Dietary Protein and Renal Function[1]

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ABSTRACT

Protein intake has been recognized as a modulator of renal function for over half a century. This review analyzes the renal response induced by changes in habitual protein intake and with acute amino acid infusion or a meat meal in humans and animals. The pattern and magnitude of changes in GFR and creatinine clearance are examined along with a discussion of the effect of the variability of these measurements among individuals and populations on the interpretation of clinical studies. Potential mechanisms of protein-induced changes in GFR and creatinine clearance are examined, including changes in the hormonal milieu, glomerular hemodynamics, and other intrarenal processes. Habitual dietary protein consumption varies significantly with respect to age, gender, and lean body mass—factors that are well known to influence GFR. This correlation raises the possibility that (1) variation in dietary protein intake may account, at least in part, for the differences in renal function among individuals; and (2) the level of protein intake should be assessed in defining the normal range of renal function.

Key Words: Renal hemodynamics, GFR, creatinine clearance, hyperfiltration, dietary protein, amino acids, kidney

In health, many factors influence the GFR and creatinine clearance. Chief among them, and well known to nephrologists, are age, gender, body size, pregnancy, and dietary protein. Because of these factors, GFR and creatinine clearance are typically adjusted for body size (surface area) and compared with

normative tables for age, gender, and pregnancy, and recently, Lew and Bosch (1) proposed that creatinine clearances should also be adjusted for habitual dietary protein intake. Indeed, for over a half a century, it has been recognized that protein intake modulates GFR (2,3). Interest in this topic has been revitalized by increasing evidence of the importance of protein intake on the progression of renal disease (4,5). An understanding of the processes involved in the renal adaptation to changes in protein intake may provide insight into the pathophysiology of progression, as well as potential therapeutic strategies for its retardation. The purpose of this article is to review the effects of dietary protein on renal function, assessed from measurements of GFR and creatinine clearance, both in health and in renal disease. It is not our purpose to review the effects of dietary protein on the progression of renal disease. Despite the completion of several controlled trials (6-10), the utility of low-protein diets to retard progression remains unresolved and this question is the basis of ongoing clinical trials (11,12).

We will first review normal variation in dietary protein intake. Next, we will explore issues regarding measurements of GFR and creatinine clearance in individuals and in populations, which are essential for a proper interpretation of the studies of the effect of dietary protein on renal function. We will subsequently review the effects of habitual protein intake and acute protein loads on both GFR and creatinine clearance, including a discussion of the proposed mechanisms for these responses.

NORMAL VARIATION IN PROTEIN INTAKE

Protein accounts for 14 to 18% of energy intake in the United States; the average intake is roughly 90 to 100 g/day (13-16). The major sources of protein in the diet are meat, fish, and poultry (48%), followed by dairy products (18%) (17,18). Within the United States population, there is considerable variation in protein intake, associated in large part with age and gender. For example, among men 20 to 24 yr old, average protein intake is 105 ± 17 g/day (15,19). With aging, there is a gradual reduction in absolute protein intake by approximately 15% by 70 yr of age (15). For women, protein intake is 30 to 50% lower than in men for all age groups (19,20). This variation in protein intake parallels variation in body compo-

sition, especially muscle mass. Cross-sectional studies reveal approximately 40% lower muscle mass in women than in men—proportions that are maintained despite an age-associated decline in muscle mass in both men and women by approximately 15% (21). Factoring dietary protein intake by weight does not eliminate the variation associated with age and gender. Current recommendations for protein intake (0.80 g/kg/day) do not take into account differences in age and gender (22). Nonetheless, average protein intake in the United States exceeds this recommended value by approximately 40 to 50%, indicating a surfeit of protein for most subgroups within the population (17).

Food supply and food preferences also strongly influence dietary protein intake. Average intake in developing nations is 57.3 g/day, roughly 50% of intake in the United States and other developed nations (13). In vegans, a subgroup of vegetarians who ingest no animal products, average protein intake is 20 to 40% less than in lacto-ovo-vegetarians and omnivores (23,24).

In summary, the average protein intake in the United States and other developed nations is large and far exceeds the recommended daily allowance. However, there are wide variations in protein intake associated with differences in age, gender, body size, and dietary preferences. As shown below, these differences are mirrored by differences in GFR and creatinine clearance.

DETERMINANTS AND MEASUREMENT OF GFR AND CREATININE CLEARANCE

Assessing the studies that examine the effects of protein feeding and changes in habitual protein intake on renal function requires an understanding of the variability in renal function among individuals and over time in an individual, as well as an appreciation for the limitations of methods for the measurement of GFR and creatinine clearance.

Variability in GFR in Health and Disease

As discussed above, variability in GFR among individuals is associated, in part, with differences in age, gender, and body size (Figure 1). The surface area correction was first introduced to minimize variability in urea clearance results among normal adults and children (25–27). This correction is appropriate, because body surface area is more closely related to metabolic activity and renal size than are weight or height (28). The conventional value of 1.73 m^2 represents the mean surface area of men and women 25 yr of age. Nonetheless, adjusted mean GFR among 20- to 30-yr-old men is approximately 8% higher than among normal women of the same age
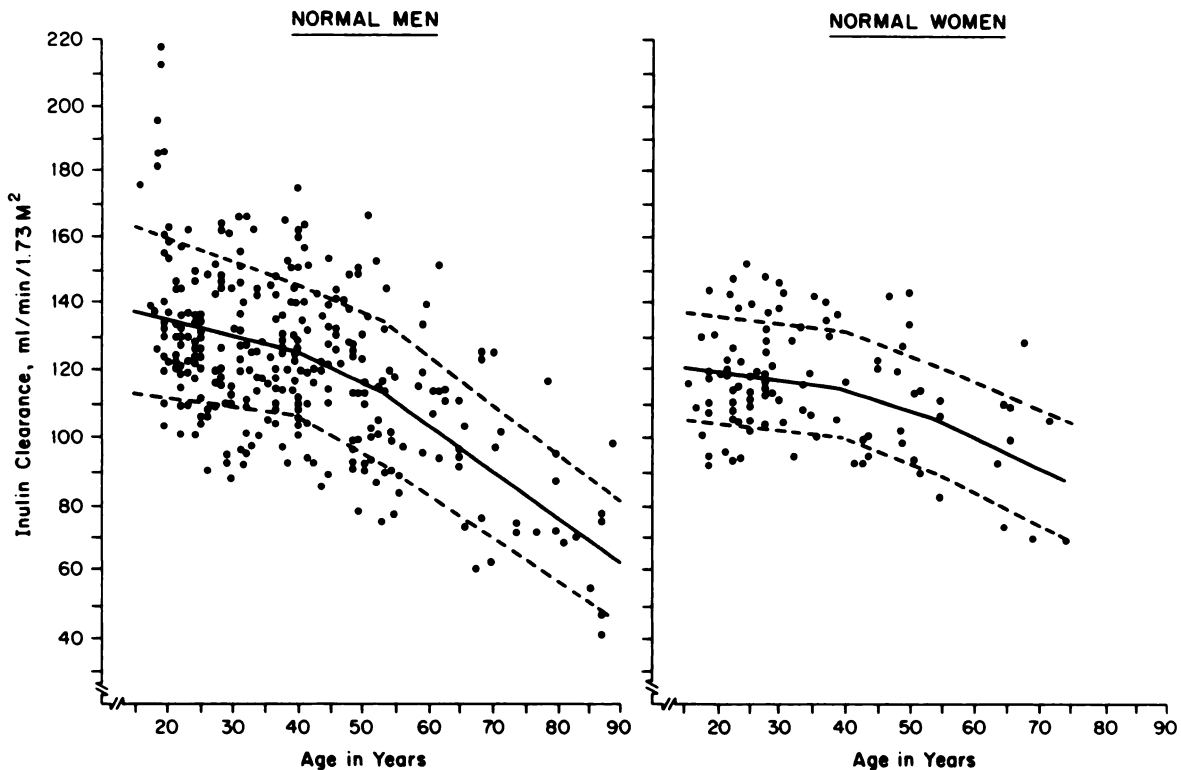

Figure 1. Normal values for GFR, adjusted for body surface area, in men and women of various ages. Reproduced from reference 30 with permission.

(130 and 120 mL/min/1.73 m², respectively) (29,30). In addition, GFR declines with age, in men and women alike. Both cross-sectional and longitudinal studies in normal men have demonstrated a decline by approximately 10 mL/min/1.73 m² per decade after the age of 30 yr (30). Thus, during the 50 yr from age 30 to 80, normal GFR declines by almost 40%, from approximately 130 to 80 mL/min 1.73 m². Cross-sectional studies in normal women indicate roughly similar results, but comparable longitudinal studies have not been performed. However, even after adjustment for age, gender, and body size, considerable variability among normal individuals remains: the coefficient of variation (CV, defined as the standard deviation divided by the mean) is approximately 15% for GFR (29,30).

Of course, GFR is also affected by renal disease, and for this reason, GFR is usually considered an index of the severity of renal disease. It follows that the variability in GFR among patients with renal disease reflects the variability in the severity of the disease, in addition to the factors previously discussed and, thus, may be considerably greater than among normal individuals. It is worthwhile noting, however, that renal disease causes multiple structural and functional abnormalities within the glomerulus that are not necessarily reflected by the level of GFR, especially in its early stages (31,32). Hence, GFR may not accurately reflect the severity of structural injury. In general, the structural and functional alterations correlate better in more advanced disease (33).

Measurement of GFR

GFR is measured indirectly as the renal clearance of an ideal filtration marker, such as inulin (29). A variety of low-molecular-weight substances, including [¹²⁵I]iothalamate, [⁹⁹ᵐTc]DTPA, and [⁵¹Cr]EDTA, have been shown to approximate the behavior of an ideal filtration marker and are most frequently used to estimate GFR in clinical studies (34). Irrespective of the filtration markers, measurements of GFR are limited by their imprecision, which further complicates analysis of the effects of factors, including dietary protein, on GFR (35). A typical procedure for measuring the clearance of inulin or a radioisotope-labeled filtration marker includes four 30-min urine collections, each bracketed by serum collections. The clearance is calculated for each urine collection, and the test result is expressed as the average of the four clearance measurements. The precision of the measurement is inversely related to the variability among the four clearance measurements (intratest variability) and variability from day to day (intertest variability). At normal GFR, the mean intratest and intertest CV for inulin and radioisotope-labeled filtration markers are approximately 10 and 7.5%, respectively. The cause of the imprecision in GFR measurements is, in part, incomplete bladder emptying and, in part, true variability in renal function during the clearance procedure and from day to day.

Measurement and Variability of Creatinine Clearance

Analysis of the effect of dietary protein on creatinine clearance, independent of its effect on GFR, requires an understanding of the determinants of creatinine clearance other than GFR and of the methods for its measurement (36). In practice and in many studies, including the recent study by Lew and Bosch (1), creatinine clearance is calculated from the creatinine excretion in a 24-h urine sample and a single measurement of serum creatinine concentration. We will briefly discuss determinants and measurement of both parameters and variability in creatinine clearance measurements.

In the steady state and in the absence of extrarenal elimination of creatinine, renal excretion equals generation. Creatinine, the end-product of creatine metabolism, is generated in proportion to muscle mass (Figure 2) (37,38). In normal men, 1.6 to 1.7% of the total creatine pool is converted to creatinine daily. After its release from muscle, creatinine is distributed throughout total body water and excreted by the kidneys. Hence, creatinine excretion is also related to muscle mass and varies with age, gender, and body mass (39). Among free-living individuals, the CV of daily creatinine excretion ranged from 10 to 15% (40,41). By contrast, persons on a metabolic ward had a CV ranging from 4 to 8% (42).

Creatinine is excreted by tubular secretion in addition to glomerular filtration. Hence, it is not an ideal filtration marker: its clearance exceeds GFR at all levels of renal function, with the difference between creatinine clearance and GFR representing the clearance of creatinine due to tubular secretion. As expected, creatinine clearance also varies with age, gender, and body size. The mean difference between creatinine clearance and GFR in normal subjects is approximately 10 to 15 mL/min/1.73 m², but it varies widely, due in part, to the imprecision in measurements. In patients with renal disease, however, the mean difference is greater. On average, clearance of creatinine due to tubular secretion is greatest (up to 25 mL/min/1.73 m²) when GFR is reduced moderately (40 to 80 mL/min/1.73 m²). At lower GFR, the difference is less, but the ratio of clearance of creatinine to GFR may exceed 2.0 (43).

There are several commonly used methods for the measurement of creatinine (36,44,45). Consequently, the normal range for serum creatinine varies among laboratories, depending on the type of calibration of equipment. In addition, regardless of the
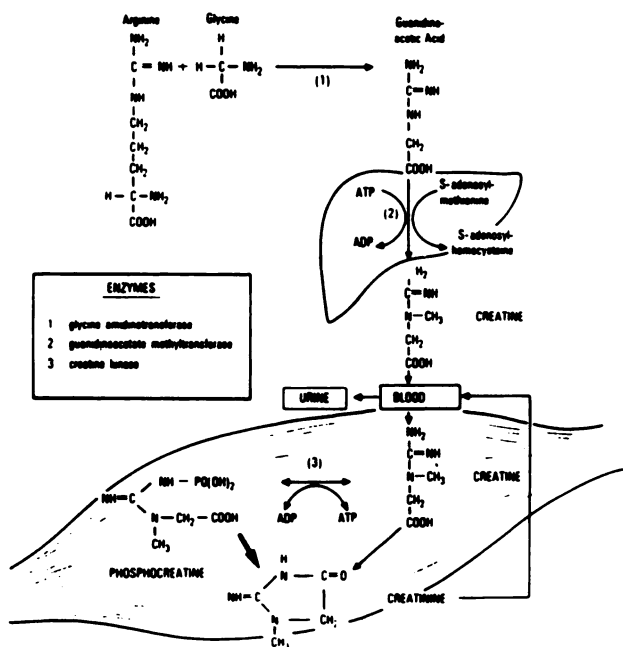
Figure 2. Pathways of creatinine metabolism. Reproduced from reference 37 with permission.

method, the measurement of serum creatinine is imprecise within the normal range. In one study, the CV for repeated measurements from aliquots from serum samples within the same "run" was 25.1, 7.3, and 1.9%, respectively, for samples with creatinine concentrations of 0.42, 1.32, and 4.38 mg/dL (46). Consequently, it may be difficult to interpret day-to-day differences in serum creatinine, especially in concentrations in the normal range, which are of most interest in detecting physiologic influences in GFR. Because of the higher concentration of creatinine in urine, the measurement of urine creatinine is more precise.

Similar to GFR, variability in creatinine clearance within the normal population adjusted for age, gender, and body size is roughly 15% (47). However, in contrast to GFR, the intertest CV for creatinine clearance appears higher than for the population CV. In several studies, the mean intertest CV for creatinine clearance on two successive days ranged from 10 to 27% (48–50). Of course, a major source of variability in 24-h creatinine measurements is incomplete urine collections. Other sources of variability include imprecision of serum creatinine measurement (as discussed above), variability in creatinine generation, and variability in renal function.

Effects of Variability in GFR and Creatinine Clearance Measurements on Clinical Studies

A consequence of the large variability in GFR among individuals is that comparisons of populations

may require a large number of individuals in order to detect differences in GFR between the populations (34). For example, if the CV among individuals within two populations is relatively low and the true difference in GFR between the populations is large, then it is necessary to study only a small number of subjects to detect the difference in GFR. However, if the CV is high, as it is in heterogenous populations, such as patients with renal disease, then it is necessary to study a large number of subjects. Similarly, if the true difference in GFR is small, as it is in subgroups within the normal population, such as the difference between men and women, a large number of subjects is also necessary. For these reasons, it may be difficult to detect differences in GFR among populations. In addition, a consequence of the large variability in GFR from time to time is that the effects of changes in dietary protein on GFR must be large in order to be detected (34). These limitations imposed by measurement variability may obscure the true effects of dietary protein on renal function and may account for some of the inconsistent results that we discuss below.

DIETARY PROTEIN AND GFR

A large body of experimental data has amassed both in experimental animals and humans that indicates that acute protein loads and changes in habitual protein intake significantly alter GFR and RPF rate. As in pregnancy-induced hyperfiltration and hyperemia, a wide variety of mechanisms for this interaction have been proposed; however, to date, no single factor has been identified to explain this phenomenon (51–53). Indeed, it appears that the hyperfiltration and hyperemia induced by an acute protein or amino acid load might be due to the combined effects of changes in the hormonal milieu as well as to direct effects on renal processes. The following sections will address the effects of habitual protein intake on glomerular function as well as the effects of meat meals and amino acid infusions. An in-depth analysis of the experimental data regarding the mechanism of renal hyperfiltration and hyperemia in response to protein loading is beyond the scope of this editorial review and has been reviewed elsewhere (53).

Effects of Habitual Protein Intake on Glomerular Function

Habitual protein intake, GFR, and creatinine clearance are directly related in both humans and animals. The magnitude of this response differs substantially among species, with humans having the fewest fluctuations in GFR associated with changes in habitual dietary protein. In dogs, transition from a "cracker meal" diet (carbohydrate) to a meat diet

resulted in 50 to 100% increases in GFR, findings that are echoed in seals and, to a lesser extent, rats (2,3,54,55). Pullman et al. (56) placed healthy humans on low (0.1 to 0.4 g/kg/day), medium (1.0 to 1.4 g/kg/day), and high (2.6 g/kg/day) protein diets for 2 wk and found increases in inulin clearances by only 9 and 22% (from 95 to 104 and 116 mL/min), respectively. RPF rate (p-aminohippurate clearance) responded in a similar fashion, and thus, the filtration fraction was unchanged—a finding that is universal in all studies of acute and chronic protein loading (see below). These modest changes in GFR and RPF with dietary protein manipulation have subsequently been verified by several investigators (57–60). However, others have noted little or no change in GFR in normals who have increased (61,62) or decreased (62,63) dietary protein. In summary, nearly all studies demonstrate an effect of habitual protein intake on GFR; however, the magnitude of this response is discrepant, ranging from nonsignificant to approximately 20%. This discrepancy may be explained by design characteristics of the individual studies, including the extent of dietary protein manipulation, the duration of study diet, the age of subjects, the method of GFR and RPF determination and their time-to-time variability.

The importance of the duration of protein restriction has not been formally addressed, although it may have important implications regarding the interpretation of studies of manipulations in habitual protein and subsequent changes in GFR. In each of the above trials, study diet was maintained for ≤3 wk; however, in studies of subjects in whom the dietary pattern was maintained for months to years, the differences in GFR are more pronounced. In vegetarians, creatinine clearance was 40% lower than in omnivores (1,60). Similarly, in patients with chronic malnutrition, GFR was 27 to 64% lower than after repletion of nutritional status (64–67). These studies suggest that renal adaptation might require a prolonged time period. In one study, near normalization of creatinine clearance was observed after only 1 month of feeding of children with kwashiorkor (65), suggesting that large changes in renal function in response to changes in habitual dietary protein intake can occur within only 1 month, although a substantially longer interval may be required to achieve the full effect.

The delayed response of GFR to changes in habitual protein intake raises the possibility of structural as well as hemodynamic alterations. Indeed, renal enlargement and hyperfiltration have been noted in patients receiving total parenteral nutrition (68,69). Conversely, the kidneys of Jamaican children who died with malnutrition were smaller than those of age-matched children who died of other causes (64). In addition, kidney sizes of well-nourished Jamaican

children were smaller than those of their age-matched American counterparts, perhaps reflecting the higher protein content of the American diet (64). Another example of combined hyperfiltration and renal enlargement is diabetes mellitus. Recently, Tuttle et al. (70) noted an enhanced amino acid–induced hyperfiltration response in poorly controlled insulin-dependent diabetics that was normalized after 14 days of strict glycemic control. Concurrent with this normalization was a reduction in whole-kidney size and a modest reduction in "habitual" protein intake (1.35 ± 0.11 to 1.14 ± 0.08 g/kg/day). Although the effect of protein loading in diabetics remains controversial, the data of Tuttle et al. (70) point to an association of protein-induced hyperfiltration, renal enlargement, and alterations in the hormonal milieu. The mechanisms underlying these associations require further examination. Potentially, changes in habitual protein intake may expand or contract the glomerular capillary surface area or alter tubular functions, such as tubuloglomerular feedback (see below).

Animal studies support an interaction of hemodynamic and structural changes in the response to changes in habitual dietary protein. In general, GFR and RPF change in parallel with modification of dietary protein, indicating a hemodynamic basis for the response. However, measurements of the determinants of single-nephron GFR (SNGFR) reveal structural changes as well (71). In severely protein-deprived rats, SNGFR was 35% lower than in controls on an isocaloric diet. The decrease was due to a 25% reduction in glomerular capillary plasma flow rate as well as a 50% reduction in the ultrafiltration coefficient (71). The glomerular cross-sectional area was also reduced, suggesting that the low ultrafiltration coefficient resulted from a decrease in effective filtration surface area. Conversely, it was shown many years ago that rats fed high-protein diets had an increase in overall kidney size (72). Both glomerular enlargement and tubular enlargement are apparent. In one study, rats on a high-protein diet (35% casein) had hypertrophy of the tubular epithelium (particularly the inner stripe of the outer medulla) and an increase in glomerular cross-sectional surface area as compared with rats on a low-protein diet (10% casein) (73). It is controversial whether the increase in glomerular cross-sectional area represents hypertrophy, hyperplasia, or the effect of increased blood flow and glomerular capillary pressure. Most recently, insulin-like growth factor (IGF-I) has been noted to be higher in the liver and glomeruli of rats fed a high-protein diet (36% protein) as compared with that in rats on a low-protein diet (9%) (74). IGF-I is known to induce renal hyperemia and hyperfiltration when infused into fasting rats (74,75) and thus might contribute to both the hemodynamic and

hypertrophic responses to changes in habitual protein intake. In summary, both animal and human studies suggest a significant effect of habitual dietary protein intake on renal hemodynamics and structure.

Effect of Meat Meals and Amino Acid Infusions on Glomerular Function

In 1932, H.W. Smith and coworkers observed a 100% increase in GFR in dogs fed a raw meat meal (2). It is now well recognized that GFR, RPF, and splanchnic blood flow rate increase within 1 h after a meat meal and remain elevated for several hours (53). As with changes in habitual protein intake, the magnitude of this response is highly species dependent, with humans having a less robust response than seals, dogs, or rats (2,55,58–60,76–84). Interestingly, the increment in creatinine clearance after a meat meal appears greater than the increment in GFR. Reasons for this discrepancy will be discussed in a later section. Attendant with renal hyperfiltration and hyperemia are a brisk diuresis and natriuresis. Several lines of evidence indicate that this postprandial response relates to protein and not to other components of the diet. First, the infusion of amino acids into the stomach or intravenously mimics the response to a meat meal. A range of potency of individual amino acids has been identified with nonessential amino acids generally being the most potent and branched chain amino acids having little or no stimulatory effect (85–87). Second, the ingestion of carbohydrate and fat meals failed to induce changes in renal hemodynamics (2,80). Finally, the infusion of equivalent electrolyte and osmotic loads (78) or the catabolic byproducts of meat (sulfate and urea) (88,89) did not alter renal hemodynamics.

Response to acute loads likely explains the effect of intermittent feeding. In rats fed only on alternate days for a 25-wk period, GFR and RPF were approximately 20% higher on the feeding days as compared with the fasting days (90). Similar results were observed in rats maintained on an 8-h feeding–16-h fasting schedule (91). In humans receiving parenteral nutrition 12 h/day, creatinine clearance was 70% higher during the infusion period as compared with during the subsequent 12-h rest period (69). The response to protein feeding also may explain, in part, time-to-time variability in GFR. An example might be the small diurnal variation in GFR (an approximately 10% increase late in the day) observed in humans by some (30,60), but not all, investigators (92). Diurnal variation of GFR has also been noted in quadriplegics, arguing against a role for physical activity in this effect (93).

Another important question is whether habitual protein intake may condition the renal response to an acute protein load. In one study, normals conditioned on a low-protein diet for 3 wk had a rise in GFR in response to a protein meal that was nearly double the response observed when the same subjects were conditioned on a normal protein diet (58). In another study, the percent rise in RPF and GFR was not different in normals conditioned on a high (2 g/kg/day) and low (0.44 g/kg/day) protein diet for 6 days (59). This discrepancy might reflect the longer duration of the conditioning in the first study. Interestingly, in both studies, the baseline GFR was lower during conditioning with a low-protein diet. A study of the response to an acute protein load in individuals on habitually low-protein diets, such as vegans, would help to clarify this issue.

Indeed, the renal adjustments to acute changes in protein intake have been postulated by Brenner et al. (4) to reflect evolutionary adaptations of the kidney to accommodate the excretory needs of intermittently fed carnivores. Modern-day humans ingest an uninterrupted diet of high-protein content, which would be expected to result in a higher steady-state GFR and RPF than their intermittently fed predecessors, and perhaps a less-pronounced acute response to a protein load.

Mechanism of Protein-Induced Hyperfiltration

Discerning the mechanism of this acute renal hyperfiltration and hyperemia response to protein and amino acids has been a topic of intense investigation. The reader is referred to a review by A.J. Premen for an in-depth analysis (53). The infusion of an amino acid solution in chronically protein-deprived rats resulted in a 40% increase in SNGFR due predominantly to an increase in the glomerular capillary plasma flow rate and a small increase in the glomerular transcapillary hydraulic pressure gradient (ΔP); the glomerular capillary ultrafiltration coefficient (K_f) was unaffected (94). In humans, a mild increase in ΔP without a change in barrier size-selectivity after a protein meal has been estimated by the use of fractional dextran clearance profiles (95). Taken together, these studies suggest a disproportionate reduction of preglomerular versus postglomerular resistance, leading to an increase in the two determinants of SNGFR—glomerular capillary flow rate and ΔP. Whether this response is due to an intrarenal or a systemic effect of amino acids has not been clarified.

Studies directly infusing amino acids into the renal artery have yielded conflicting results. In the isolated perfused kidney, a model characterized by extreme hyperemia, the addition of either a mixture of amino acids (96) or L-Arg (but not D-Arg) (97) to the perfusate results in a further increase in flow rates. However, in vivo, an intrarenal artery infusion of serine, alanine, and proline in rats led to a transient rise in RBF (13%) but failed to increase GFR, whereas an iv infusion led to marked elevations of GFR and RPF

(30%) (87). These latter data strongly suggest that systemic effects play a role in the renal response to amino acids. The effect of an intraportal infusion was equivalent to that of an iv infusion, indicating that direct delivery to the liver does not enhance the renal response.

An intrarenal effect is supported by studies that suggest that acute dietary protein loads and acute amino acid infusions may modulate tubuloglomerular feedback (98,99). The enhanced filtered load of amino acids is postulated to augment sodium-dependent amino acid uptake between late proximal and early distal tubules, thereby reducing sodium delivery to the macula densa, a signal known to decrease tubuloglomerular feedback, leading to a reduction in preglomerular resistance. Indeed, there is both structural and functional evidence for enhanced tubular activity. As discussed previously, rats fed a high-protein diet have disproportionate thickening of the inner strip of the outer medulla due to hypertrophied thick ascending limbs (73). Functionally, a high-protein diet led to both an increased Na^+/K^+ ATPase activity in the medullary thick ascending limb (100) as well as to enhanced urinary concentrating ability (73).

The ingestion of a protein-rich meal results in the stimulation of a variety of intestinal and pancreatic hormones, including glucagon (53). Although high-dose glucagon is capable of increasing GFR, the levels achieved after a meat meal are well below those required for renal hemodynamic effects. Thus, glucagon alone is unlikely to be responsible for the hemodynamic response. Several investigators have shown that the renal response to a protein or amino acid load is inhibited by a concurrent infusion of somatostatin in both rats and humans (57,94,101–105). Although somatostatin blocks the release of glucagon, it also has inhibitory effects on a wide variety of endocrine and exocrine systems (53). This somatostatin blockade can be overcome by a concurrent infusion of glucagon, insulin, and growth hormone, at doses to achieve levels similar to those after amino acids alone (105), a finding that strongly supports a role for these metabolic hormones. Others have postulated that the release of a hepatically derived factor, termed glomerulopressin, mediates protein-induced hyperemia (106). However, to date, this substance has yet to be characterized, and as discussed above, other studies have called into question the role of the liver in the renal hemodynamic effects of protein (53,107).

Irrespective of whether renal hyperfiltration and hyperemia occur via intrarenal or systemic mechanisms, the nature of the factor responsible for vasodilation remains unknown. A number of investigators have postulated a role for renal prostaglandins in the hyperemic response (82,108–110), yet an increase in the urinary excretion of vasodilatory pros-

tanoids is not a universal finding (78,111). Nonetheless, cyclooxygenase inhibitors have been shown to blunt the hyperemic response to a meat meal (82,108,110). Modest stimulation of PRA has been observed by some investigators (95,109,112). In addition, rats placed on a high-protein diet were found to have enhanced renal cortical expression of renin mRNA, but not angiotensinogen mRNA (in either the kidney or liver) (113). However, angiotensin-converting enzyme inhibitors do not appear to block the response. Most recently, a role for endothelium-derived relaxing factor (EDRF) has been postulated on the basis of a marked reduction in amino acid–induced vasodilation and hyperfiltration by N^ω-mono-methyl-L-arginine, a functional inhibitor of EDRF production (84,114). It is noteworthy that IGF-I, which as discussed above is elevated with high-protein diet (74), has been identified as an endothelium-dependent vasodilator leading to EDRF production (115). Considering the wide range of findings outlined above, it is likely that postprandial hyperemia and hyperfiltration involve the recruitment of a number of systems culminating in renal hemodynamic effects.

In summary, acute protein and amino acid loads induce renal hyperfiltration and hyperemia in conjunction with a diuresis and natriuresis. The physiologic mechanism of this response has yet to be determined, although it likely involves both hormonal and direct renal effects. It is likely that similar mechanisms are involved in the modulation of GFR by habitual changes in protein intake.

Effects of Renal Disease on the Response to Protein Feeding

Numerous studies have addressed the effect of dietary protein on renal function in experimental animals. We will focus on the model of renal disease induced by ablation of renal mass in Munich-Wistar rats, in which most of the determinants of GFR have been measured directly. Over a wide range of renal mass (no ablation, unilateral nephrectomy, or 1⅓ nephrectomy), rats fed a 40% protein diet had a higher GFR than did those maintained on a 6% protein diet (73, 107, and 97% higher, respectively) (116). In this model of renal disease, SNGFR is elevated because of increases in both ΔP and glomerular capillary plasma flow rate, the result of proportionately greater afferent versus efferent arteriolar vasodilation (117). With high-protein feeding, these findings are accentuated.

The long-term effect of a high-protein diet in ablation-induced renal disease in rats is to accelerate structural and functional injury, whereas a low-protein diet conveys both structural and functional protection (117). Similar findings have been observed in several other experimental models of renal disease

(118,119). In humans, the protective effect of protein restriction is most apparent in diabetic nephropathy (9,120) and in advanced renal disease (8), but its application to patients with mild to moderate renal insufficiency is still being studied (11,12). Because of the potentially confounding influence of dietary protein on the progression of renal disease, it is difficult to assess the effects of habitual protein intake on GFR in humans with renal disease. Thus, we will restrict our analysis to the response to an acute protein load.

In one carefully performed study, both the qualitative and quantitative responses to a protein-rich meal were nearly identical in patients with moderately severe glomerular disease as compared with normals (95). For patients with glomerular disease, the mean peak rise in GFR was 8.5 mL/min/1.73 m², which was approximately 16% of the baseline GFR (53 ± 8 mL/min/1.73 m²). By comparison, the mean peak rise in RPF was more pronounced, 149 mL/min/1.73 m², which was 33% of the baseline RPF (452 ± 86 mL/min/1.73 m²). Analysis of fractional dextran clearances was consistent with an increase in ΔP, a decrease in K_f, and an increase in RBF (95). A similar response was observed in patients with chronic renal disease (GFR < 50 mL/min/1.73 m²) maintained on a low-protein diet (30 to 40 g/day) for 1 month and then switched to a high-protein diet (80 to 90 g/day). The increases in GFR and RPF were roughly equivalent to those in normals (121).

Thus, despite preexisting elevations of SNGFR and glomerular capillary plasma flow rates in renal disease, protein-induced hyperfiltration and hyperemia are retained. In this respect, the renal response to a protein load in renal disease is similar to that observed in pregnancy: hyperfiltration and hyperemia are augmented (122).

DIETARY PROTEIN AND CREATININE CLEARANCE

A number of the studies cited above have used creatinine clearance as an index of GFR. Special consideration must be given to these studies, because alterations in protein intake may have independent effects on the individual parameters involved in calculating creatinine clearance. These effects raise questions regarding the utility of this test when studying the effects of dietary protein on GFR and may easily lead to erroneous conclusions. The following section will review the effects of dietary protein on creatinine clearance, other than its effect on GFR.

Effects on Creatinine Generation

In principle, alterations in creatinine generation would lead to parallel and proportionate changes in

serum concentration and urinary excretion of creatinine, without a change in creatinine clearance. However, the detection of changes in serum concentration and urinary excretion rate depend on the timing and variability of measurements. Inaccurate or imprecise detection of these changes would lead to the erroneous conclusion that creatinine clearance had changed as a result of a change in creatinine generation.

Dietary protein affects creatinine generation by several mechanisms. First, as discussed above, the total body pool of creatine is closely correlated with total muscle mass, which in turn is related to protein intake (37,42,123). Alterations in diet that lead to changes in muscle mass would be expected to cause parallel changes in the size of the creatine pool and creatinine generation. Second, the creatine pool is also affected by the ingestion of creatine, which derives primarily from meat (containing 3.5 to 5 mg of creatine per gram) (123–126). The elimination of creatine from the diet decreases the creatine pool and the generation of creatinine by as much as 30% (42,127,128). Conversely, supplementing the diet with creatine leads to the expansion of the creatine pool and increased creatinine generation (42,129–131). Third, the ingestion of creatinine affects creatinine generation directly, without affecting the size of the creatine pool. Creatinine is contained principally in meat and derives from the nonenzymatic breakdown of creatine during cooking. Ingested creatinine is rapidly absorbed from the gut, leading to a transient increase in serum concentration and urinary excretion (Figure 3) (132,133). The ingestion of a similar quantity of uncooked meat does not increase serum and urinary creatinine.

Effects on Renal Creatinine Excretion

Obviously, protein-induced hyperfiltration leads to increased creatinine filtration and increased creatinine clearance. However, it is not known whether protein-induced hyperfiltration is also associated with an increase in the tubular secretion of creatinine. We analyzed nine studies including 54 normal adults in whom GFR and creatinine clearance were measured simultaneously before and after the administration of a protein or amino acid load (Table 1) (58,59,76,77,134). The mean increment in creatinine clearance slightly exceeded the mean increment in GFR (by an average of 8 mL/min; range, –2 to 25 mL/min), suggesting a small but consistent protein-induced augmentation of the tubular secretion of creatinine as well as GFR. Interestingly, in one study of patients with renal disease (95), the increment in creatinine clearance did not exceed the increment in GFR.
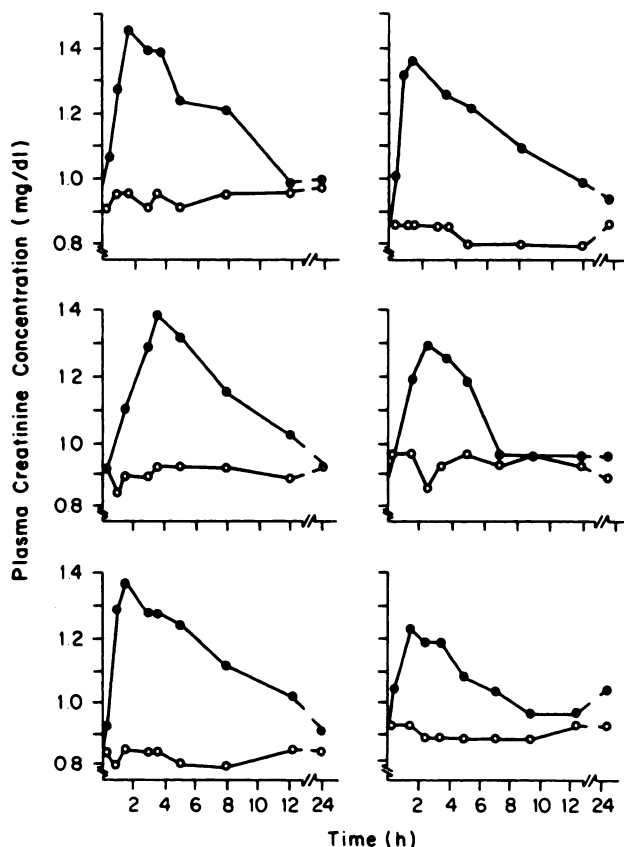
Figure 3. Effect of meat intake on plasma creatinine concentration in six healthy subjects. Solid circles represent values after a meal containing cooked meat protein. Open circles represent values after a meal devoid of meat protein. Reproduced from reference 133 with permission.

TABLE 1. Comparison of effects of protein loads on inulin and creatinine clearances[a]

Investigator	N	ΔC_{In}	ΔC_{Cr}	$\Delta C_{Cr} - \Delta C_{In}$
			(mL/min)	
Bergstrom et al.	8	18	23	+5
(59)	8	13	19	+6
Bosch et al. (76)	5	29	27	−2
Viberti et al. (58)	6	8	19	+11
Mansy et al. (134)	7	13	19	+6
	5	21	29	+8
Solling et al. (77)	8	12	37	+25
	7	12	16	+4
Total and Mean ± S.D.	53	16 ± 7	24 ± 7	+8 ± 8

[a] Abbreviations: ΔC_{In}, mean change in inulin clearance after a protein load; ΔC_{Cr}, mean change in creatinine clearance; $\Delta C_{Cr} - \Delta C_{In}$, difference in mean change in creatinine and inulin clearances.

Effects on Creatinine Measurement

We are not aware of interference with laboratory methods for the measurement of serum or urine cre-

atinine concentration by alterations in protein intake within the range that we have discussed. However, as we discussed above, because serum creatinine measurements are imprecise within the normal range, estimates of the level and changes in the level of creatinine clearance during alterations in protein intake are also expected to be imprecise. In addition, we suspect that the timing of measurements in some studies may have led to the erroneous conclusion that creatinine clearance had changed, when in fact, only creatinine generation had changed. Such an error would be likely to occur if creatinine clearance is estimated from a 24-h urine collection and only a single measurement of serum creatinine, especially if the serum sample is obtained after an overnight fast. For example, in an individual with normal renal function, the midday ingestion of 4 oz of cooked ground beef containing 40 g of protein (a quarter-pound hamburger) would be expected to increase the urinary excretion of creatinine by up to 350 mg, with only a transient increase in serum creatinine. If the serum sample is obtained the morning before or the morning after the urine collection, the increase in serum creatinine would not be detected, and creatinine clearance would be calculated erroneously to increase by as much as 24 mL/min.[3] This increase in clearance is similar in magnitude to the increase observed by Lew and Bosch (1) for a similar increment in dietary protein intake (40 g, equivalent to 6 g of urea nitrogen excretion).

In summary, creatinine generation and, to a lesser extent, secretion are altered by dietary protein. Creatinine clearance studies are also influenced by the precision of measurements and the timing of plasma sampling relative to protein intake. We suspect that these effects account for the larger effect of meat meals on creatinine clearance than on GFR. For these reasons, we believe that studies of the renal hemodynamic effects of dietary protein should use inulin, iothalamate, DTPA, or EDTA as filtration markers.

CONCLUSIONS

The habitual level and transient changes in protein intake appear to have multiple effects on renal function, both in normal individuals and in patients with renal disease. In general, these effects on GFR, creatinine generation, and perhaps tubular secretion of creatinine may be homeostatic, regulating the excretion of nitrogenous wastes in accordance with nitrogen intake.

Despite rigorous efforts, the mechanism of acute protein-induced hyperfiltration has not been defined. The response in humans is similar in nature to that of a wide variety of mammalian species (although

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[3] Assuming a serum creatinine of 1.9 mg/dL, an initial urinary creatinine excretion rate of 1,380 mg/day, and a final urinary creatinine excretion rate of 1,730 mg/day. Initial creatinine clearance would be 96 mL/min and final creatinine clearance would be 120 mL/min.
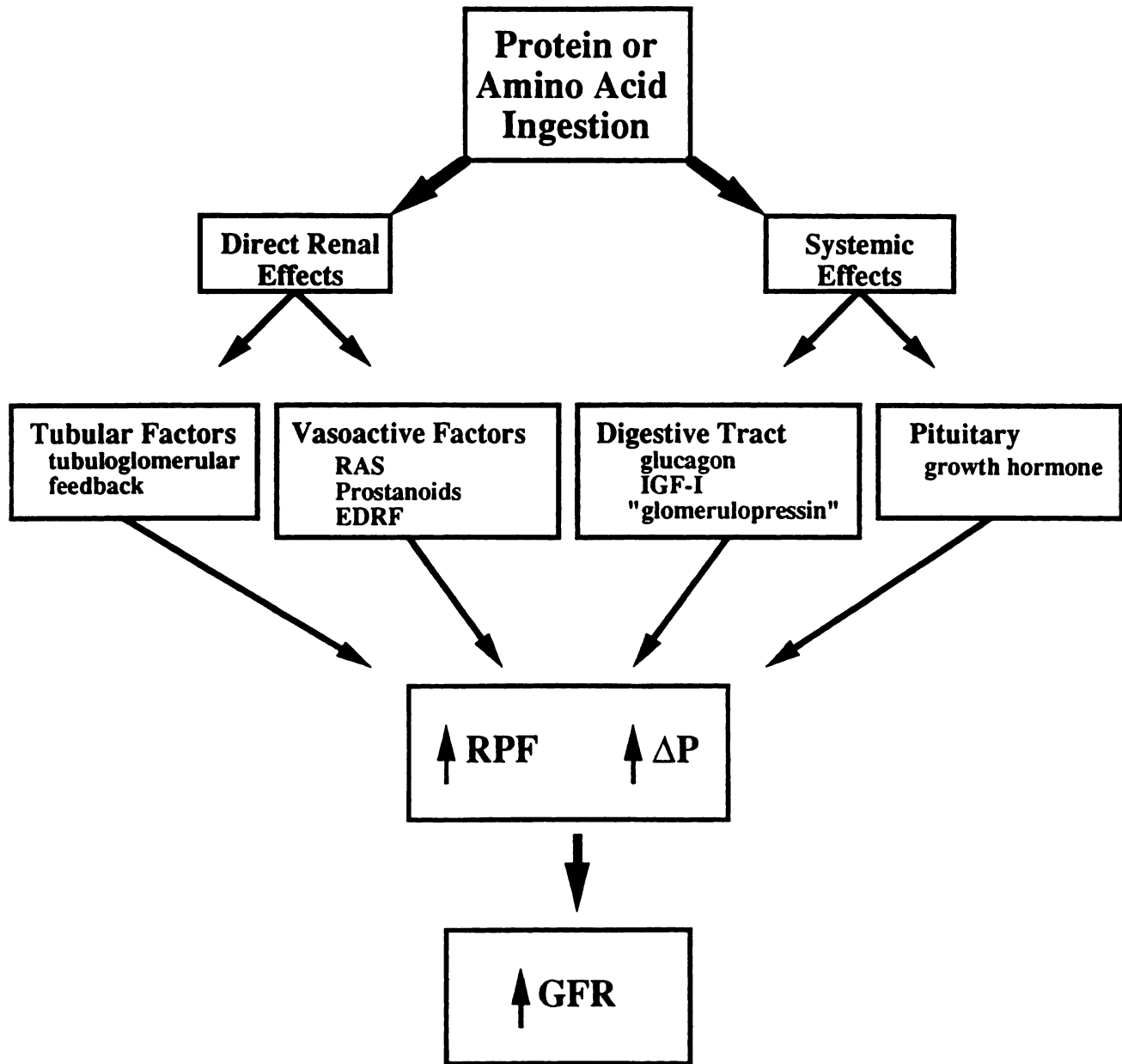
Figure 4. Potential mechanisms for the renal hyperfiltration after an acute ingestion of protein or amino acids. RAS, renin angiotension system.

less robust), and thus, we believe that the animal data provide a valid experimental model. In Figure 4, we have summarized the potential mechanisms of protein-induced hyperfiltration, in which we arbitrarily divide the potential mechanisms into systemic and direct renal effects. Note that many of the known modulators of glomerular hemodynamics have been implicated in this response, including renin/angiotensin, prostanoids, and EDRF. Although not depicted, it is likely that the systemic factors participate in this response by adjusting these local vasoactive factors.

There is also substantial evidence that habitual protein intake is a determinant of basal GFR in normal humans. As with the acute protein-induced hyperfiltration, the magnitude of effect is small as compared with that in other mammalian species; however, this may be due to the short-term nature of the studies. Renal hemodynamic adaptation to changes in habitual dietary protein occurs within 3 wk, although it may take considerably longer to reach a steady state. Studies of humans with prolonged dietary changes in protein intake, such as certain vegetarians (vegans), patients with malnutrition, or

patients receiving chronic total parenteral nutrition, indicate more substantial changes in GFR, which are paralleled by changes in kidney size. The pattern of the renal hemodynamic response to changes in habitual protein intake is similar to that seen with acute protein/amino acid loading, leading us to believe that similar physiologic processes are involved. However, habitual changes in dietary protein are also attended by structural changes as manifested by increased glomerular cross-sectional and whole-kidney size. The factor(s) triggering these morphologic changes and the effect of glomerular enlargement on GFR have yet to be determined.

What is the importance of these effects on the clinical evaluation of renal function? It has been suggested that creatinine clearance should be interpreted in association with knowledge of dietary protein intake in order to assess the adequacy of renal function (1). We believe that clinicians should consider a very low-protein intake to be a possible cause of lower-than-normal renal function. However, we suggest that there are not yet sufficient data on the relationship of renal function to dietary protein to redefine the limits of normal. Additional studies should be performed, measuring GFR in a large number of subjects on a variety of protein intakes. The magnitude and timing of the response to short-term alterations in protein intake should be defined, as should the effect of the habitual diet in conditioning the response. In addition, we should also investigate the role of variation in dietary protein in other normal conditions and in diseases in which variations in GFR are observed. These questions raise the intriguing possibility that variations of GFR between men and women, with body size, during aging, in pregnancy, in early diabetes, in early hypertension, and among patients with renal disease are due, in part, to variations in protein intake. These studies should take into account the aforementioned limitations of variability in GFR measurements and the effects of dietary protein on creatinine clearance in addition to the effects on GFR. Understanding the magnitude and the mechanism of the effects of dietary protein on GFR will illuminate the determinants of normal renal function and may aid in our understanding of the pathophysiology of renal disease.

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