progression of the renal disease. Another suggestion is that if a linear decline in 1/serum creatinine is valid for all patients with a variety of renal diseases, then patients can serve as their own controls and there is no need to compare different patient groups (57). Although the 1/serum creatinine versus time plots have been used to assess the progression of renal disease and the effect of therapeutic interventions, this approach has several problems. In many of the published studies, failure to consider loss of muscle mass, changes in creatinine intake, spontaneous stabilization of renal function, and particularly the effects of frequent follow-up visits and blood pressure–control measures may account for the beneficial effects of protein restriction on the progression of renal disease reported using the reciprocal of serum creatinine concentration (21).

MECHANISMS RESPONSIBLE FOR PROGRESSION OF CHRONIC RENAL DISEASE

Systemic Hypertension and Intraglomerular Hemodynamics

Systemic hypertension affects the kidney adversely and may cause renal disease (as in hypertensive nephrosclerosis) or accelerate loss of function in kidneys with established parenchymal disease (6). Careful documentation of the effects of hypertension control on the progression of renal disease in humans is limited, however. Hypertension may play a role in the progression of diabetic nephropathy, as suggested by evidence that proteinuria was present in diabetic patients with high blood pressure but not in normotensive diabetics matched for age, sex, body weight, and duration of diabetes (71). At the Joslin Clinic, hypertension was found in 81% of diabetics with microalbuminuria but in only 32% of matched controls without microalbuminuria (47). A genetic predisposition to hypertension was proposed as a major determinant of diabetic nephropathy (47). Evidence that blood pressure control amelior-

ates renal damage in experimental models of renal disease and in human glomerulonephritis and diabetic nephropathy has been reviewed recently (6). The mechanisms by which hypertension damages the kidney are not completely understood. It may produce vascular hypertrophy, which in turn leads to ischemic glomerulosclerosis, or it may induce glomerulosclerosis by causing intraglomerular hypertension and increasing glomerular blood flow.

Progression of renal insufficiency after a critical reduction in renal mass may be due to increased glomerular perfusion and elevated intraglomerular capillary pressures (15). According to this postulate, as affected glomeruli cease to function as a result of global sclerosis, less severely compromised glomeruli undergo further compensatory hyperperfusion, with resulting intraglomerular hypertension, which leads to injury, progressive sclerosis, and eventually total loss of glomeruli. The mechanisms by which intraglomerular hypertension develops and modifies glomerular cell functions so as to bring about sclerosis have not been identified. Several experimental maneuvers, including protein restriction, that suppress the early hemodynamic changes in the remnant glomeruli of rats with subtotal nephrectomy also reduce the extent of later glomerular changes, as predicted by the postulate (15). A low-protein diet reduces glomerular hypertension and subsequent glomerulosclerosis in rats with a remnant kidney (15). Conversely, as discussed below, high-protein diets increase glomerular hypertension and glomerulosclerosis.

Dietary Lipids and Hyperlipidemia

In experimental animals, increased cholesterol intake results in progressive glomerulosclerosis (41). A decrease in the levels of serum cholesterol and/or triglycerides ameliorate(s) glomerulosclerosis in spontaneously obese rats, rats with a remnant kidney, or rats with the nephrotic syndrome (39, 40). Exercise training, which reduces serum levels of cholesterol and triglycerides, decreases glomerulosclerosis and improves renal function in rats with a remnant kidney (28). Diets rich in linoleic acid, a precursor of arachidonic acid, decrease hypertension, the severity of proteinuria, and the degree of glomerulosclerosis and renal insufficiency in rats with subtotal renal ablation (29, 35). These effects may be mediated by prostaglandins. At least two mechanisms could explain how prostaglandins influence progressive renal disease: (*a*) they may directly affect renal hemodynamics, and (*b*) they may influence the coagulation system and platelet-endothelial cell interactions.

Hyperphosphatemia and Calcium Deposition

Increased phosphate excretion per nephron and hyperphosphatemia develop in untreated patients with progressive renal failure. A reduction in protein intake decreases phosphorous intake. Phosphorus restriction per se limits pro-

gressive renal insufficiency in rats with a remnant kidney or experimental glomerulonephritis (3). Thus, some of the benefits of protein restriction on the progression of renal disease might derive from concomitant phosphorous restriction (3). Studies of dietary protein restriction without a change in phosphorous intake indicate, however, that decreased protein intake per se can be beneficial (3). Data also indicate that phosphorus restriction, without protein restriction, can slow the progression of experimental renal disease (3). The mechanisms by which reduced phosphorus intake ameliorates the progression of renal disease are not known. Phosphate depletion may modify glomerular hemodynamics by decreasing cardiac output. It may affect leukocyte function and inhibit inflammatory responses. It could reduce the deposition of calcium-phosphorous at the site of renal injury. These mechanisms are not mutually exclusive, and all may contribute to the beneficial effects of phosphorus restriction (3).

Cellular Immunity

Progressive glomerulosclerosis is frequently associated with infiltration of the interstitium by inflammatory cells, particularly macrophages and lymphocytes. Proteinuria and declining renal function in various glomerular diseases in animals and humans have been associated with macrophage infiltration (9, 92). Macrophages are potentially destructive cells that can generate reactive oxygen species, engage in phagocytosis, and release enzymes capable of degrading collagen and elastin (64). Renal lesions characterized by the presence of macrophages, although progressive, are not usually associated with evidence of necrosis or acute destruction, however. Therefore, the contribution of immune cells to glomerulosclerosis may be related to their potential to modulate the biologic activity of intrinsic renal cells, particularly mesangial cells, rather than to their capacity to cause direct renal damage. Macrophages can stimulate the proliferation of fibroblasts and the synthesis of collagen, both prominent characteristics of interstitial nephrosclerosis. In addition, macrophages release interleukin-1, which can in turn release proteases that degrade collagen and elastin (64). Macrophage-derived factors also stimulate the proliferation of endothelial cells and enhance the capacity of endothelial cell surfaces to activate platelets and attract other monocytes (64). Therefore, infiltrating cells may contribute to the progression of renal disease in several models of renal disease and in human glomerulonephritis.

Renal Growth and Hypertrophy

Glomerulosclerosis is frequently associated with glomerular hypertrophy. Glomerular size increases after subtotal nephrectomy in animals and humans. Unilateral nephrectomy, which accelerates glomerulosclerosis in experimental models of glomerulonephritis, minimal change disease, and diabet-

ic nephropathy, stimulates the hypertrophy of affected glomeruli (46). In diabetes mellitus, glomerular hypertrophy precedes the development of nephropathy (95). Glucocorticoids, which accelerate glomerulosclerosis in rats with subtotal nephrectomy, promote renal hypertrophy and suppress collagenase activity (101). Other maneuvers that modify glomerulosclerosis also affect glomerular hypertrophy.

EFFECTS OF PROTEIN INTAKE ON RENAL FUNCTION

Short- or long-term administration of amino acids or protein-rich diets (12, 49, 51, 67, 74, 76) increases GFR between 22 and 100% in animals and humans; the magnitude of the rise depends in part on the amount ingested, the timing of the study in relation to when the food was eaten, and the control dietary conditions. Most studies have also indicated a significant but less marked rise in renal blood flow (12, 49, 74, 76, 80), although two groups found no change in renal blood flow 1 to 2 h after a protein-rich meal (26, 98).

In Experimental Animals

Dietary protein content affects the GFR in rats. Schoolwerth et al (91) found higher inulin clearances in rats fed a high-protein diet (40% casein) than in rats fed a low-protein diet (6% casein). Pennell et al (73) also found lower GFR values in weanling rats fed an 8% casein diet than in rats fed a normal protein diet (20% casein). GFR averaged 1.1 ± 0.16 ml/min/g of kidney weight in rats fed an 8% casein diet. The kidney weight averaged 293 mg. Absolute inulin clearance in these rats averaged approximately 0.3 ml/min. In rats fed 20% casein, kidney weight averaged 500 mg, with a GFR of 0.62 ml/min. When expressed per gram of kidney, the inulin clearance averaged 1.24 ± 0.12 ml/min in these normal rats, a value not markedly different from that found in protein-depleted rats. These results suggest that decreased protein intake reduces kidney mass and that this reduction is the main factor responsible for the lower GFR in these growing rats.

Micropuncture studies in rats have shown that a high-protein diet (40% casein) is associated with increased glomerular plasma flow and filtration rate per nephron compared with the rates of rats fed a low-protein (6%) diet (34, 94). Alternate-day feeding causes substantial oscillations in GFR and renal blood flow in normal rats through mechanisms independent of changes in extracellular fluid volume alone (27). Rats fed on alternate days had lower values for GFR and renal blood flow than rats of the same age fed ad libitum.

Dogs fed a high-protein meal showed acute increases in GFR and renal blood flow (51, 67, 96). Sheep fed a 14% protein diet had a mean GFR of 2.2 ml/min/kg body weight as compared with a GFR of 1.5 ml/min/kg body weight in sheep fed a 4.9% protein diet. These values are significantly

different from each other. Renal plasma flow was also lower in sheep fed the 1.9% protein diet (79).

In Humans

Pullman et al (77) found that increased protein intake increased GFR, effective renal plasma flow (ERPF), and the maximum transport of *p*-aminohippurate in normal adults. Table 1 summarizes the effects of receiving one of three different protein intakes for one week on GFR and ERPF in humans. Conversely, Nielsen & Bank (65) found no effect of changes in protein intake on renal function in normal subjects. Normal subjects fed a calorie-deficient diet, in which the distribution of calories among protein, fat, and carbohydrate was not controlled, had a fall in GFR when measured by creatinine clearance (89). In adults and children with protein-calorie malnutrition, a decrease in GFR and renal plasma has been reported (44). Klahr & Alleyne (42) found low values for GFR and renal plasma flow (RPF) in 10 adults with protein malnutrition. Values for both measurements increased significantly after protein repletion.

Hostetter (31) examined the renal hemodynamic response to a meat meal in 10 normal volunteers studied after they ate an average of 3.5 g/kg body weight of lean cooked beef-steak and, on a separate day, after they ingested a sodium-and-water load equivalent to that in the meat meal. As measured at 3 h after the meat meal or the sodium-and-water load, the GFR of those who ate the meat meal was 28% higher than that of subjects who had the salt load (90 $\pm$ 8 vs 114 $\pm$ 6 ml/min/1.73 m^2, $P<0.05$). Compared with basal values, GFR increased by 15% at 3 h after the meat meal, but this difference did not achieve statistical significance. Some subjects did not have an increase, and in those who did, the increase ranged from 5–46%. Renal blood flow increased, apparently because of decreased renal vascular resistance. Thus, in humans a meat meal causes vasodilation, an increase in GFR, and natriuresis. Changes in GFR after protein administration may be influenced by the type of protein

Table 1 Effect of protein intake on glomerular filtration rate and effective renal plasma flow in normal humans.[a] Adapted from Pullman et al (77)

Diet (g protein/kg body weight/day)	GFR[b] (ml/min)	ERPF (ml/min)
2.3 to 3.0	117.3 $\pm$ 4.3	640.2 $\pm$ 18.5
1.0 to 1.4	104.2 $\pm$ 2.9	570.8 $\pm$ 17.6
0.1 to 0.4	95.2 $\pm$ 3.1	538.2 $\pm$ 21.1

[a] Data are mean and SEM.
[b] GFR = Glomerular Filtration Rate; ERPF = Effective Renal Plasma Flow.

ingested. A milk-based protein did not increase creatinine clearance immediately but did raise it after 3–4 days (38).

Individuals with chronic renal disease and basal GFR values below 50 ml/min/1.73 m^2 did not show increased GFR after a protein meal (10). This lack of increase was suggested to reflect a lack of renal functional reserve, i.e. a setting in which functional nephrons were filtering maximally. By contrast, patients with a single kidney with or without renal disease (GFR values of 23–70 ml/min/1.73 m^2) had a significantly greater increase in GFR after an acute protein load than normals (86). In 24 patients with chronic renal insufficiency, GFR and RPF were measured after 4 weeks receiving a diet containing 30–40 g of protein/day and subsequently on a diet with 80–90 g of protein/day (90). There was a 20% increase in GFR on the high-protein diet, which did not depend on baseline GFR, as described also by others (99). Thus, patients with renal insufficiency had changes in GFR with long-term modification of protein intake. In contrast, a protein load in diabetic patients caused a fall in GFR, despite no changes in RPF or blood pressure (11). Conversely, diabetic patients with elevated creatinine clearance had decreased GFR when dietary protein was reduced from 3.5 to 1.5 g/kg/day, which suggests that increased protein intake may account for part of the increase in GFR that occurs in diabetic patients (48).

Mechanisms by which Protein Intake Affects Renal Function

The mechanisms by which protein ingestion or amino acid infusion increase GFR and RPF are not clear, although suggestions include changes in hormonal levels and/or renal production of eicosanoids, changes in tubuloglomerular feedback, alterations in renal metabolism, and release of known or unknown vasodilators.

Dietary protein or amino acid infusion stimulate insulin, growth hormone, and glucagon release, and pharmacologic doses of glucagon and growth hormone can increase GFR and RPF (19, 60, 72). Normal subjects given somatostatin plus amino acids intravenously had no increase in GFR and RPF (17). Concomitant infusion of growth hormone, insulin, and glucagon at levels that reproduced the blood concentrations of these hormones seen with amino acid infusion increased GFR and RPF. This result suggests that one or more of these hormones accounts for the elevated GFR seen after amino acid infusion. Since physiologic or pharmacologic increases in plasma insulin levels do not change GFR or RPF, a role for this hormone seems unlikely. Since after infusion of arginine hydrochloride RPF and GFR increased to a similar degree in normal and growth hormone–deficient individuals and plasma levels of growth hormone rose only in normal subjects, this peptide may not be the mediator of the increase in GFR (30). A role for glucagon is not firmly established because pharmacologic concentrations of this hormone

are required to increase GFR and RPF in dogs, and the increase is more pronounced when glucagon is administered into the portal vein (75). Thus, the increase in GFR after a protein meal may be mediated by some unidentified, vasoactive substance of hepatic origin. Indeed, acute protein ingestion reportedly did not increase GFR in patients with liver disease (20).

Inhibition of prostaglandin synthesis in subjects eating a normal-sodium diet attenuates the amino acid effect on RPF and GFR (87). The increment in GFR and RPF after amino acid infusion in normal subjects is blunted by a low-sodium diet (20 mEq/day); captopril administration restores the response (87). This effect may be related to changes in glomerulotubular balance (see below). These results suggest a role for prostaglandins and/or angiotensin in the renal functional response to amino acid infusion. Rosenberg et al (83) examined the effect of low- (0.55 g/kg/day) and high- (2 g/kg/day) protein diets on GFR and hormone production in 12 adults with a variety of glomerular diseases. The high-protein diet increased the plasma levels of renin and aldosterone and the urine excretion of prostaglandin E, and 6-keto-prostaglandin F_1, the stable metabolite of prostacyclin, rose.

Studies in dogs have excluded urea and sulfate derived from the protein as stimuli to the increased GFR (66, 67). Administration of a comparable salt-and-water load does not result in increases in GFR and RPF similar to those found after a meat meal. The lack of changes in hematocrit and protein concentration in blood also argue against an expansion of plasma volume being responsible for the increase in GFR.

Measurements of prostaglandins indicate that at least prostaglandin E_2 (PGE_2) is not increased after a one-time administration of a meat meal in humans (31). Stahl et al (97) found, however, that partially nephrectomized rats fed a high-protein diet had increased GFR and PGE_2 production. Indomethacin administration decreased GFR. Rats fed a low-protein diet had lower GFR values and decreased PGE_2 production. In these rats indomethacin did not decrease GFR. Increased glomerular production of PGE_2 was suggested to mediate the increase in GFR seen in rats fed a high-protein diet. Feeding weanling rats a low-protein diet decreases GFR and RPF and reduces markedly the urinary excretion of PGE_2 (23). Angiotensin II was elevated in these rats, and inhibition of the angiotensin-converting enzyme increased GFR in rats fed a low-protein diet to a level similar to that in rats fed a 23% protein diet. Thus, decreased PGE_2 production and increased angiotensin II synthesis may mediate the decrease in GFR and RPF observed in rats fed a low-protein diet.

Since dopamine increases RPF, GFR, and solute excretion, intrarenal dopamine was suggested as the mediator of several of the renal effects of protein (103). A protein load increased dopamine levels in plasma (when carbidopa, a dopamine decarboxylase inhibitor, was present) and caused

natriuresis and increased osmolar clearance (103). Without carbidopa, plasma dopamine did not rise, but dopamine excretion promptly increased.

Atrial peptide infusion increases GFR, but it probably does not mediate the renal hemodynamic changes observed after a meat meal because: (*a*) sodium intake and markers of plasma volume suggest no greater stimulus toward atrial peptide secretion after the meat meal, and (*b*) in animals, atrial peptide administration increases GFR to a greater extent than RPF (53), a pattern somewhat different from that observed after a meat meal.

Whether specific amino acids increase GFR directly or through some mediator is also unknown. Glycine can increase GFR when infused intravenously in dogs (74). An infusion of mixed amino acids has a similar effect in rats (56). Brezis et al (16) examined the functional effects of different amino acid mixtures in the isolated perfused rat kidney. Addition of either an amino acid mixture or 2 mM glutamine to the glucose-containing perfusate markedly decreased renal vascular resistance. Oxygen consumption increased, which suggested metabolism of amino acids by tubular cells. Amino acid–induced vasodilation was blocked by antimycin or rotenone, inhibitors of mitochondrial respiration, or when the kidney was perfused with α-aminoisobutyrate or other nonmetabolizable amino acids. The conclusion was that enhanced renal metabolism accounted for the decreased vascular resistance.

To study the mechanism for the increase in single-nephron GFR in response to protein, Seney & Wright (94) evaluated the tubuloglomerular feedback mechanism in rats with subtotal nephrectomy. The rats were fed isocaloric diets containing 6 or 40% casein for 10 days prior to study. Rats fed the 40% casein diet required a greater tubular flow rate to initiate a decrease in single-nephron GFR (93). A 40–50% decreased sensitivity of the tubuloglomerular feedback mechanism was observed, which lead to the conclusion that a high-protein diet causes failure of the normal mechanisms controlling GFR. The mechanism may be related to enhanced reabsorption of sodium and chloride in the loop of Henle. The increased reabsorption is most likely due to a marked hypertrophy of the thick ascending limb of Henle in rats fed a high-protein diet (13, 36).

In summary, the mechanism(s) underlying the variable increase in GFR in response to an acute protein load is (are) not completely characterized. The increase in GFR may be conditioned by the level of dietary protein intake, protein source, volume status, etiology of the renal disease, activity of the renin-angiotensin system, and production of renal eicosanoids. In contrast to the variable response of GFR to short-term protein loads, more long-term changes in protein intake apparently affect the level of GFR. How this change in GFR relates to the progression of renal insufficiency has not been defined.

EFFECTS OF PROTEIN ON THE PROGRESSION OF RENAL DISEASE

Most studies into the mechanisms by which an initial loss of renal function causes inexorable progression toward renal insufficiency have used experimental animal models. The most widely used model is one in which renal mass is decreased by ligating several terminal branches of the renal artery to one kidney and contralateral nephrectomy. This procedure decreases renal mass by approximately 60–85%. The animals develop proteinuria, hypertension, and glomerular sclerosis in the remnant kidney (15, 78). Although these abnormalities were first described in this animal model by Chanutin & Ferris in 1932 (18), the pathogenesis remains obscure, especially the relation of the renal infarction to the elevated blood pressure that follows.

One of the consequences of this remarkable decrease in renal mass is a marked hypertrophy of the remnant kidney. This hypertrophy is accompanied by marked increases of plasma flow and GFR per nephron (15). At the same time, structural alterations occur. All three glomerular cell types are involved. Adhesion of epithelial cells to Bowman's capsule may be seen in severely involved glomeruli. In some areas epithelial cells are detached from their underlying basement membrane. There is a prominent increase in mesangial cells and matrix (81). Despite a reduction in total GFR, the absolute excretion of protein, primarily albumin, by the remnant kidney is increased. A close linkage among glomerular hyperperfusion, hyperfiltration, and structural changes was suggested in studies involving dietary protein restriction. Feeding a low-protein diet to rats with a remnant kidney largely prevented the striking increases in glomerular plasma flow and capillary pressure that lead to hyperfiltration. Also, the accompanying proteinuria and structural alterations of epithelial cells are less severe (15).

In Experimental Animals

A substantial literature related to the potential harmful effects of dietary protein on renal function in normal animals or animals after subtotal nephrectomy has appeared since the 1920s. The evidence for a role of protein intake on the progression of renal disease in experimental animals was reviewed in detail in 1983 (43) and again in 1988 (45).

Work done in the past decade indicates that a low-protein diet given to rats shortly after subtotal nephrectomy but prior to the development of established renal disease attenuates the development of proteinuria, glomerular sclerosis, uremia, and eventual mortality (15). In rats with subtotal nephrectomy, the cause of progressive renal damage was proposed to be increases in glomerular pressures and flows; the beneficial effect of a low-protein diet was attributed

to normalization of these parameters. These studies (33) used rats fed a protein-restricted diet (6% protein) compared with rats fed higher-than-normal levels of dietary protein (40%), and the diets were initiated immediately after the decrease in renal mass.

Nath et al (62) examined the effect of protein restriction on the progression of established renal disease. After subtotal nephrectomy, rats were fed a standard rat chow (24% protein) ad libitum for 3 months. They were then grouped on the basis of serum creatinine concentration and fed isocaloric diets containing 6 or 20% protein. The groups were not pair fed. Three months later (6 months after subtotal nephrectomy), rats fed the 6% protein diet had decreased proteinuria despite higher GFR values. Histologic changes were similar in the two groups. Apparently, protein restriction can preserve renal function in rats with subtotal nephrectomy and established renal injury.

Hostetter et al (32) have shown that the extent of glomerular sclerosis and proteinuria is directly related to the amount of renal mass removed initially. The development of renal disease is also influenced by the age at which renal mass is removed. Rats underwent uninephrectomy at birth, 2, 4, and 8 weeks of age (69). Rats were fed a 22% protein diet and followed for 48 weeks. Weight gain and creatinine clearance were similar in all groups. Renal hypertrophy was greater in rats nephrectomized at 0 and 4 weeks than in the 8-week group. Proteinuria, hypoalbuminemia, and glomerular sclerosis were more severe in rats nephrectomized at a younger age than in those nephrectomized at 8 weeks. These data suggest that renal hypertrophy may mediate the glomerular sclerosis (69).

Diets low in protein may limit progressive renal disease but also retard normal growth. The effects of protein intake on nutritional status, renal function, and histology have been examined in rats with adriamycin-induced nephrotic syndrome (68). Animals were pair fed isocaloric diets containing 30, 10, or 5% protein. Rats fed 30% protein had marked proteinuria, diffuse glomerular sclerosis, and renal insufficiency by 24 weeks. Rats fed 5% protein had less proteinuria and stable renal function but developed malnutrition, as judged by weight loss and hypoproteinemia. Rats fed 10% protein also had stable renal function and less proteinuria and histologic damage, but they did not grow normally and hypoproteinemia persisted. This report underscores the need for additional information on the level of dietary protein that attenuates progression of renal disease but that also maintains adequate nutrition in the nephrotic syndrome. Renal function and growth were also examined after 23 weeks in three groups of rats—normal, subtotal renal ablation, and sham-operated—pair fed isocaloric diets containing 6, 14, or 22% protein. All rats fed a 6% protein diet did not grow normally. Growth was normal in rats fed the 14 or 22% protein diet. Rats with subtotal renal ablation fed 22% protein had died by 14 weeks. Although proteinuria was

greater in rats fed the 14% protein diet than in rats fed the 6% protein diet, creatinine clearance and survival were comparable. The conclusion was that rats with subtotal nephrectomy fed the 14% protein diet had normal growth and improved survival (25).

The origin of the protein used may also be important. The effect of feeding diets containing either 24% soya protein or 24% casein over a 3-month period was examined in normal rats and rats with a remnant kidney (102). Rats fed the soya lived longer and had less renal hypertrophy, proteinuria, and glomerular sclerosis than rats fed casein. Although the source of dietary protein may be important, differences in the absorption and utilization of the two proteins used in this study may account for the results obtained.

Most of the evidence for a beneficial role of protein restriction on the progression of renal disease has been obtained in rats, a species prone to develop spontaneous renal disease with time. The influence of dietary protein on renal function and morphology may be different in the dog. Dogs with a 75% decrease in renal mass were fed for 4 years diets containing 56, 27, or 19% protein (82). Greater GFR and RPF values were found in dogs fed diets containing 27 or 56% protein than in dogs eating 19% protein. No group of dogs had hypertension, deterioration of GFR, or increase in proteinuria, however. Although glomerular pathology seemed to increase with dietary protein, in most dogs histologic changes were minimal and did not correlate with GFR. There was also no correlation with dietary protein intake in 2 dogs that died of uremia. Thus, dogs respond to renal ablation differently than rats do. Others do not agree with this conclusion (14). Whether dogs require a greater loss of renal mass to develop progressive renal disease is unclear. Four years of feeding dogs different protein intakes, however, should have been sufficient to detect any potential harmful effects of protein on renal function. Since the development of progressive glomerular sclerosis and the response to dietary protein differs among species, extrapolation of results obtained in rats with subtotal renal ablation to humans with renal disease may not be warranted.

In Humans

The past decade has seen renewed interest in the use of low-protein diets in the treatment of progressive renal insufficiency, due mainly to the suggestive evidence that a low protein intake may slow or even halt the progression of renal failure. Several reported trials support the concept that protein restriction may modify the course of progressive renal disease. Because most of the published studies (24) are uncontrolled, however, the results are difficult to evaluate.

Two different protein-restricted diets have been used in patients with progressive renal disease: (*a*) a diet containing 0.6 g/kg/day of protein and (*b*)

a more restricted diet containing 0.3 g/kg/day of protein predominantly of "high biological value" supplemented with either essential amino acids or a mixture of essential amino acids and ketoanalogs of essential amino acids.

In a retrospective study, Johnson et al (37) analyzed the effect of restricted protein intake and reduced phosphorus absorption on serum creatinine concentration in patients with renal failure. The rise in serum creatinine concentration was less in these patients than in patients with unrestricted diets. The potential effects of frequent follow-up and blood pressure control were not considered, however. (37). Maschio et al (55) restricted dietary protein and phosphorus in 75 patients with chronic renal disease and followed them for 18 to 76 months. They reported a change in the slope of 1/serum creatinine in patients with moderate (mean serum creatinine concentration, 2.18 mg/dl) or severe (mean serum creatinine, 4.2 mg/dl) renal failure compared with that of patients ingesting an unrestricted diet. Most of the patients had hypertension; however, no description was given regarding blood pressure control or differences in the degree of hypertension in the different groups. Also, whether the patients fed restricted diets were seen more often than the untreated patients is unclear. The same group also examined the effects of a diet providing 0.6 g of protein/kg of body weight in patients with chronic glomerulonephritis, polycystic kidney disease, or chronic pyelonephritis (70). The control group consisted of patients with one of the three diseases listed above who ate an average of 70 g/day of protein. All three protein-restricted groups had slower progression of renal disease than control patients. Because the control groups were apparently studied retrospectively, evaluating the claim that deterioration of renal function was slowed is difficult.

The response of different renal diseases to protein restriction was also examined by El Nahas et al (22). Deterioration of renal function was slowed only in the group with tubulointerstitial disease. No beneficial effect was detected in patients with polycystic disease or hypertensive nephrosclerosis, and an equivocal benefit was observed in those with chronic glomerulonephritis.

The value of low-protein diets supplemented with various essential amino acids and ketoanalogs of essential amino acids in arresting the progression of renal disease is not clear. Certain studies suffer from the drawback that prospective and retrospective data are compared (4). Attman et al (5) found that GFR continued to decrease over a mean follow-up period of 5 months in diabetic patients with severe renal insufficiency (GFR in the range of 7.5 ml/min) receiving a diet containing 20–30 g/day of protein and supplemented with essential amino acids. After one year, only 2 of 21 patients had not reached end-stage renal failure that required transplantation or initiation of dialysis. In contrast, Zeller et al (104) have reported, in preliminary form, a beneficial effect of dietary protein restriction over 10 to 15 months in patients

with diabetic nephropathy in a randomized, prospective study in which blood pressure was well controlled.

In another study, 24 patients with chronic renal failure received a diet containing 20–30 g of protein supplemented with amino acids and their ketoanalogs (59). Renal functional deterioration slowed in 10 of 17 patients. At enrollment into the study, 6 of these patients had serum creatinine concentrations of 8 mg/dl or higher; that value showed no tendency to decline over an average of 22 months. As in other studies, the role of adequate blood pressure control during the prospective phase of the study and the possibility of spontaneous stabilization of renal function cannot be discerned. The authors state "there is no evidence that progression of chronic renal failure is slowed by more frequent visits" (8). This conclusion, however, may not be warranted, since the number of visits during the prospective follow-up period of 20 months appears to be similar to that during the average retrospective evaluation period of 32 months. This similarity would suggest more frequent visits in the follow-up period (59).

Barsotti (7) reported that a very low protein diet supplemented with ketoacids can slow progression of renal disease in patients who demonstrated renal functional deterioration while receiving a conventional low-protein diet. Walser et al (100) also suggested a therapeutic advantage of a ketoacid-containing diet. A role for ketoacids in this effect was suggested. Five compliant patients who showed a decrease in GFR while receiving a very low protein diet plus essential amino acids had a significant slowing of progression after the diet supplement was changed to ketoacids. In 6 other patients whose serum creatinine concentration was greater than 7.5 mg/dl, however, no effect of ketoacids on progression was observed. Adequate nutrition was apparently achieved in all patients, when assessed by body weight, creatinine excretion in the urine, and levels of serum proteins (100).

Rosman et al (84) studied 149 patients fed either a low-protein or an unrestricted, control diet for at least 18 months. In patients whose creatinine clearances ranged from 10–30 ml/min/1.73 m^2, the treatment consisted of 0.4 g protein/kg body weight. Patients with creatinine clearances greater than 30 ml/min received diets containing 0.6 g protein. No apparent adverse effects of the diets on body weight, or levels of serum calcium, albumin, and alkaline phosphatase were noted. Blood pressure control was the same in both groups. The authors concluded that protein restriction ameliorated the progression of renal disease. Also, low-protein diets appeared to decrease proteinuria in some patients. A word of caution is warranted. Some of the patients in this study received diets containing less than the minimum daily requirement for protein, which could affect the nutritional state of such patients during long-term therapy. Also, in patients with only slightly elevated serum creatinine concentration, a decline in renal function may be difficult to detect.

Acchiardo et al (1) also found slower progression of renal insufficiency, assessed by 1/serum creatinine, in patients ingesting 0.55 g protein/kg of body weight than in patients ingesting an unrestricted diet. No evidence of malnutrition was evident in these patients after one year on the restricted diet, as assessed by anthropometric measurements, levels of serum albumin, protein catabolic rate, and nerve conduction velocity.

Twelve patients receiving a diet containing 0.2 g protein/kg/day and about half of the amount of ketoacids usually prescribed for a period of 6–12 months had significant decreases in serum levels of urea, phosphate, and parathyroid hormone (52). Four of the subjects maintained a stable renal function for over a year. Serum albumin or transferrin levels did not change; however, body weight, creatinine excretion, and anthropometric measurements decreased significantly, which suggests loss of lean body mass with this severely restricted diet. Of note was the finding that the levels of plasma proteins were not a good indicator of inadequate nutrition.

The clinical course of 349 patients with renal insufficiency given a protein-restricted diet (0.6 g of protein, 40 kcal/kg body weight and 700 mg of phosphorus daily) has been reported recently (54). The authors claimed that over a mean follow-up period of almost 3 years, approximately 65% of the patients had no evidence of progression of their renal disease. There was also no evidence of malnutrition. Since changes in serum creatinine were used to evaluate functional deterioration, these data should be interpreted with caution, however.

EFFECTS OF PROTEIN ON TESTS USED TO ASSESS PROGRESSION OF RENAL DISEASE

Most studies on the influence of dietary protein on renal disease have used the slope of 1/serum creatinine vs time to assess progression. Since approximately 20% (range 10–30%) of creatinine generated may be derived from creatinine and creatine in meat, restriction of meat in the diet would be expected to decrease serum creatinine, which results in an elevation in the 1/serum creatinine. This change may be interpreted as an effect of the low-protein diet on the progression of renal disease even if the dietary restriction had not affected renal functional deterioration. Indeed, excretion of creatinine in the urine decreases after the initiation of a low-protein diet in patients with renal disease (59, 84). This decrease is probably due to decreased creatinine generation. A progressive and subtle decrease in muscle mass as a consequence of protein-restricted diets in patients with renal disease also may result in stabilization or a decrease in the levels of serum creatinine. This change, again, may be misinterpreted as an effect on the deterioration of renal function when 1/serum creatinine is used to assess progression. As discussed above,

protein restriction also decreases the levels of BUN even when renal function is deteriorating.

MECHANISMS BY WHICH PROTEIN RESTRICTION MAY AFFECT PROGRESSION OF CHRONIC RENAL DISEASE

If indeed changes in protein intake affect the progression of renal disease, they may do so through several mechanisms. Protein restriction decreases intraglomerular pressure and glomerular plasma flows in animals with experimental renal disease (15, 62). Occasionally protein restriction may decrease systemic arterial blood pressure (85). Consequently, protein restriction may have a beneficial effect on progression through decreases in intraglomerular pressure and flows. Protein restriction may also reduce renal hypertrophy in remnant nephrons and prevent some of the changes that lead to progressive disease. In addition, it decreases the degree of proteinuria in humans and in experimental animals, presumably by affecting the permeability of the glomerular capillary wall (15). A correlation between the degree of proteinuria and the progression of renal disease has been suggested.

Protein restriction may also affect immune mechanisms. The course of the renal disease could be modified by feeding a low-protein diet to rats with antitubular basement membrane antibody–mediated interstitial nephritis (2). The protective effect of protein restriction may have been due to impaired T cell–mediated injury.

Increased protein intake may be harmful to the interstitium because of increased ammonia production (61). Thus, dietary protein restriction might interfere with the progression of renal disease by reducing the dietary acid load and consequently the production of ammonia in the surviving nephrons (61). This effect, in turn, could inhibit activation of the complement system with its inflammatory and cytotoxic consequences.

Protein restriction may decrease the levels of serum lipids and may also decrease the movement of lipoproteins across glomerular capillary walls. If lipids play a role in the progression of renal disease, protein restriction may influence the progression of renal insufficiency by decreasing serum lipids. In addition, a reduction in protein intake is accompanied by a reduction in phosphorus intake. Phosphorus-calcium deposition may play a role in the progression of renal disease, and a decrease in protein intake may decrease the load of phosphorus and decrease renal damage (3).

Also, Nath et al (63) have suggested that renal hypertrophy results in metabolic alterations and increased oxygen consumption in remnant nephrons. Increased oxygen consumption may lead to renal damage because aerobically respiring cells such as those of the renal cortex sequentially reduce

oxygen to water through reactions that generate small amounts of potentially toxic oxygen radicals. Protein restriction by decreasing GFR and hence the filtered load of sodium may also decrease tubular cell metabolism and thus decrease in this way the generation of oxygen radicals. Clearly, therefore, protein restriction may influence the progression of renal disease through several different mechanisms.

SUMMARY

In summary, protein restriction appears to be of benefit in certain types of renal disease. Studies measuring GFR and using a concomitant control group are necessary to answer this question with certainty, however. The mechanisms by which changes in dietary protein influence the progression of renal insufficiency have not been defined. Further studies are needed to identify those patients and renal diseases that may benefit from dietary restriction of protein. Long-term studies designed to assess carefully the nutritional impact of prolonged periods of protein restriction on individuals with renal insufficiency are also required.

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