Homocysteine (Hcy) is an amino acid metabolite that has been implicated, in retrospective and prospective studies, as a potential atherogenic agent and risk factor for cardiovascular disease (CVD) (1–3). Hyperhomocysteinemia, the state of elevated plasma Hcy levels, is very common among patients with chronic renal insufficiency (defined as the range of kidney function below normal but above that requiring renal replacement therapy) and occurs almost uniformly in the end-stage renal disease (ESRD) population (4). This is of particular importance for the latter group of patients, in which CVD is the major cause of death. In fact, these patients may have up to a 30 times higher risk of CVD-related death than the general population (5). Interestingly, traditional cardiac risk factors may not be able to account for this high mortality rate (6). Despite the abundance of data on Hcy metabolism, the pathogenesis of hyperhomocysteinemia in renal disease remains unclear. A better understanding of this deranged state would advance current knowledge of renal physiologic processes, as well as efforts to find an effective therapy. Although there is abundant evidence suggesting that the kidney plays a prominent role in Hcy metabolism, there is considerable controversy surrounding the extent and mechanisms of this role. This article introduces the issues of Hcy plasma flux, protein binding, and general metabolism, and reviews amino acid/Hcy metabolism in normal kidneys, including the effects of dietary intake on this process. It then reviews the association between Hcy and the GFR, amino acid/Hcy metabolism in diseased kidneys, and insights gleaned from Hcy-lowering trials. It concludes with the hypothesis that the hyperhomocysteinemia of renal disease is primarily attributable to reduced renal clearance and intrarenal metabolism.

Plasma Hcy Levels, Protein Binding, and Flux

Average fasting plasma total Hcy levels for healthy human subjects in the current era of flour and grain folic acid fortification range between 6 and 12 μM (Table 1) (7), with “moderate” hyperhomocysteinemia occurring when levels are between 12 and 30 μM, “intermediate” hyperhomocysteinemia occurring when levels are between 31 and 100 μM, and “severe” hyperhomocysteinemia occurring when levels are greater than 100 μM (8). In normal subjects, approximately 75% of total plasma Hcy is bound via a disulfide bond, to protein, primarily albumin, [bound Hcy (bHcy)], while the remaining 25% exists in a free unbound form [free Hcy (fHcy)] (Figure 1) (9,10). fHcy is composed almost entirely of oxidized, disulfide-linked heterodimers (Hcy-cysteine) or homodimers (Hcy-Hcy, or homocysteine), with perhaps 1 to 2% existing in a reduced sulphydryl state (11). Unfortunately, fHcy is inherently unstable, and accurate levels may be difficult to measure. Of importance, only the fHcy fraction is thought to be freely filtered at the glomerulus. The fHcy/bHcy ratio varies among renal Hcy handling and should be considered when measuring Hcy plasma flux and renal clearance. The underlying cause of hyperhomocysteinemia in renal disease is not entirely understood but seems to involve reduced clearance of plasma Hcy. This reduction may be attributable to defective renal clearance and/or extrarenal clearance and metabolism, the latter possibly resulting from retained uremic inhibitory substances. Although the currently available evidence is not conclusive, it seems more likely that a reduction in renal Hcy clearance and metabolism is the cause of the hyperhomocysteinemic state. Efforts to resolve this important issue will advance the search for effective Hcy-lowering therapies in patients with renal disease.
species. For example, in contrast to humans, approximately 65 to 75% of Hcy in rats is in the free form (12).

Hcy production occurs in all cells as a consequence of the normal methylation process (Figure 2). The Hcy volume of distribution in healthy subjects was observed to be approximately 0.4 L/kg, similar to that in subjects with severe renal insufficiency (13). Intracellular Hcy levels rise with enhanced intracellular Hcy production and/or inhibition of intracellular metabolism. To maintain low intracellular levels of this putatively cytotoxic substance, Hcy that is not metabolized within the cell is exported to the plasma compartment (14,15). Calculations based on steady-state kinetics in healthy adult humans estimate that 1.2 mmol of Hcy, or approximately 5 to 10% of the total daily cellular production, is delivered daily to the plasma compartment (16,17). Because Hcy is constantly produced and exported by cells, it must also be constantly cleared for plasma levels to remain within 10% of baseline values, as they do in healthy human subjects (18). Plasma Hcy levels are not known to be actively regulated.

Hyperhomocysteinemia is a condition in which the regulation of intracellular Hcy levels is disrupted and Hcy export to the plasma compartment is accelerated and/or normal Hcy plasma clearance is decreased. Human kinetic studies suggest that hyperhomocysteinemia in those with vitamin B₁₂ or folate deficiency is caused by enhanced tissue export of Hcy (19). In contrast, hyperhomocysteinemia in renal disease is related to reduced plasma Hcy clearance (13). The underlying cause of this reduction is unknown but involves a defect in renal and/or extrarenal clearance. As noted below, the kidney likely plays an important role in Hcy clearance and metabolism.

**General Metabolism**

Hcy is an endogenous sulfur-containing amino acid intermediate of the essential amino acid methionine and is not obtained from the diet. An overview of the metabolic pathway is presented in Figure 2. Methionine enters the one-carbon metabolic cycle either through the dietary consumption of

---

**Table 1. Comparison of ranges of total Hcy levels in different populations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Geometric Means (µM)</th>
<th>10th to 90th Percentile Total Hcy Levels (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal disease</td>
<td>24</td>
<td>12 to 39</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>15</td>
<td>9 to 25</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>15</td>
<td>9 to 25</td>
</tr>
<tr>
<td>Normal renal function (population-based controls)</td>
<td>9</td>
<td>6 to 12</td>
</tr>
</tbody>
</table>

a Hcy, homocysteine. Modified from reference 7, with permission.

b Renal transplant recipients receiving standard immunosuppressive therapy and patients with chronic renal insufficiency receiving no immunosuppressive drugs, with equivalent renal function.

c In the current era of folic acid-fortified cereal grain flour.

---

![Figure 1. Homocysteine (Hcy) and the major related disulfides in normal human plasma. Reprinted from reference 9, with permission.](image-url)
methionine-containing protein or through endogenous protein breakdown. It is then converted intracellularly to S-adenosylmethionine (SAM), which functions as a universal methyl donor for a variety of important acceptors, including nucleic acids, neurotransmitters, hormones, and phospholipids. S-Adenosylhomocysteine, a byproduct of these reactions, is hydrolyzed to form Hcy and adenosine. This reaction actually favors the production of S-adenosylhomocysteine, although the normally rapid egress or metabolism of intracellular Hcy and adenosine allows this reaction to continue forward (20). Hcy then follows one of the following two metabolic pathways: (1) remethylation to methionine by methionine synthase using vitamin B12 (cobalamin) as a cofactor and 5-methyltetrahydrofolate as a substrate; or, alternatively, by betaine/Hcy methyltransferase in the presence of betaine (in human subjects, the latter reaction is mainly confined to the liver and kidney); (2) transsulfuration to cystathionine by cystathionine β-synthase, in an irreversible vitamin B6 (pyridoxal-5-phosphate)-dependent reaction; cystathionine is then degraded by cystathionase to α-ketobutyrate, ammonium, and cysteine.

Folate or B vitamin deficiencies and inborn errors of metabolism are well recognized causes of hyperhomocysteinemia (14). Folate and vitamin B12 deficiencies cause fasting Hcy levels to increase by impairing Hcy remethylation. Vitamin B6 deficiency, in contrast, primarily affects transsulfuration and tends to induce hyperhomocysteinemia after a methionine load (14). Most healthy people without inborn errors of metabolism can be successfully treated for hyperhomocysteinemia with modest vitamin supplementation, such as daily doses of 0.4 mg of folic acid (21). Despite the greatly increased prevalence of hyperhomocysteinemia among patients with renal disease, these patients are not disproportionately affected by vitamin deficiencies (22) or inborn metabolic defects (23).

Normal Kidneys and Hcy Handling

Amino Acid Metabolism

It is well established that the kidney plays a major role in amino acid metabolism. Unbound amino acids are freely filtered at the glomerulus, where the filtered load reflects the plasma amino acid concentration and GFR. Approximately 450...
mmol of amino acids are filtered daily (24). More than 99% of amino acids are then reabsorbed along the proximal renal tubule, with only approximately 5 mmol being ultimately excreted in the urine (24,25). An alternative mechanism of cellular uptake is via the tubule cell basolateral surface. This occurs mainly in distal tubule cells, possibly to provide metabolic substrates to cells in which luminal amino acid delivery is decreased (24). Hcy may potentially be taken up in this way as well, because cystine, an amino acid that shares an uptake mechanism with homocystine, is known to be taken up in this manner (24). These tubular metabolic processes can be quite complex, with tubule cells producing and exporting certain amino acids while simultaneously taking up and degrading others (24–26).

**Hcy Metabolism**

The kidney seems to be just as capable of filtering and metabolizing Hcy as it does other amino acids. Hcy has a molecular mass of 135 D (27), which is well within the filtration range of normal glomeruli. Assuming plasma Hcy concentration of 3 μM (10) and a normal GFR of 125 ml/min, the daily amount of filtered Hcy would be approximately 0.5 mmol. As with other amino acids, there is abundant evidence that filtered Hcy is avidly reabsorbed and only minimally excreted (6 μmol/d, or 1%) in the urine (10,11,28,29). As described below, this may be an underestimation of the true filtered load of Hcy.

Tubular uptake mechanisms specific for Hcy have been identified. Kinetic studies of minced rat renal cortical tissue identified low-Keq/high-affinity and high-Keq/low-affinity homocystine uptake systems, the former shared with cystine and the dibasic amino acids arginine, ornithine, and lysine (30). This finding is supported by studies in which rats and human subjects exhibited dramatically increased urinary homocystine levels of these enzymes are found primarily in liver and kidney (33). In human subjects, appreciable amounts (Figure 2) (33). In human subjects, appreciable levels of these enzymes are found primarily in liver and kidney tissue. Compared with liver, the kidney contains more betaine/Hcy methyltransferase (300%) and less cystathionase and methionine synthase (30 and 50%, respectively) (14,34). Measurements of the enzyme cystathionine β-synthase in two tissue samples identified small amounts, compared with liver. However, cystathionine β-synthase gene expression has been documented in the kidney (35,36). Although both enzymatic pathways can theoretically be used, in vitro and in vivo rat experiments demonstrated that Hcy was metabolized primarily via transsulfuration (12,37). Some hypothesize that the kidney may compensate for changes in glomerular filtration by up- or downregulating these biochemical pathways, thereby keeping constant the amount of Hcy returned to plasma (38). Under this model, an increase in GFR would lead to increased Hcy filtration and tubular reabsorption. In this case, renal Hcy-metabolizing enzymes would be upregulated. Conversely, when the GFR decreases, intrarenal Hcy metabolism also would fall. The effect of these alterations ensures that changes in Hcy filtration do not affect renal Hcy export to plasma. In summary, as with other amino acids, the healthy kidney has the capability to filter, reabsorb, and metabolize Hcy, which it may routinely do in large amounts. In addition to the filtered load, Hcy uptake may also occur on the basolateral tubule cell surface.

Arteriovenous (A-V) studies, which represent an accepted method of measuring the capacity of an organ to extract a particular substance from blood, have been performed in normal rat and human kidneys. Hcy extraction is determined by simultaneously measuring Hcy concentrations in the arterial system and in the renal vein and calculating the difference, while taking into account renal plasma flow and Hcy lost in the urine. A-V studies in rats have consistently demonstrated that the kidney is capable of clearing Hcy in large quantities. A study in six healthy postprandial rats demonstrated a positive renal A-V difference of approximately 20% of arterial levels (28). This value would be equivalent to approximately 1 mmol of Hcy in human subjects, or 80% of the load delivered daily to plasma. When an acute hyperhomocysteinemic state was precipitated by Hcy infusion, rat kidneys manifested appreciable reserve and increased Hcy extraction by fourfold (12). However, differences in the fHcy/bHcy ratio among species may extrapolate to human subjects problematic. The only published A-V study in humans observed that 20 fasting subjects with normal renal function exhibited, on average, no significant renal extraction of Hcy (39). However, differences in experimental conditions between the studies make direct comparisons difficult. Additionally, the results of that study do not exclude renal extraction of up to 30 to 40% of the presumed daily Hcy production. The renal A-V difference may also be altered in the postprandial state. This is supported by renal A-V experiments in dogs that demonstrated alterations in renal amino acid handling after amino acid intake (40) and data on the effects of protein intake on renal Hcy filtration, as described below.

**Effects of Dietary Intake on Hcy Filtration**

Experimental data suggest that food intake affects Hcy protein binding and, consequently, Hcy glomerular filtration. A carefully performed study in healthy human subjects fed a protein-rich meal demonstrated a significant postprandial increase in plasma Hcy levels, which peaked at 8 h (18). Of particular importance, fHcy levels increased more rapidly and to a greater extent than did bHcy levels, peaking 2 to 4 h after the meal by 34 ± 20%, or 0.6 ± 0.3 μM (mean ± SD), compared with premeal levels. The fHcy/bHcy ratio also increased, by a mean of 49 ± 16%. The authors observed synchronous fluctuations in the free/bound ratios of aminothiols (Hcy, cysteine, and cysteineglycine). They hypothesized that a change in the free/bound levels of one of the aminothiols triggers a cascade of thiol-disulfide exchange reactions, leading to altered ratios for the others. These intriguing results are supported by previous studies in healthy and homocystinuric
subjects (41–43). Studies that did not demonstrate an increase in postprandial fHcy or total Hcy levels were limited by dietary protein load size or inadequate follow-up periods or lacked fractionated Hcy measurements (44–46).

These results may help explain how diet-related increases in Hcy levels are normalized. Dietary methionine-containing protein loads increase plasma levels of Hcy and cysteine. Disulfide exchange reactions and competition for protein binding cause a disproportionate increase in fHcy levels, allowing excess Hcy in the free form to be filtered by the kidney. The increase in fHcy levels may also accelerate extrarenal uptake. Therefore, a combination of increased renal Hcy filtration and possibly upregulation of intrarenal degradative pathways would lead to increased plasma clearance.

Recent data on the effects of N-acetylcysteine (NAC), a mucolytic agent and treatment for acetaminophen overdose, on aminothiol protein binding and renal excretion support this hypothesis. NAC has a free sulfhydryl group, which preferentially interacts with cysteine and other endogenous sulfhydryl-containing substances, including Hcy, displacing them from their protein binding sites and forming mixed disulfides (e.g., NAC-Hcy and NAC-cysteine) (47). Human subjects treated with NAC orally or intravenously demonstrate almost immediate, dramatic, and dose-dependent reductions in total plasma Hcy and cysteine levels (48–50). NAC administration also increases the fHcy/bHcy ratio and urinary Hcy and cysteine excretion (49,50). In summary, these results suggest that disruption of Hcy protein binding, by either diet or drugs, can transiently increase fHcy levels, leading to increased glomerular filtration and renal metabolism.

If this hypothesis is confirmed, it will be necessary to reassess the calculated amount of Hcy delivered to the plasma compartment (1.2 mmol). This value was derived from Hcy loading studies that assumed that Hcy was cleared from plasma at a constant rate. However, dietary protein loads may acutely accelerate renal Hcy clearance, making it difficult to extrapolate this result to a nonfasting setting. For similar reasons, the amount of Hcy filtered daily at the glomeruli will also need to be recalculated. Not only can dietary protein intake acutely increase fHcy levels, but protein itself can cause temporary elevations in GFR, further increasing fHcy clearance. The mechanism of the latter process is not entirely understood but is probably neurohormonal and/or hemodynamic in nature (51).

**Diseased Kidneys and Hcy Handling**

**Association between Hcy Levels and GFR**

Data on the relationship between Hcy levels and GFR are consistent with the presumption that normal kidneys play a prominent role in plasma Hcy handling. Hcy levels increase as renal function declines and progresses to ESRD, with the vast majority (>85%) of dialysis patients ultimately experiencing mild-to-moderate hyperhomocysteinemia (5). GFR values estimated from serum creatinine or calculated creatinine clearance is consistently and inversely correlated with plasma Hcy levels (52,53). However, the precursor molecule for creatinine is creatine. Creatine accounts for approximately 90% of all methyl group donations from S-adenosylmethionine and is therefore closely linked to Hcy production (Figure 2) (17). It is not clear, then, whether creatinine inversely predicts Hcy levels because it is a marker of GFR or simply because it is linked to Hcy production via a common biochemical pathway. Studies using highly accurate GFR measurements (with iohexol and 51Cr-ethylenediaminetetraacetate) were performed in healthy and diabetic adults, a large proportion of whom exhibited normal serum creatinine levels (1.3 to 1.5 mg/dl) (38,54,55). Those studies confirmed the strong inverse relationship between Hcy levels and renal function, even in the range of minimally reduced to supranormal GFR (60 to 165 ml/min). They also demonstrated that creatinine lost its predictive value after controlling for GFR, suggesting that the predictive strength of creatinine is associated with its role as a GFR marker. Other, more sensitive, markers of GFR, such as cystatin C, confirm the relationship between GFR and Hcy by independently predicting fasting Hcy levels in renal transplant recipients and patients with coronary artery disease with normal plasma creatinine levels (56,57). In conclusion, a strikingly consistent inverse relationship exists between Hcy levels and renal function. It has been observed using multiple GFR markers over a broad range of renal function, from severe renal insufficiency to a level of GFR far above the uremic range. This relationship is powerful indirect evidence that elevated Hcy levels in renal disease are intimately linked to kidney function.

**Plasma Protein Binding**

Absolute fHcy, bHcy, and total Hcy levels are all increased in renal disease, although the proportion of fHcy remains constant or decreases (58,59). Therefore, uremic subjects, who are often hypoalbuminemic, tend to exhibit a greater proportion of protein-bound Hcy. It is possible that retained uremic plasma proteins play a role in binding Hcy. Additional studies are needed to confirm the proportion of fHcy, the effects of retained uremic solutes on Hcy binding, and the potential toxicities of reduced Hcy, fHcy, and bHcy in the uremic milieu.

**Amino Acid Metabolism**

Amino acid handling and elimination are profoundly altered as a result of uremia-induced malnutrition, retained toxins, deranged hormonal levels, increased urinary amino acid excretion, and, of particular relevance here, altered capacity of the kidney to clear, degrade, and synthesize certain amino acids (25,26,60). Reductions in plasma levels of essential amino acids, such as tryptophan, leucine, isoleucine, valine, and lysine, and increases in levels of cystine, citrulline, methylhistidine, glycine, hydroxyproline, and total nonessential amino acids are commonly observed in renal disease (25). Although normal urinary amino acid excretion is minimal, it increases with progressive renal insufficiency. This may be because of higher plasma concentrations of certain amino acids, leading to increases in the filtered load and subsequent filtrate flow rate in the few remaining functioning nephrons (24). This latter process tends to decrease the time of contact between amino acids...
and renal tubular cells, impairing the ability of these cells to take up and metabolize filtered amino acids (24,25). Increased tubular amino acid secretion may also theoretically contribute to the higher excretion rate.

Renal and Extrarenal Hcy Metabolism

The fact that hyperhomocysteinemia in kidney disease is the result of defective clearance of Hcy from plasma rather than increased delivery to plasma was demonstrated in a kinetic study of eight subjects with severe renal insufficiency who were given oral and intravenous Hcy loads (13). Plasma Hcy clearance in these subjects was reduced by 70%, compared with control subjects and subjects with isolated folate or vitamin B₁₂ deficiencies. This result can be ascribed to a decrease in intrarenal Hcy clearance resulting from a reduction in functioning renal mass and/or a decrease in extrarenal clearance, perhaps attributable to retained uremic solutes that inhibit metabolism. Unfortunately, studies of Hcy handling in the renal disease population are sparse. As with amino acids in general, urinary Hcy excretion increases progressively with renal disease. Subjects with a calculated creatinine clearance of 19 ml/min and urinary Hcy levels of 1.4 μmol/l were estimated to excrete 15% of filtered Hcy via the urine (13). Whether renal disease affects the specific metabolic pathways is not known, but a stable isotope study with four hyperhomocysteinemic subjects undergoing hemodialysis demonstrated decreased Hcy remethylation with a trend toward lower transsulfuration, compared with control subjects (61).

The paucity of data on Hcy extraction and metabolism by diseased kidneys makes it impossible to definitively identify the source of the clearance defect. There is good evidence that normal kidneys play a major role in amino acid and Hcy clearance and metabolism. The existence of Hcy-metabolizing enzymes and uptake systems in renal tubular cells has been confirmed, and Hcy extraction studies in animal kidneys documented significant Hcy uptake (12,28,30,36). Without implicating other complex processes, it seems reasonable to expect that the loss of metabolically active kidney tissue normally involved in Hcy handling would decrease Hcy clearance and increase plasma levels. The inverse relationship between Hcy levels and GFR, which is consistent throughout a nonuremic range of kidney function, supports the premise that it is reduced renal function, not the accumulation of uremic toxins, that causes Hcy levels to increase.

An alternative theory involves currently unidentified uremic substances that inhibit normal extrarenal Hcy metabolism. The liver is considered the most likely target organ, given its major regulatory role in protein metabolism, its high levels of Hcy-metabolizing enzymes, and its capacity to export massive amounts of Hcy in vitro (15). Although an in vitro study demonstrated that folic acid transport was inhibited in the uremic milieu (62), two subsequent, well-designed trials using the reduced folates l-folinic acid and l-5-methyltetrahydrofolate to decrease Hcy levels in patients with ESRD found no evidence of impaired folate absorption, transport, or conjugation (63,64). Another study demonstrated abnormal hepatic sulfur amino acid metabolism in uremic rat livers, although levels of Hcy-metabolizing enzymes were no different than those in a pair-fed group (65). By finding no significant renal Hcy extraction in fasting adults, the human A-V study can be interpreted as indirectly supporting this hypothesis as well.

Hcy-Lowering Trials

In contrast to healthy patients, those with renal disease and hyperhomocysteinemia are partially refractory to all available treatments, including vitamin B₆, vitamin B₁₂, folic acid and its reduced forms, betaine, and serine (4). This is a consistent finding in patients with renal disease. Moreover, resistance to treatment increases as renal function declines. Hyperhomocysteinemia in chronic renal insufficiency can often be normalized with supraphysiologic folic acid treatment, such as doses of 2 to 5 mg/d (66,67), whereas the majority of patients with ESRD fail to normalize with doses as high as 60 mg (68). This phenomenon was reflected in one study that compared the responsiveness of renal transplant recipients and dialysis patients, with equivalent levels of hyperhomocysteinemia, to supraphysiologic doses of folic acid and B vitamins. Despite being treated with lower vitamin doses, the renal transplant recipients exhibited much larger reductions in Hcy levels, with a significantly greater percentage of patients experiencing normalization of levels (50 versus 5%) (22). One important issue confounding the interpretation of these Hcy-lowering studies is that many of them include relatively vitamin-deficient subjects. In fact, when compliance with a vitamin supplement (e.g., Nephrocap [Fleming & Co., Fenton, MO] or Nephrovite [R&D Laboratories, Marina Del Rey, CA]) was enforced in patients with ESRD, ensuring that all subjects were vitamin-replete, the effect of even massive doses of vitamin supplementation became negligible (69). How can this striking resistance to treatment be explained? If normal kidneys play a primary role in clearing and metabolizing Hcy, then the atrophic, nonfunctioning, renal parenchyma in ESRD would not significantly respond to vitamin supplementation, no matter how high the dose. Alternatively, uremic solutes may effectively inhibit extrarenal Hcy metabolism. The fact that a minority of patients with ESRD do respond, albeit in an attenuated manner, to supraphysiologic vitamin supplementation suggests some level of residual metabolic renal function and/or enhanced extrarenal Hcy metabolism. It may also suggest a vitamin-deficient state at baseline.

There has been some concern that common genetic polymorphisms affecting Hcy metabolism, in particular the methylenetetrahydrofolate thermolabile mutation (C677T), have significant effects in patients with renal disease, including ESRD. However, this defect has been demonstrated to cause fasting hyperhomocysteinemia only in the setting of low folate levels, regardless of renal function (70). Consequently, this mutation has a negligible effect among dialysis patients who are folate replete (71,72).

Routine hemodialysis treatments acutely decrease Hcy levels by approximately 30 to 40%, but levels quickly increase to their elevated pretreatment values (27,73). There are ongoing attempts to manipulate the dialysis modality to improve Hcy clearance. High-flux dialysis membranes, which have the ca-
pacity to clear large plasma molecules, including potential uremic inhibitory substances, have no significant long-term Hcy-lowering effect (27). Of interest, increasing the frequency of dialysis may lead to significantly lower fasting Hcy levels (74). One potential explanation for this is that Hcy diffuses directly into the dialysate, and more frequent dialysis allows a lower steady-state level to be reached. Alternatively, uremic inhibitory factors may be removed, facilitating normal Hcy metabolism.

Conclusion

Hcy has been demonstrated to be an independent CVD risk factor. Patients with kidney disease, for whom exceptionally high rates of cardiovascular morbidity and death are observed, exhibit disproportionately elevated plasma with Hcy levels. Hcy levels increase as renal function declines, patients become increasingly refractory to the usual Hcy-lowering therapies. The role of the kidney in plasma Hcy handling is an area of ongoing research. Current data suggest that the healthy kidney plays a major role in Hcy clearance and metabolism, as it does with other amino acids. Renal Hcy filtration and clearance may be affected by dietary protein intake and should be measured under nonfasting conditions. Confirmation of this effect would mandate a reassessment of previously accepted values for the daily amount of Hcy delivered to plasma and filtered by the kidney.

The underlying cause of hyperhomocysteinemia in renal disease is not yet understood, although reduced plasma Hcy clearance is the most proximate cause. Data extrapolated from the normal state and other indirect evidence suggest, but do not prove, that hyperhomocysteinemia is primarily attributable to decreases in Hcy plasma clearance and metabolism by decreased functioning renal mass. An alternative hypothesis involving unidentified uremic inhibitory substances that block normal extrarenal Hcy metabolism cannot be fully discounted at this time and may also contribute. Efforts to resolve this important issue and improve Hcy-lowering strategies for renal patients are refractory to standard therapies must continue.

Acknowledgments

This material is based on work supported by the United States Department of Agriculture, under agreement 581950-9-001. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the United States Department of Agriculture.

References

17. Mudd SH, Poole JR: Labile methyl balances for normal humans on various dietary regimens. Metabolism 24: 721–735, 1975


