Consequences of low plasma histidine in chronic kidney disease patients: associations with inflammation, oxidative stress, and mortality

Makoto Watanabe, Mohamed E Suliman, Abdul Rashid Qureshi, Elvia Garcia-Lopez, Peter Bárány, Olof Heimbürger, Peter Stevenrinkel, and Bengt Lindholm

ABSTRACT

Background: Histidine is considered as an antiinflammatory and antioxidant factor. Histidine deficiency may contribute to an impaired nutritional state in patients with chronic kidney disease (CKD).

Objective: We aimed to investigate the consequences of plasma histidine deficiency in CKD patients.

Design: CKD patients (n = 325; 203 M) with a median age of 54 y (range: 19–70 y) were evaluated shortly before the beginning of renal replacement therapy. The median glomerular filtration rate was 6.4 mL/min (range: 0.8–14.5 mL/min). Nutritional status was assessed by subjective global assessment. Survival was followed for up to 60 mo; 101 patients died.

Results: Plasma histidine concentrations were significantly lower in CKD patients with history of cardiovascular disease, presence of plaques, protein-energy wasting, and inflammation. Plasma histidine was negatively associated with age, C-reactive protein, interleukin-6, leukocytes, thrombocytes, fibrinogen, hepatocyte growth factor, adhesion molecules, insulin-like growth factor-1, and 8-hydroxy-2'-deoxyguanosine and was positively associated with handgrip strength, hemoglobin, S-albumin and fetuin-A. A multivariate regression analysis showed that histidine concentrations were independently associated with hepatocyte growth factor, hemoglobin, and fetuin-A. In unadjusted analysis, a low histidine concentration was associated with all-cause mortality (log rank chi-square test = 8.9; P = 0.002). After adjustment for age, sex, cardiovascular disease, inflammation, diabetes mellitus, serum S-albumin, and amino acid supplementation, the association between low histidine and mortality remained significant (hazard ratio: 1.55; 95% CI: 1.02, 2.40; P < 0.05).


INTRODUCTION

Patients with chronic kidney disease (CKD) generally have a normal pattern of plasma amino acids (AAs) — ie, high plasma concentrations of several nonessential AAs (NEAAs) and low concentrations of most essential AA (EAs) (1–7). Specifically among NEAAs, the plasma and intracellular concentrations of histidine are low in uremia patients (2, 7).

Histidine has been considered as a dietary EAA for human infants and is generally designated as a NEAA for adult humans (8). However, in CKD patients, histidine is referred to as a conditional EAA, because CKD patients generally fail to attain nitrogen balance by following a diet low in histidine (8). Early in the 1970s, Bergström et al (9) reported that histidine is indispensable for uremia patients and that the addition of histidine to EAA supplements improves the nitrogen balance, which suggested that histidine promotes net nitrogen synthesis in CKD patients. Kopple and Swendsen (10) reported that, with ingestion of a histidine-deficient diet, nitrogen balance gradually becomes negative, serum albumin decreases, serum iron rises, and hematocrit falls. Moreover, histidine is well known as an efficient scavenger of the hydroxyl radical and singlet oxygen (11), and it can protect LDL cholesterol against oxidation (12).

The mechanisms behind the alterations of AA concentrations in uremia are not fully understood. Among several factors, a state of inflammation-related wasting in CKD patients may also contribute to these alterations (13). The prevalence of protein-energy wasting (PEW) in CKD patients is high, and inflammation is more prevalent in malnourished patients than in those with a healthy nutritional status (14). Because histidine supplementation alone (15) or with other AAs (16) may improve nutritional status and because wasting in CKD patients is strongly interrelated to inflammation and CVD (14), it is possible that histidine may have a unique association with these conditions.

Hepatocyte growth factor (HGF), a pleiotropic cytokine, is a mesenchymal glycoprotein with the potential for stimulating cell growth, tissue regeneration, and even angiogenesis (17). HGF can stimulate protein production by hepatocytes in a dose-dependent manner (18). In addition, it has been shown that HGF synthesis is stimulated in the liver by branched-chain AAs (19, 20).
SUBJECTS AND METHODS

Patients

Three hundred twenty-five CKD patients (203 male) with a median age of 54 (range: 19–70) y were evaluated shortly before the beginning of kidney replacement therapy; the median glomerular filtration rate was 6.4 mL/min (range: 0.8–14.5 mL/min). The study exclusion criteria were age > 70 y, overt infectious complications, and unwillingness to participate in the study. The causes of CKD were diabetic nephropathy in 102 (31%), chronic glomerulonephritis in 88 (27%), polycystic kidney disease in 35 (11%), nephrosclerosis in 13 (4%), collagen disease in 14 (4%), congenital disease in 5 (1%), other causes in 19 (5%), and unknown causes in 49 (15%) patients.

One hundred nine patients (34%) had clinical signs of cerebrovascular, cardiovascular, or peripheral vascular disease (or all 3) at the start of the study. Of these 109 patients, 67 had one or more myocardial infarctions or clinical signs of ischemic heart disease (angina pectoris) or had undergone coronary artery bypass surgery; 31 patients had peripheral ischemic vascular disease; 34 patients had a history of stroke or cerebral bleeding; and 5 patients had a history of an aortic aneurysm. In the first 100 patients participating in this study, the right and left carotid stenosis were scored as the absence of plaques/L50871 defined as a localized intima-media thickness of 9HDI; Advanced Technology Laboratory, Bothwell, WA) patients participating in this study, the right and left carotid plaque occurrence was scored as the absence of plaques/L50871/L50140 defined as a localized intima-media thickness of 9HDI; Advanced Technology Laboratory, Bothwell, WA)

The study protocol was approved by the Ethics Committee of Karolinska University Hospital Huddinge, Stockholm, Sweden, and informed consent was obtained from each patient. The patients were investigated as part of an ongoing prospective study (14).

Outcome ascertainment

Survival was determined from the day of examination until 5 March 2006, and the median follow-up period was 27 (range: 3–60) mo. The patients were censored at death or when they completed the 5-y follow-up period; there was no loss of follow-up of any patient. Within the follow-up period, 101 patients (31%) died and 125 patients (38%) underwent transplantation.

Nutritional status assessment

Subjective global nutritional assessment was used to evaluate the overall protein-energy nutritional status (23). Subjective global nutritional assessment included 6 subjective assessments. Three were based on the patient’s history of weight loss, incidence of anorexia, and incidence of vomiting, and 3 were based on the subjective grading of muscle wasting, the presence of edema, and the loss of subcutaneous fat. On the basis of 3 assessments, each patient was given a score that reflects the nutritional status, as follows: 1 = normal nutritional status, 2 = mild PEW, 3 = moderate PEW, and 4 = severe PEW. Thus, PEW was defined as an subjective global nutritional assessment score of >1. Body mass index (BMI) was defined as the body weight (in kg) divided by the square of patient height (in m). Lean body mass was evaluated by using dual-energy X-ray absorptiometry (DXA). The study exclusion criteria were age > 70 y, overt infectious complications, and unwillingness to participate in the study. The causes of CKD were diabetic nephropathy in 102 (31%), chronic glomerulonephritis in 88 (27%), polycystic kidney disease in 35 (11%), nephrosclerosis in 13 (4%), collagen disease in 14 (4%), congenital disease in 5 (1%), other causes in 19 (5%), and unknown causes in 49 (15%) patients.

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Laboratory methods

After an overnight fast, venous blood samples were taken for analysis. The samples were kept frozen at −70 °C if not analyzed immediately. Plasma histidine concentrations were measured with the use of reversed-phase HPLC and fluorometric detection, as described elsewhere (26). Serum HGF was determined by using a solid-phase enzyme-linked immunosorbent assay (ELISA). Plasma interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and insulin-like growth factor 1 concentrations were analyzed in serum by immunometric assays on an IMMULITE Analyzer (DPC, Los Angeles, CA) according to the instructions of the manufacturers. High-sensitivity C-reactive protein (CRP) was measured by nephelometry. Hemoglobin, leukocyte, S-albumin, creatinine, total cholesterol, triacylglycerol, and HDL cholesterol were analyzed by using routine methods. Glomerular filtration rate was estimated as the mean of urea and creatinine clearances. Serum fetuin-A concentrations were measured by
using a sandwich immunoenzymometric assay using 2 polyclonal human fetuin-A–specific antibodies (Epitope Diagnostics Inc, San Diego, CA). Serum 8-hydroxy-2’-deoxyguanosine (8-OHdG) was measured by using a competitive ELISA kit (Japan Institute for Control of Aging, Shizuoka, Japan). Serum concentrations of the soluble adhesion molecules—soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cellular adhesion molecule-1 (VCAM-1)—were measured by immunoenzymatic assay using commercially available standard kits (Immunotech, Marseille, France).

Statistical analysis

All values were shown as medians and ranges unless indicated otherwise. *P* < 0.05 was considered to be significant. Comparisons between 2 groups were assessed, as appropriate, with Wilcoxon’s rank-sum test for continuous variables and with Fisher’s exact test for nominal variables. Correlations were performed by using the Spearman rank test (ρ). To evaluate the sensitivity and specificity of plasma histidine, as a predictor of mortality, a receiver operating characteristic (ROC) analysis was performed. The optimum cutoff value, with the combination of the highest sensitivity and specificity, was calculated. The more the area under the curve (AUC) approaches 1, the higher the predictive value. Survival analyses were made with the Kaplan-Meier survival curve or the Cox proportional hazard model. The hazard ratio (HR) for mortality was presented as HR (95% CIs). To evaluate the predictive value. Survival analyses were made with the Kaplan-Meier survival curve or the Cox proportional hazard model. The hazard ratio (HR) for mortality was presented as HR (95% CIs).

RESULTS

The median plasma histidine concentration of the studied 225 CKD patients was 74 (range: 12–214) µmol/L. The prevalence of CVD, plaques (*n* = 105), diabetes mellitus, PEW, and inflammation (defined as CRP ≥ 10 mg/L) were 34%, 72%, 32%, 32%, and 35%, respectively, in all CKD patients. Compared with their respective counterparts, plasma histidine concentrations were significantly lower in patients with PEW (82 ± 26 and 71 ± 24 µmol/L, respectively; *P* < 0.0001), inflammation (81 ± 25 and 71 ± 24 µmol/L, respectively; *P* < 0.0001), history of CVD (80 ± 25 and 71 ± 24 µmol/L, respectively; *P* < 0.001) (**Figure 1**), and plaques (80 ± 24 and 69 ± 22 µmol/L, respectively; *P* = 0.01). There were no significant differences in plasma histidine concentration between diabetic and nondiabetic patients (79 ± 28 and 77 ± 24 µmol/L, respectively) (**Figure 1**) or between male and female patients (78 ± 26 and 76 ± 24 µmol/L, respectively).

Sixty-nine patients (31%) were receiving supplementation with AAs (Aminess N; Recip AB). The prevalence of patients with wasting or inflammation did not differ significantly between the patients receiving AAs and those not receiving AAs. The plasma concentration of histidine was significantly higher in patients receiving AA supplements, whereas plasma concentrations of HGF and CRP were significantly lower in the patients receiving AA than in nonsupplemented patients (**Figure 2**). Moreover, hemoglobin concentrations were significantly higher in patients receiving than in patients not receiving AA supplements (110 ± 14 and 102 ± 14 g/L, respectively; *P* < 0.001).

The baseline clinical and laboratory data of the patients, who were divided into 2 groups based on the median (74 µmol/L) of plasma histidine, are summarized in **Table 1**. Patients with low histidine concentrations were older, had higher prevalence of clinically manifest CVD and documented presence of plaques, were more often malnourished, and more likely to have inflammation than were patients with high histidine concentrations. Plasma histidine concentrations were negatively correlated with HGF (**Figure 3**), insulin-like growth factor 1, CRP, IL-6, leukocyte count,
Histidine range (µmol/L) 12–74 75–214

Male (%) 60 64

Age (y) 58 (22–70)² 50 (19–70)³

BMI (kg/m²) 23.9 (13.3–37.8) 24.4 (16.2–38.6)

GFR (mL·min⁻¹·1.73 m²⁻¹) 6.0 (0.8–14.1) 6.6 (3.0–14.5)

Protein-energy wasting (%) 42 23³

Cardiovascular disease (%) 42 23³

Carotid plaques (%) 87 53³

Inflammation (%) 43 27³

Diabetes mellitus (%) 32 32

Lean body mass (kg) 49 (28–73) 50 (30–72)

Hand grip strength (kg) 28 (6–53) 31 (7–62)³

nPNA (g·kg⁻¹·d⁻¹) 0.68 (0.21–1.20) 0.67 (0.39–1.28)

IGF-1 (ng/L) 138 (25–558) 185 (44–562)³

S-Albumin (g/l) 33 (15–45) 35 (8–51)

Thrombocytes (10⁹/L) 295 (79–822) 247 (58–567)

Leukocytes (10⁹/L) 8.4 (2.8–39.3) 7.5 (3.6–22.4)

Cholesterol (mmol/L) 5.4 (2.4–10.6) 5.2 (1.7–10.7)

Creatinine (µmol/L) 652 (2–1382) 703 (295–1860)

C-reactive protein (mg/L) 5.4 (2.4–10.6) 5.2 (1.7–10.7)

C-reactive protein (mg/L) 7.9 (0.2–163) 3.9 (0.2–218)³

Interleukin-6 (pg/mL) 7.2 (0.8–46.5) 5.6 (0.8–112)³

TNF-α (pg/mL) 9.9 (3.1–18.1) 9.8 (3.8–70.0)

Fibrinogen (g/L) 5.0 (2.3–11.2) 4.5 (2.2–11.2)³

8-OHdG (ng/mL) 0.69 (0.21–2.42) 0.67 (0.13–3.80)

sVCAM-1 (ng/mL) 1330 (608–2795) 1273 (492–4238)³

sICAM-1 (ng/mL) 253 (132–551) 241 (99–655)³

Fetuin-A (g/L) 0.22 (0.03–0.83) 0.25 (0.06–0.92)³

HGF (ng/mL) 3.5 (0.6–30) 2.8 (0.5–102)³

¹Low histidine, ≤74 µmol/L; high histidine, >74 µmol/L. GFR, glomerular filtration rate; nPNA, normalized protein equivalent of nitrogen appearance; IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-α; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; sVCAM-1, soluble vascular cellular adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; HGF, hepatecty growth factor.

²Median; range in parentheses (all such values). Wilcoxon rank-sum test.

³,⁴Significantly different from low-histidine group: ³P < 0.05; ⁴P < 0.001.

⁵Fisher’s exact test.
in chronic kidney disease patients

TABLE 2
Spearman rank correlation coefficients (ρ) for plasma histidine concentration in relation to pertinent variables in chronic kidney disease patients

<table>
<thead>
<tr>
<th></th>
<th>ρ</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>−0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (mL·min⁻¹·1.73 m²⁻)</td>
<td>0.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Hand grip strength (kg)</td>
<td>0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>nPNA (g·kg⁻¹·d⁻¹)</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-1 (ng/L)</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocytes (10⁹/L)</td>
<td>−0.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>0.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thrombocytes (10⁹/L)</td>
<td>−0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-Albumin (g/L)</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>−0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>−0.11</td>
<td>NS</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>−0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>−0.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>−0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>−0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8-OhD (ng/mL)</td>
<td>−0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>sVCAM-1 (ng/mL)</td>
<td>−0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICAM-1 (ng/mL)</td>
<td>−0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fetuin-A (g/L)</td>
<td>0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HGF (ng/mL)</td>
<td>−0.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 FGR, glomerular filtration rate; nPNA, normalized protein equivalent of nitrogen appearance; IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-α; 8-OhD: 8-hydroxy-2‘-deoxyguanosine; sVCAM-1, soluble vascular cellular adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; HGF, hepatocyte growth factor.

DISCUSSION

Plasma and intracellular concentrations of histidine are decreased in CKD patients, and Bergström et al (9) reported that the addition of histidine (included in an EAA supplement) to uremia patients improved nitrogen balance and promoted net protein synthesis without any increase of the blood urea concentration. On the basis of the present study and the results of a study by Kopple and Swendseid (10), histidine has been considered to be an EAA in uremia patients. Moreover, it was shown by Kult (15) that a daily oral supplementation of 1.5 g histidine, with no other AA, for 12 wk resulted in higher concentrations of total protein, albumin, prealbumin, and the complement components C1q, C3c, C3, C1s inactivator, and C3 activator in 42 CKD patients with a glomerular filtration rate < 10 mL/min. Currently, oral and intravenous supplementation of AAs to uremia patients and the use of AA-based peritoneal dialysis solutions in general includes histidine because of its status as a conditional EAA in uremia and its associated beneficial effect on the nitrogen metabolism and nutritional status. The mechanism or mechanisms behind the deranged metabolism of AAs and the causes of low extracellular and intracellular histidine concentrations in uremia are unclear. PEW is common in CKD patients and is suggested as one of the causes of AA deficiency (16, 27). Indeed, in the present study, the patients with PEW had lower concentrations of histidine, which were also associated with nutritional markers, than did the patients without PEW. However, the findings of the present study

TABLE 3
Stepwise multivariate regression model of predictors of plasma histidine in chronic kidney disease patients

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>P</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>67.14</td>
<td>10.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HGF (ng/mL)</td>
<td>−2.33</td>
<td>0.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fetuin-A (g/L)</td>
<td>19.91</td>
<td>7.67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>0.18</td>
<td>0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>8-OhD (ng/mL)</td>
<td>−9.82</td>
<td>3.83</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

1 HGF, hepatocyte growth factor; 8-OhD, 8-hydroxy-2‘-deoxyguanosine. The multivariate regression model included the following parameters: age, sex, wasting, history of cardiovascular disease, diabetes mellitus, amino acid supplement, S-albumin, hemoglobin, HGF, 8-OhD, and fetuin-A. Total adjusted r² = 0.14.
suggest that the low plasma concentration of histidine in CKD is attributed not only to wasting, but also to inflammation.

We have reported that inflammation has an independent role as a contributing cause of low plasma AAs in CKD patients (13). In the current study, histidine was indeed low in patients with inflammation and was inversely correlated with several inflammation markers. In contrast, it has been reported that histidine may have an influence on the inflammatory cascade, and histidine has been reported to have potent antiinflammatory and antioxidative properties (28). Son et al (29) reported that histidine in a dose-dependent manner inhibits oxidative stress– and TNF-α–induced IL-8 secretion at the transcriptional level and also abolishes the NF-κB–dependent activation of IL-8 promoter induced by TNF-α. In addition, histidine supplementation could effectively down-regulate IL-6 and TNF-α in a diabetic mice model. In rheumatoid arthritis patients, oral administration of histidine was reported to improve grip strength and walking speed and to reduce the rate of erythrocyte sedimentation (30). It has been suggested that the absence of histidine led to γ-globulin aggregation and inflammation and, furthermore, that exogenous histidine would then prevent the aggregation of gamma globulin and the consequent inflammatory reaction (30). Thus, the present findings and those of previous studies suggest that histidine may have antiinflammatory effects and that the plasma concentration of histidine may be associated with the inflammation state and is not regulated only by nutritional status in CKD patients. This possibility is supported by our observation that supplementation of AAs, including histidine, was associated with low CRP.

HGF is mainly cleared by the liver; only <10% is cleared by the kidneys (31). Higher concentrations of HGF correlate with the progression and prognosis of many diseases. In CKD patients, HGF accumulates (21) and its concentration is associated with inflammation (22). In the current study, histidine showed a significant independent negative association with HGF, and the patients with high HGF concentrations thus had low plasma histidine concentrations. Moreover, the patients receiving supplementation with AAs, which includes histidine, had lower concentrations of circulating HGF than did the patients not receiving AA supplementation, which suggests that the administration of AAs, including histidine, may have a beneficial effect in reducing HGF or that patients with low HGF were more likely to receive AA supplementation.

Moreover, in the present study, plasma histidine was negatively associated with 8-OHdG, a biomarker of oxidative stress on DNA, which suggests an association between histidine deficiency and oxidative damage in CKD patients. Histidine is one of the most vulnerable AAs to oxidative reactions by metal-catalyzed oxidation and lipid peroxidation, and it may be one of the origins of protein carbonyls (32). Several studies have indicated that the antioxidative effects of histidine and carnosine are based on their ability to scavenge free radicals and to chelate divalent metal ions (33) and that these substances effectively inhibited glucose-induced oxidation and glycation in human LDL (34). It was reported that histidine and carnosine concentrations in rat tissues could be increased by dietary supplementation, and that this supplementation could contribute to antioxidative protection in those tissues (35, 36). Overall, although the current study lacks a mechanistic explanation, its findings suggest that histidine may have a role as an antiinflammatory and antioxidative stress factor, and that the use of histidine as a supplementary compound may prevent or suppress complications in CKD patients by reducing inflammation and oxidative stress and by improving nutritional status and nitrogen metabolism. However, because only one oxidative stress marker was analyzed in the present study, and, furthermore, because the association between plasma histidine and 8-OHdG concentrations was rather weak, speculation about a direct association between histidine concentration and antioxidant capacity should be viewed cautiously. Because both histidine and 8-OHdG concentrations are related to the degree of renal failure and to factors associated with uremia, such as a state of chronic inflammation, it is not possible to establish, in the current study, the validity of 8-OHdG as a “true” biomarker of oxidative stress.

It us interesting that, in the present study, a low plasma histidine concentration was associated with CVD and the presence of carotid plaques, which are thought to be related to inflammation and oxidative stress. Also, in univariate and multivariate analyses, a low histidine concentration was associated with a worse survival—i.e., a nearly 55% greater risk for mortality, independent of potential confounders and risk factors. Moreover, in the present study, hemoglobin was associated with histidine concentrations in univariate and multivariate analyses, and patients who received AA supplements had higher concentrations of hemoglobin than did patients not receiving AA supplementation. These findings accord with the observations by Cho et al (37) and Kopple and Swendseid (10) of a gradual decline in hemoglobin and hematocrit concentrations in healthy young men receiving a low-histidine diet and with Kopple and Swendseid’s observations in CKD patients (10). However, histidine supplementation as such failed to improve anemia in uremia patients, whether they were undergoing dialysis or not (38, 39).

Some limitations of the present study should be considered. First, determination of a single sample at a certain time may fail to reflect the natural course of the disease. Second, this was a post hoc analysis in a study that was not initially designed to examine such associations, which may limit the value of the study. Third, the study does not provide a mechanistic explanation, and, therefore, further studies are needed in this area.

In conclusion, these findings suggest that a low plasma concentration of histidine is associated with inflammation, oxidative stress, PEW, and mortality in CKD patients. The potential beneficial value of histidine supplementation may be not only an improvement of nutritional status and nitrogen metabolism (15) but also histidine’s own antiinflammatory and antioxidant properties. Because supplementation with histidine alone in CKD patient has, to our knowledge, been studied only once (15), such potential effects remain to be confirmed in further prospective randomized studies in CKD patients.

The authors’ responsibilities were as follows—MW: design of the study, analysis of data, and writing the manuscript; MES: analysis of data and writing the manuscript; ARQ: analysis of data and writing the manuscript; OH: design of the experiment and collection of data; PB: design of the experiment and collection of data; PS: design of the experiment, collection and analysis of data, and writing the manuscript; and BL: design of the experiment, analysis of data, and writing the manuscript. BL is affiliated with Baxter Healthcare Inc, and PS is a member of the advisory board of Gambro. None of the other authors had a personal or financial conflict of interest.
REFERENCES


