

# Hyperhomocysteinemia, Malnutrition, and Inflammation in ESRD Patients

Mohamed E. Suliman, Peter Stenvinkel,  
 Peter Bárány, Abdul Rashid Qureshi, and Bengt Lindholm

Hyperhomocysteinemia is a risk factor for cardiovascular disease in the general population, but in end-stage renal disease patients some studies show a reverse association, i.e. higher levels of homocysteine are associated with better clinical outcome. In this brief review, we review the evidence that malnutrition, hypoalbuminemia, inflammation and diabetes mellitus may lower circulating levels of homocysteine. As these factors are strong predictors of clinical outcome, this may explain why lower homocysteine levels in end-stage renal disease patients are associated with worse clinical outcome. We conclude that these factors need to be taken into account in multivariate models evaluating the impact of hyperhomocysteinemia as a risk factor in end-stage renal disease patients.

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Cardiovascular disease (CVD) is highly prevalent in end-stage renal disease (ESRD) patients in whom it is the major cause of death, and cardiovascular complications accelerate as renal function is progressively lost.<sup>1</sup> ESRD is associated with a high prevalence of traditional risk factors (eg, hypertension, diabetes mellitus [DM], dyslipidemia, and smoking); however, these risk factors cannot explain adequately the high CVD-related mortality rate in ESRD patients. Instead, other factors such as the high prevalence of malnutrition, hypoalbuminemia, inflammation, and hyperhomocysteinemia also are thought to contribute to the increased CVD-related mortality rate in ESRD. In this brief review, we discuss hyperhomocysteinemia as a cardiovascular risk factor in ESRD patients and the influence of malnutrition/inflammation on the relationship between hyperhomocysteinemia and morbidity and mortality in ESRD.

## Hyperhomocysteinemia in ESRD

Homocysteine (Hcy) is a nonprotein, sulfur-containing, amino acid intermediate in the metabolism of methionine, an essential amino acid found both in animal and plant proteins. Although vascular and hematologic abnormalities associated with an increased Hcy level lead to a proatherogenic and prothrombotic milieu, the atherogenic mechanism(s) are not fully clear. Suggested mechanisms include direct cytotoxic effects of Hcy on endothelial cells, endothelial activation of factor V, a growth-promoting effect of Hcy on smooth muscle cells, reduction of endothelial protein C activation, and increased oxidative stress.<sup>2</sup> Indeed, several epidemiologic studies indicate that even a mildly increased plasma total Hcy (tHcy) is an independent and graded risk factor for atherosclerosis in the general population.<sup>3-5</sup> However, not all prospective cohort studies are consistent with this finding<sup>4</sup> and a large vitamin intervention study did not confirm this finding.<sup>6</sup> In fact, it still is debated whether a modest increase in tHcy level is only a marker of atherosclerosis (or factors associated with atherosclerosis) or if it is in itself a real cause of cardiovascular insult.<sup>7</sup> Experimental studies suggested that the reduced form of Hcy, rather than tHcy, may be the Hcy fraction that exerts the toxic effects on the vasculature.<sup>2</sup> Recently, it was reported that the level of reduced Hcy increases in parallel to the level of tHcy in both ESRD patients and healthy patients.<sup>8</sup>

A variety of factors may cause hyperhomocysteinemia.

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Divisions of Baxter Novum and Renal Medicine, Department of Clinical Science, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden.

Address reprint requests to Bengt Lindholm, MD, PhD, Divisions of Baxter Novum and Renal Medicine, Department of Clinical Science, Karolinska University Hospital Huddinge, K-56, S-141 86 Stockholm, Sweden.  
 E-mail: bengt.lindholm@klinvet.ki.se

Besides nutritional deficiencies of B vitamins and genetic factors (C677T mutation of methylenetetrahydrofolate reductase), renal failure is one of the most frequent clinical causes of hyperhomocysteinemia. However, the mechanism(s) by which renal failure leads to hyperhomocysteinemia is not completely clear, although several processes may explain the close correlation between kidney function and the plasma tHcy concentration. The normal range of tHcy is 3 to 15  $\mu\text{mol/L}$ , and a tHcy level less than 10  $\mu\text{mol/L}$  is considered desirable. In patients with ESRD, the tHcy level increases 2 to 3 times or more, and the prevalence of hyperhomocysteinemia is more than 90%.<sup>9</sup> Thus, uremic hyperhomocysteinemia appears to be an inherent feature of ESRD together with many other proven or suspected uremic toxins. However, the ability of tHcy to predict cardiovascular events or mortality in ESRD patients is controversial.<sup>9</sup>

## Hyperhomocysteinemia as a Predictor of Clinical Outcome in ESRD

Although some studies confirm and report higher levels of tHcy in ESRD patients with CVD,<sup>10-14</sup> others report paradoxically lower tHcy levels or no difference in tHcy levels in CVD patients.<sup>15-19</sup> Prospective studies showed either a graded increase in relative risk with the increase of tHcy levels<sup>20-22</sup> or a worse outcome in patients with lower tHcy levels.<sup>18,19,23,24</sup> Moreover, some studies using surrogate end points for atherosclerosis and thrombosis failed to show a causal relationship,<sup>25,26</sup> and a recent randomized trial using different doses of folic acid for over 3 years failed to find differences in cardiovascular events and the mortality rate in ESRD patients.<sup>23</sup> Although further clinical trial studies are required to show a causal relationship, it may be difficult (if a benefit is verified) to distinguish whether this is caused by a reduction of the Hcy level or caused by a direct beneficial effect of folic acid on endothelial function.<sup>27</sup>

No doubt the observed discrepancies in the studies evaluating the relationship between plasma tHcy level and outcome in uremic patients can be attributed partially to differences in study design and population (ie, selection bias). Indeed, in some of the previous studies, the sample sizes were relatively small and study populations were heterogeneous. Most of these studies did not take into account such confounding risk factors as differences in type of dialysis, duration of dialysis, race, genetic variations, and prevalence of comorbidities.

In recent years, many studies have emerged showing that the plasma tHcy level is related inversely to the clinical outcome in ESRD patients<sup>18,19,23,24,28</sup> and the term *reverse epidemiology for Hcy* has been suggested.<sup>29</sup> The reverse association in ESRD patients compared with the general population is not unique for tHcy. Various cardiovascular risk factors in the general population such as cholesterol, blood pressure, and body size all seem to have inverse associations with mortality in ESRD.<sup>29,30</sup> Although the reason(s) for the inverse asso-

ciations in dialysis patients are not clear, several possible explanations have been suggested including survival bias and discrepancies between competitive risk factors.<sup>29</sup>

Among the most important confounding factors that seem to influence tHcy levels in uremic patients are hypoalbuminemia, malnutrition, inflammation, and diabetes mellitus. These factors all are prevalent in ESRD patients and have been considered as factors that initiate or aggravate atherosclerosis in these patients. Therefore, these factors may cause or at least accentuate this reverse association. Indeed, a recent study by Liu et al<sup>31</sup> showed that the presence of inflammation and malnutrition in ESRD reverses the association between cholesterol and mortality rate in dialysis patients. Also, Fleischmann et al<sup>32</sup> suggested that better nutrition might account for the risk paradox in hemodialysis patients who are overweight and hyperlipidemic yet despite this have a better survival rate.

## Malnutrition

Malnutrition is a common finding in ESRD patients, both during conservative therapy and during hemodialysis or peritoneal dialysis treatment. Depending on the parameter measured, the prevalence of malnutrition in dialysis ranges from 18% to 75%.<sup>20,33-35</sup> Malnutrition has been reported to affect various body compartments differentially, but those most frequently involved are adipose tissue and somatic and visceral proteins. Protein loss mainly involves skeletal muscle, connective tissues, the immune system, and plasma proteins.<sup>36</sup>

Malnutrition and hypoalbuminemia (although they are not synonymous they are highly related) are strong risk factors for increased morbidity and mortality in patients with ESRD.<sup>37-40</sup> However, although malnutrition is among the strongest predictors of mortality in ESRD patients, it generally is not reported to be a prominent direct cause of death and accounts for less than 5% of deaths.<sup>1,40</sup> In addition, malnutrition and hypoalbuminemia have been considered factors that initiate or aggravate atherosclerosis in nonuremic individuals and also could have effects on cardiac structure and function,<sup>41</sup> and many links have been proposed by which malnutrition in uremic patients might predispose to CVD.<sup>40</sup> On the other hand, CVD may lead to malnutrition, mediated by factors such as physical inactivity, sympathetic overactivity, and chronic inflammation.<sup>42,43</sup> For example, cardiac failure patients commonly suffer from anorexia with reduced nutritional intake and suffer from hypermetabolism caused by dyspnea, fever, or increased sympathetic activity. Reduced physical activity caused by fatigue also reduces somatic proteins and lean body mass. Overhydration with congestion may contribute to low serum albumin levels. A link between the presence of CVD and hypoalbuminemia in ESRD patients has been reported,<sup>33,44</sup> and that ESRD patients with CVD more frequently are malnourished, as evaluated by subjective global assessment of nutritional status (SGA), and have lower serum creatinine and plasma insulin-like growth factor-1 levels than patients without CVD.

## Inflammation

It is now well-established that ESRD is a state of chronic systemic inflammation. Several studies<sup>45</sup> have shown that chronic inflammation is highly prevalent in ESRD patients, irrespective of dialysis modality, with increased levels of serum C-reactive protein (CRP) and proinflammatory cytokines such as interleukin-6. Although multiple factors might be related to chronic inflammation in ESRD patients, causes of inflammation in this patient group are not well understood. However, clearly both nondialysis-related factors and the dialysis procedure per se may be responsible for the high prevalence of inflammation.<sup>45,46</sup>

After the observation by Bergström et al<sup>47</sup> in 1995 that an increased CRP level predicted survival in hemodialysis patients, several studies have confirmed further that chronic inflammation is associated with overall and cardiovascular mortality in ESRD patients.<sup>37,48-51</sup> Inflammation plays a key role in the atherosclerotic process<sup>52</sup> and it has been found that inflammation contributes to increased cardiovascular morbidity in ESRD patients.<sup>37,53-57</sup> It also should be emphasized that proinflammatory cytokines may have atherogenic effects.<sup>58-60</sup> Further support for this association is that the circulating levels of potent inhibitors of vascular calcification such as fetuin and matrix Gla protein are reduced by inflammation, suggesting that inflammation may contribute to vascular calcification in hemodialysis patients.<sup>61</sup>

Although several factors contribute to impaired nutritional status in uremic patients, inflammation may be one of the most important causes of malnutrition. Indeed, increased levels of cytokines may be one of the most important factors of wasting in ESRD patients.<sup>62,63</sup> The effects of cytokines on nutritional status may result from their catabolic effects on protein metabolism, their direct action on the gastrointestinal system, or indirect effects mediated by cytokines in the central nervous system, resulting in anorexia.<sup>64</sup> Furthermore, increased levels of proinflammatory cytokines may mediate malnutrition by increasing protein hydrolysis and muscle protein breakdown via activation of nuclear factor- $\kappa$  B<sup>65</sup> or the ubiquitin-proteasome proteolytic system.<sup>66</sup> Also, it has been suggested that leptin, which is up-regulated by proinflammatory cytokines, may mediate anorexia.<sup>67</sup>

Thus, there is a strong association between inflammation and malnutrition in ESRD patients and the serum albumin level is low in both of these conditions.<sup>34</sup> Inflammation and nutritional status in ESRD patients influence serum albumin concentrations through their effects on albumin catabolism and synthesis, respectively.<sup>68</sup> Because malnutrition and inflammation often are combined in uremic patients,<sup>34,40,69,70</sup> we have proposed that at least 2 types of malnutrition may occur in ESRD patients. Type 1 malnutrition is associated with anorexia because of the uremic syndrome. The inadequate nutritional intake is the predominant cause and can be treated effectively by increasing the nutritional intake. Type 2 malnutrition mainly is cytokine driven and is characterized by more marked hypoalbuminemia than in type 1 malnutrition, increased protein catabolism, and an inflammatory response, as evidenced by higher levels of CRP and proinflam-

matory cytokines. In type 2 malnutrition, inflammation and comorbid disease are the predominant causes and this condition is more difficult to treat by nutritional means unless the inflammation and comorbidities are treated first.

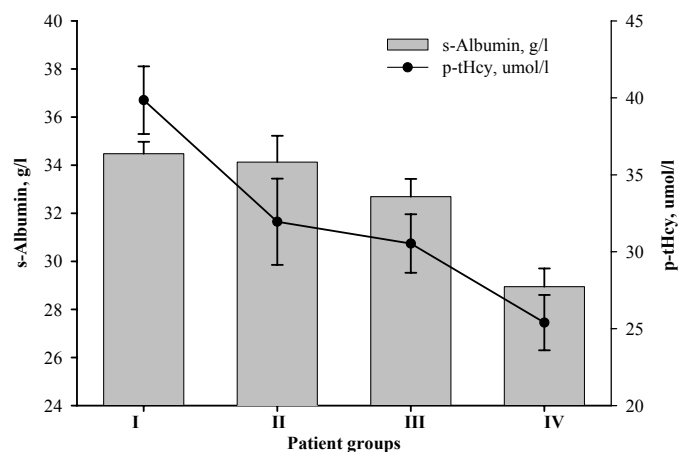
Moreover, malnutrition and inflammation are associated strongly with CVD<sup>70,71</sup> and it has been suggested that malnutrition in part is the consequence of cardiac failure, or is caused by infection/inflammation, which also triggers the development of atherosclerotic CVD, contributing to high mortality rates.<sup>40</sup> Indeed, malnutrition is more common in patients with inflammation and CVD, and both malnutrition and inflammation predict outcome in dialysis patients. The observation that malnutrition and inflammation are interrelated with atherosclerosis forms the basis for the concept of the malnutrition, inflammation, atherosclerosis (MIA) syndrome,<sup>70</sup> which is thought to be a major factor in the majority of premature deaths in ESRD patients.<sup>72</sup>

## Influence of Hypoalbuminemia, Malnutrition, Inflammation, and Diabetes Mellitus on Hcy

The serum albumin level is used commonly in clinical practice as an indicator of nutritional status based on the concept that the level of serum albumin reflects the visceral protein status and that hypoalbuminemia is prevalent in ESRD patients with protein malnutrition.<sup>33</sup> However, the serum albumin level is more than a marker of nutritional status because it is influenced by many nonnutritional factors, which in turn may affect nutritional status such as high age, protein losses (renal or by dialysis), fluid overload, infection, and other causes of inflammation that elicit a cytokine-mediated acute phase response (albumin behaves like a negative acute phase protein). Hence, the serum albumin level may be far from an ideal marker of nutritional status in ESRD patients but may to a large extent reflect various comorbid states that may be linked more directly than malnutrition to increased mortality.

Serum albumin is a powerful predictor of tHcy level.<sup>15,19,73</sup> Hcy mainly exists in plasma as a protein-bound form with albumin being the main Hcy binding protein. A positive correlation between plasma tHcy level and serum albumin level has been reported in ESRD patients in many studies.<sup>74</sup> This not only may be related to the high albumin binding of Hcy but also may indicate a nutritional component of tHcy (see later). The association between serum albumin level and tHcy level persists over time. In a longitudinal follow-up study in ESRD patients for 12 months after the start of dialysis treatment, we found a strong correlation between changes in tHcy levels and changes in serum albumin levels.<sup>9</sup>

Moreover, some of the studies with a reversed association in ESRD patients have shown a strong correlation between tHcy and serum creatinine levels, even stronger than that seen with serum albumin levels.<sup>24</sup> Because serum creatinine is not only an indicator of dialysis dose and efficiency but also an indicator of muscle mass and nutritional state, this asso-



**Figure 1** Influence of malnutrition (SGA > 1), inflammation (CRP < 10 mg/L), and malnutrition plus inflammation on serum albumin and plasma tHcy levels in ESRD patients (n = 274). Group 1 (n = 133), patients without malnutrition and without inflammation; group 2 (n = 40), patients with malnutrition only; group 3 (n = 45), patients with inflammation only; and group 4 (n = 56), patients with both malnutrition and inflammation. Data presented are mean  $\pm$  SE. The plasma tHcy and serum albumin levels were significantly different among the 4 patient groups ( $P < .0001$ ) and lower in patients with malnutrition and/or inflammation than in patients without malnutrition and inflammation.

ciation also may indicate a nutritional component of tHcy in dialysis patients. However, unlike serum albumin levels, the serum creatinine level may be less, or not at all, associated with inflammation. The correlation between tHcy and serum creatinine concentration also could be the result of the metabolic association between creatinine and homocysteine. The formation of creatine, the precursor of creatinine, depends on methyl donation by S-adenosylmethionine to become S-adenosylhomocysteine, leading to the formation of Hcy.

In addition, plasma tHcy level is associated with subjective and objective nutritional markers and protein intake in dialyzed and nondialyzed patients, and patients with signs of malnutrition have lower plasma tHcy levels than patients with normal nutritional status.<sup>19,24,28,75</sup> The impact of nutrition also is supported by the observation that tHcy levels increase in malnourished continuous ambulatory peritoneal dialysis (CAPD) patients receiving an amino acid-based peritoneal dialysis solution.<sup>76</sup> The presence of inflammation may complicate this relationship further by suppressing serum albumin, an important binding site for tHcy. This is supported by our recent findings in ESRD patients before the start of dialysis treatment in which the inflamed patients had lower tHcy levels than the noninflamed patients, and CRP and other inflammation markers were correlated negatively with tHcy levels.<sup>28</sup> The influence of inflammation on tHcy was suggested further by the finding that the presence of both inflammation and malnutrition in the ESRD patient was associated with a more marked reduction in tHcy level than the reduction caused by the presence of malnutrition without inflammation.<sup>28</sup> Figure 1 shows this relationship in ESRD patients and shows that the plasma tHcy and serum albumin

levels were lower in patients with inflammation or malnutrition compared with patients without inflammation and malnutrition, and these levels were reduced further if patients had both malnutrition and inflammation.

The presence of DM also may influence this relationship. Some studies in ESRD patients<sup>15,24,77</sup> and in diabetic patients without overt nephropathy<sup>78</sup> showed lower plasma tHcy levels in diabetic patients than in nondiabetic patients. The mechanism(s) responsible for the reduction of tHcy levels in patients with DM is unknown. In a recent study in ESRD patients,<sup>15</sup> we found lower serum albumin levels and a higher prevalence of malnutrition in diabetic patients than in nondiabetic patients, which might have influenced the plasma tHcy levels. Because the prevalence of DM is high in ESRD patients its presence further complicates this relationship.

## Summary

Based on these observations it seems that various confounding factors probably are responsible for the reverse associations between tHcy and the mortality rate. The effect of hypoalbuminemia especially, whatever the cause (eg, malnutrition inflammation and/or DM), on tHcy levels may obscure the detrimental effect of hyperhomocysteinemia on outcome in ESRD patients. Malnutrition and inflammation are strong predictors of CVD, but they also are strong predictors of serum albumin level, which is a major determinant of tHcy levels. This may explain the reverse association in recent literature between tHcy levels and clinical outcome in uremic patients. The reverse association may not be confined to chronic dialyzed patients, but also exists in predialysis patients. In a recent study,<sup>28</sup> we found that a low tHcy level at the start of dialysis therapy was associated with hypoalbuminemia, inflammation malnutrition, and worse outcome.

Because hyperhomocysteinemia is highly prevalent in ESRD patients, the paradoxical reverse association between tHcy level and clinical outcome in ESRD patients does not as such contradict a possible role for Hcy in the vascular pathogenesis leading to atherosclerosis, considering that even a mild increase above the normal tHcy level appears to be a risk factor for CVD in the general population. Hence, almost all ESRD patients may have had long-standing increased plasma tHcy levels within a range that makes them prone to develop atherosclerosis even in the absence of a linear relationship. On the other hand, malnutrition inflammation, which is associated with lower serum albumin and tHcy levels, may overwhelm this relationship and thus may be responsible for the inverse association. In other words, hyperhomocysteinemia may represent one of many factors in uremia that contribute to a general increase in the risk for CVD. However, because hyperhomocysteinemia is an inherent feature of uremia and therefore an increased risk caused by this complication is a more or less constant consequence of uremia, the impact (if any) of incremental changes in the tHcy level may not be significant compared with many other risk factors such as malnutrition and inflammation, which are more variable. It can be argued that adjusting for markers of nutrition and/or inflammation will eliminate the risk factor reversal

phenomenon in multivariate models including that seen for tHcy in ESRD patients, and such adjustments are warranted in future studies in this area.

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