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Factors predicting malnutrition in hemodialysis patients: A cross-sectional study

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Factors predicting malnutrition in hemodialysis patients: A cross-sectional study. Signs of protein-energy malnutrition are common in maintenance hemodialyis (HD) patients and are associated with increased morbidity and mortality. To evaluate the nutritional status and relationship between various parameters used for assessing malnutrition, we performed a cross-sectional study in 128 unselected patients treated with hemodialysis (HD) thrice weekly for at least two weeks. Global nutritional status was evaluated by the subjective global nutritional assessment (SGNA). Body weight, skinfold thicknesses converted into % body fat mass (BFM), mid-arm muscle circumference, hand-grip strength and several laboratory values, including serum albumin (S_{Alb}), plasma insulin-like growth factor I (p-IGF-I), serum C-reactive protein (S_{CRP}) and plasma free amino acids, were recorded. Dose of dialysis and protein equivalence of nitrogen appearance (nPNA) were evaluated by urea kinetic modeling. The patients were subdivided into three groups based on SGNA: group I, normal nutritional status (36%); group II, mild malnutrition (51%); and group III, moderate or (in 2 cases) severe malnutrition (13%). Clinical factors associated with malnutrition were: high age, presence of cardiovascular disease and diabetes mellitus. nPNA and Kt/V_{urea} were similar in the three groups. However, when normalized to desirable body wt, both were lower in groups II and III than in group I. Anthropometric factors associated with malnutrition were low body wt, skinfold thickness, mid-arm muscle circumference (MAMC), and hand-grip strength. Biochemical factors associated with malnutrition were low serum levels of albumin and creatinine and low plasma levels of insulin-like growth factor 1 (IGF-1) and branched-chain amino acids (isoleucine, leucine and valine). The serum albumin (S_{Alb}) level was not only a predictor of nutritional status, but was independently influenced by age, sex and S_{CRP}. Plasma IGF-1 levels also reflected the presence and severity of malnutrition and appeared to be more closely associated than S_{Alb} with anthropometric and biochemical indices of somatic protein mass. Elevated S_{CRP} (> 20 mg/liter), which mainly reflected the presence of infection/inflammation and was associated with hypoalbuminemia, was more common in malnourished patients than in patients with normal nutritional status, and also more common in elderly than in younger patients. Plasma amino acid levels, with the possible exception of the branched-chain amino acids (isoleucine, leucine, valine), seem to be poor predictors of nutritional status in hemodialysis patients.

Key words: malnutrition in HD, hemodialysis and malnutrition, nutrition status in HD, subjective global nutritional assessment, predictors of nutritional status in HD.

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Protein-energy malnutrition and wasting are present in a large proportion of patients with chronic renal failure. This may be a consequence of multiple factors, including disturbances in protein and energy metabolism, hormonal derangements, infections and other superimposed illnesses, as well as reduced food intake because of anorexia, nausea and vomiting, caused by uremic toxicity. After commencement of maintenance dialysis treatment, most of the overt symptoms of uremia diminish or disappear and the patients generally experience increased well-being and improved appetite. However, several reports show that the prevalence of protein-energy malnutrition in dialysis patients is high. In hemodialysis (HD) patients between 23 to 76% are reported to be malnourished, the variability presumably being related to factors such as age, case mix, co-morbid conditions and quality of dialysis therapy [1–7].

During recent years, several studies in HD patients have shown an association between signs of malnutrition, particularly low serum albumin, and increased morbidity and mortality [8–11]. However, the extent to which this reflects a cause-effect relationship is not clear, since several co-morbidity factors, which are of more importance as causes of death *per se*, may have secondary effects on various parameters used to assess the nutritional status [12].

The present cross-sectional study of nutritional status was performed to assess the prevalence and degree of protein-energy malnutrition in a population of HD patients in Stockholm, Sweden. Another aim was to evaluate the relationship between various parameters used to evaluate the nutritional status and to analyze how co-morbid factors influenced these parameters. Among the biochemical measurements, we included serum C-reactive protein, considering that this acute phase protein is a marker of co-morbidity and that the acute phase response inhibits the generation of serum albumin [13, 14], which is generally used as a nutritional marker in patients with renal failure.

METHODS

Patients

All patients with chronic renal failure who were treated with maintenance HD at the various dialysis centers affiliated with the Renal Clinic, Huddinge University Hospital and who had been on hemodialysis for at least two weeks were eligible for inclusion in the present study. Of a total of 164 patients, 128 (76 males and 52

females, median age 65 years range 26 to 84 years) agreed to participate, while 36 either refused or the staff did not cooperate. The causes of renal failure in the 128 patients were diabetic nephropathy ($N = 23$), chronic glomerulonephritis ($N = 38$), polycystic kidney disease ($N = 13$), pyelonephritis and interstitial nephritis ($N = 14$), and other diseases or unknown etiology ($N = 40$). Thirteen of the diabetic patients were insulin-dependent. Seventy-seven patients had signs of cardiovascular and/or peripheral vascular disease (grouped as CVD). Of these, 20 had suffered one or more myocardial infarctions, 15 had ischemic heart disease but no prior myocardial infarction, one had an aortic aneurysm and 11 had peripheral ischemic atherosclerotic vascular disease. Nineteen patients suffered from chronic heart failure. Six patients had cerebrovascular disease with neurological symptoms, following one or more attacks of stroke; all these patients also had signs of cardiovascular disease. Of the 23 diabetic patients, 17 had CVD. Three patients had increased serum aspartate aminotransferase levels at the time of the study. Ninety-six patients had no residual renal function, defined as renal urea clearance < 0.5 ml/min.

The patients were treated with oral sodium bicarbonate, calcium carbonate and/or aluminum hydroxide, as required to prevent acidosis and hyperphosphatemia. Forty patients were taking anti-hypertensive drugs such as angiotensin-converting enzyme inhibitors, beta-blockers and calcium-blockers. Fifteen patients with residual renal function were treated with high doses of furosemide (250 to 500 mg/day) to increase urinary output and renal sodium excretion. Recombinant human erythropoietin was given to 74 patients. All patients were prescribed water soluble vitamins (B and C) as multivitamin tablets. Fourteen patients were hospitalized at the time of the investigation.

Hemodialysis (HD) was performed three times per week. Dialyzers with low-permeability, modified cellulosic membranes (cellular acetate or hemophan) were used in 120 patients; membrane surface areas were 1.0 m^2 ($N = 1$), 1.3 m^2 ($N = 7$), 1.7 m^2 ($N = 81$), 1.8 m^2 ($N = 27$) and 2.1 m^2 ($N = 4$). Eight patients were treated with high-flux polysulfone dialyzers having membrane areas of 1.3 m^2 ($N = 1$) and 1.9 m^2 ($N = 7$). The dialyzers were not reused. The protein equivalent of nitrogen appearance (PNA), which in steady state patients gives an approximation of the protein intake [15], was estimated from the determination of the urea appearance rate by urea kinetic modelling, using the single pool, variable volume model, according to Farell and Gotch [16]. The contribution of residual renal function (renal urea clearance ≥ 0.5 ml/min) was included in the calculations. Protein equivalence of nitrogen equivalence (PNA) per kg absolute body wt (ABW) was recalculated per "normalized" body wt (nBW), obtained by dividing the post-dialysis distribution volume of urea (V) by 0.58 [17]. Thus, nPNA = PNA * 0.58/V. Prescribed Kt/V_{urea} for one single dialysis was calculated from dialyzer + renal urea clearance (K), dialysis time (t) and V obtained by urea kinetic modelling [16]. Outcome Kt/V_{urea} was calculated by the Daugirdas method [18], based on the reduction in the serum urea concentration during dialysis and taking the effect of ultrafiltration into consideration. The results with the two methods were similar; we therefore prefer to present in the results only outcome Kt/V_{urea}, since its calculations is independent of technical artifacts. The contribution of renal urea clearance was added to K in the patients who had residual renal function (renal urea clearance ≥ 0.5 ml/min). Kt/V_{urea} and PNA were also related to the desirable body wt (DBW), by calculations based on the patient's height, sex and frame size match, using the Metropolitan height and weight tables [15, 19].

Forty-four healthy volunteers (24 male and 20 females, median age 34 years range 21 to 64 years) were selected for comparative analysis of nutritional status, anthropometric and biochemical variables.

The study protocol was approved by the Ethics Committee of Karolinska Institute at Huddinge University Hospital, Stockholm, and informed consent was obtained from each patient and control subject.

Nutritional status, anthropometric measurements (except absolute) and blood sampling for biochemical analyses were performed in all subjects after an overnight fast; the HD patients were investigated on a mid-week, dialysis-free day.

Subjective global nutritional assessment

Subjective global nutritional assessment (SGNA) was used to evaluate the overall protein-energy nutritional status [20, 21]. The SGNA includes six subjective assessments, three based on the patient's history of weight loss, incidence of anorexia and incidence of vomiting, and three based on the physician's grading of muscle wasting, presence of edema and loss of subcutaneous fat. Based on these assessments each patient was given a score that reflected the nutrtional status as follows: 1 = normal nutritional status, 2 = mild malnutrition, 3 = moderate malnutrition, and 4 = severe malnutrition.

Anthropometric measurements

Absolute body wt (ABW) was recorded post-dialysis with the subjects lightly dressed and without shoes; the patients were also weighed pre-dialysis. A difference in ABW from normal was recorded as the percentage of actual to desirable body wt (%A/DBW). Skinfold thickness was measured with a Harpenden caliper at four sites (triceps, biceps, subscapular and suprailiac) on the non-dominant arm of the controls and in the fistula-free arm of the uremic patients. The results were converted into density, by the method of Durnin and Womersley [22] and converted into body fat mass (BFM) by using the equation of Siri [23]. The mid-arm muscle circumference (MAMC) was derived from the triceps skinfold thickness (TSF) and mid-arm circumference (MAC) as follows: MAMC = MAC $-$ (π * TSF). Hand-grip strength (HGS) was measured using the Harpenden dynamometer. The subjects were instructed to apply as much hand-grip pressure as possible, using the dominant hand and the non-dominant hand. The measurements were repeated three times and the highest score was recorded. The individual values for anthropometric variables (BFM, MAMC, HGS) were normalized by converting them to % of controls, when included in the correlation and regression analyses. Subjective global nutritional assessment and the anthropometric measurements were made by an investigator (A.R.Q.) experienced with these methods. The investigator was not aware of the biochemical data at the time of the examination.

Biochemical analyses

Venous blood samples from HD patients and control subjects were collected immediately before the anthropometric measurements were performed. Blood was also drawn before and after the first dialysis of the week, and again before the next dialysis for

urea determinations used to calculate urea kinetics. Blood hemoglobin, total lymphocyte counts and blood glucose and serum biochemistries were analyzed by routine methods. Serum albumin was determined by the bromcresol purple method; this method underestimates albumin by about 1 g/liter compared to a reference method using immunonephelometry [24]. Serum C-reactive protein (S_{CRP}) was measured by using an immunonephelometric method (Tina-quant®; Boehringer-Mannheim/Hitachi). The upper limit for normal values was set by the laboratory at 10 mg/liter and levels below this limit were reported as normal but not quantified. Plasma insulin-like growth factor-1 (p-IGF-1) was measured following acid ethanol extraction using a commercial radioimmunoassay kit (Nichols Institute, San Juan Capistrano, CA, USA). For determination of free amino acids, heparinized blood samples were centrifuged at 3000 g for 15 minutes, plasma was deproteinized with 5-sulfosalicylic acid (final concentration 3%), and after centrifugation for another 15 minutes the supernatant was pipetted and stored at −70°C, pending analysis. The determination of free amino acids in plasma was carried out by reversed-phase, high-performance liquid chromatography (HPLC), as described earlier [25].

Statistical analyses

Data are presented as mean ± SD. A P value < 0.05 was considered to be significant. Differences between the four groups were assessed by analysis of variance (ANOVA). When the ANOVA test was significant, a Dunnett's test was used to compare the differences between the control and patient groups. Differences between the three patient groups were analyzed by ANOVA, followed by Dunn's test with Bonferroni correction for multiple comparisons between the groups. Linear trend across the groups ordered by severity of malnutrition (groups I, II and III) was tested by analysis of variance, as described by Altman [26]. Comparisons between two groups for continuous variables were made by the Student's t-test or with the Mann-Whitney test for variables which were not normally distributed and for nominal variables by the chi-squared test. Spearman's rank correlation were used to determine the correlation between 2 variables. Stepwise multiple regression analysis was used to assess the influence of multiple variables on a single variable (serum albumin, S_{Alb}), entering those variables that correlated significantly with the single variable by univariate analysis [26]. Stepwise logistic regression was used to analyze factors that independently predicted malnutrition, evaluated from SGNA.

RESULTS

Subjective global nutritional assessment

The patients were divided into three groups based on SGNA (Table 1). Forty-six patients (36%) had a normal nutritional status (group I), 65 patients (51%) were mildly malnourished (group II) and 17 patients (13%) were moderately ($N = 15$) or severely ($N = 2$) malourished and were grouped together (group III).

Clinical data

The median age was higher in groups II and III (68 and 64 years, respectively) than in group I (57 years). The proportion of female patients was higher in group III (65%) than in groups I and II (35% and 38%, respectively). The distribution of renal diseases were similar in the three groups, except for a higher percentage of diabetic patients in group III (41%) than in groups I and II (11% and 17%), respectively. The percentages of patients with residual renal function were 26% in groups I and II and 18% in group III. The prevalence of CVD was higher in group III (76%) than in group II (65%) and group I (48%). The mean blood pressure [diastolic pressure + (systolic − diastolic pressure)/3] was similar in the three groups.

Table 1. Clinical and dialysis data in 128 hemodialysis (HD) patients (mean ± SD)

	Group I	Group II	Group III
Number of subjects	46 (36%)	65 (51%)	17 (13%)
Age, years (*median and range*)	57 (26–79)	68 (32–85)	64 (33–83)
Sex, *male/female*	30/16	40/25	6/11
Patients with residual renal function, *percent*	12 (26%)	17 (26%)	3 (18%)
Glomerulonephritis	17 (37%)	20 (31%)	1 (6%)
Polycystic kidney disease	6 (13%)	5 (8%)	2 (12%)
Unknown etiology	9 (20%)	15 (23%)	6 (35%)
Diabetes mellitus	5 (11%)	11 (17%)	7 (41%)[a]
Pyelonephritis/interstitial nephritis	5 (11%)	9 (13%)	0 (0%)
Other disease	4 (8%)	5 (8%)	1 (6%)
Prevalence of cardiovascular disease	22 (48%)	42 (65%)	13 (76%)[a]
Mean blood pressure, *mm Hg*	99 ± 19	99 ± 17	98 ± 22
Dialysis data			
Months on HD (*median and range*)	28 (0.4–316)	18 (0.4–216)	13 (0.4–110)
Interdialytic weight gain, *kg*	2.33 ± 0.85	2.80 ± 0.89	2.03 ± 1.36
Length of dialysis, *hours*	4.22 ± 0.57	3.74 ± 0.39	3.78 ± 0.65
Predialysis serum urea, *mmol/liter*	27 ± 5	27 ± 7	26 ± 7
Postdialysis serum urea, *mmol/liter*	9 ± 3	9 ± 3	8 ± 3
nPNA, *g/kg body wt/day*	1.14 ± 0.27	1.08 ± 0.23	1.10 ± 0.23
PNA, *g/kg desirable body weight/day*	1.23 ± 0.27	1.00 ± 0.26[a]	0.88 ± 0.16[a]
Kt/V_{urea}	1.34 ± 0.21	1.36 ± 0.26	1.37 ± 0.22
Kt/V_{urea} (corrected to desirable body weight)	1.45 ± 0.34	1.19 ± 0.24[a]	1.13 ± 0.18[a]

[a] $P < 0.05$ compared with group I

Dialysis data

The median length of time on HD treatment was longer in group I (28 months) than in groups II and III (18 and 13 months, respectively). The dialysis time tended to be lower in groups II and III than in group I but the difference was not significant. The mean nPNA was 1.14, 1.08 and 1.10 g/kg and the mean Kt/V_{urea} was 1.34, 1.36 and 1.37 in groups I, II and III, respectively; the differences were not significant. When normalized to desirable body wt (DBW), the mean PNA was 1.27, 1.19 and 0.84 in groups I, II and III, respectively, being significantly lower in groups II and III than in group I (Fig. 1). The mean Kt/V_{urea} normalized to DBW was 1.45, 1.19 and 1.13 in groups I, II and II, respectively, being significantly lower in groups II and III than in group I.

Anthropometric data

Absolute body weight (ABW), %A/DBW, TSF, BFM and MAMC in group I were about same as in the controls (Table 2). The values tended to be lower in group II and were significantly reduced in group III, as compared to the controls and to group I. Hand-grip strength (HGS) was significantly lower in all three

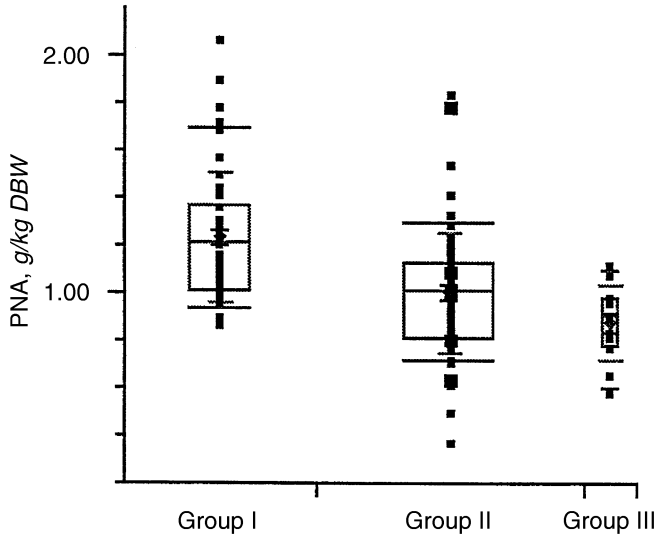

Fig. 1. Distribution between the three patient groups for protein equivalence of nitrogen appearance (PNA), normalized to desirable body wt (DBW).

patient groups than in the controls. However, when we compared HGS in group I patients ($N = 21$) with age- and sex-matched controls, there was no significant difference [Controls, females ($N = 9$) 29 ± 12, males ($N = 12$) 43 ± 8. Group I patients, females ($N = 9$) 25 ± 5, males ($N = 12$) 38 ± 10 kg]. Comparing the three patient groups, there was a significant ($P < 0.001$) linear trend towards progressively lower values for %A/DBW, TSF, MAMC, HGS and BFM with the degree of malnutrition.

Laboratory data

The levels of serum creatinine was significantly lower in group III than in groups I and II, which presumably reflects a reduced muscle mass in the moderately to severely malnourished patients (Table 3). The levels of serum triglycerides, cholesterol, phosphate, transferrin and total protein, plasma complement C3, blood standard bicarbonate, hemoglobin and lymphocyte count were similar in the three groups of patients.

The S_{Alb} concentration was significantly reduced in all three patient groups as compared to the controls. Considering that S_{Alb} in healthy subjects tends to fall with advancing age [27] and that the control group was younger than the patient groups, we compared the serum albumin concentration in 27 patients of group I with the concentration in 27 age-matched controls. The concentration in these patients was 35 ± 5 g/liter and in the matched controls 41 ± 4 g/liter; the difference is highly significant ($P < 0.0001$). In a comparison to group I, the S_{Alb} concentration was lower in group II and even more reduced in group III, with a significant linear trend ($P = 0.001$).

The p-IGF-1 concentration were skewly distributed in each group. The levels IGF-1 were within the normal range in most patients in group I, they were lower in group II, and even lower in group III, with a significant linear trend ($P < 0.001$).

Serum C-reactive protein (S_{CRP}) was normal (< 10 mg/liter) in 60 patients and elevated in 68 patients, ranging up to 120 mg/liter. The proportion of patients with $S_{CRP} > 20$ mg/liter was significantly higher in group III than in the other groups. The relationship between S_{CRP} and age is shown in Figure 2, which demonstrates that practically all patients with S_{CRP} higher than 20 mg/liter were above 50 years of age. The relationship between S_{Alb} and S_{CRP} is shown in Figure 3, demonstrating that 20 of 25 patients with S_{CRP} higher than 20 mg/liter had serum albumin values below 35 g/liter. In patients with elevated S_{CRP}, were found a negative correlation with S_{Alb} ($r = -0.48$). The various co-morbid conditions in patients with S_{CRP} higher than 20 mg/liter, present at the time when the patients were examined, are given in Table 4, which shows that the main cause of an elevated S_{CRP} was infectious disease.

The concentrations of free amino acids in plasma are presented in Table 5. The mean plasma concentrations of all essential amino acids, except lysine, phenylalanine and threonine, were lower in one or more of the patient groups than in the controls. The levels of the branched-chain amino acids, (isoleucine, leucine and valine) were reduced below the control levels in group I and the mean values gradually fall in group II and group III; a linear trend was significant ($P < 0.05$) for leucine and the sum of concentrations of the branched-chain amino acids (ΣBCAA). The sum of concentrations of the essential amino acids was lower in groups II and group III than in controls. Among the non-essential amino acids, the mean plasma levels of arginine, citrulline, glutamic acid and ornithine were increased in one or more of the patient groups, compared to the controls.

Correlations

A correlation matrix, presenting Spearman's rank correlation coefficients for the HD patients, is given in Table 6. The SGNA score was negatively correlated with the anthropometric variables (%A/DBW, HGS, BFM and MAMC), the strongest correlations being with %A/DBW ($r = -0.61$) and MAMC ($r = -0.64$). The anthropometric variables were also mutually correlated with each other with the strongest correlations being between %A/DBW and MAMC ($r = 0.73$), %A/DBW and BFM ($r = 0.52$) and BFM and MAMC ($r = 0.50$). Serum albumin was negatively correlated with the SGNA score ($r = -0.40$) and positively correlated with HGS ($r = 0.42$), MAMC ($r = 0.24$), p-IGF-1 ($r = 0.39$) and serum cholesterol (S_{Chol}; $r = 0.30$) and (weakly) with nPNA ($r = 0.20$), but not with serum creatinine (S_{Cr}). Plasma IGF-1 was more strongly correlated than S_{Alb} with HGS ($r = 0.56$) and MAMC ($r = 0.34$), that is, variables which are related to somatic muscle protein mass with S_{Cr} ($r = 0.36$), which also to some extent reflects the size of the muscle mass, and with ΣBCAA (that is, those amino acids that are mainly metabolized in muscle tissue). ΣBCAA was also correlated with MAMC ($r = 0.32$) and (more weakly) with nPNA ($r = 0.21$) and the SGNA score ($r = 0.23$). Blood standard bicarbonate was not significantly correlated with any of the anthropometric or biochemical factors used to assess protein-energy malnutrition.

Influence of age and sex

Age was negatively correlated with the SGNA score, HGS, S_{Alb}, p-IGF-1, S_{Cr} and nPNA (Table 6). Comparison of patients older than 65 years (the median age) with younger patients (Table 8) showed that a higher proportion of the elderly patients were malnourished. The elderly patients also had signs of lower somatic (muscle) protein stores (lower HGS and MAMC), lower S_{Alb} and p-IGF-1 levels and lower nPNA than the younger ones. Body fat mass (BFM), nPNA and Kt/V_{urea} were higher and S_{Cr} was lower in females than in males (Table 6).

Table 2. Anthropometric data in 128 hemodialysis (HD) patients and 44 controls (mean ± SD)

	Gender	Controls	Group I	Group II	Group III
Length, *cm*	male	180 ± 8	179 ± 6	174 ± 7	169 ± 6[bc]
	female	164 ± 8	162 ± 8	163 ± 8	163 ± 9
Actual body weight (ABW), *kg*	male	74 ± 7	78 ± 9	67 ± 10[a]	62 ± 10[bc]
	female	62 ± 11	66 ± 14	54 ± 9	48 ± 15[ac]
ABW in *% of desirable body weight*	male	99 ± 3	107 ± 2	95 ± 12	84 ± 8[c]
	female	101 ± 21	110 ± 18	90 ± 12	73 ± 6[bc]
Triceps skinfold thickness, *mm*	male	10.4 ± 3.7	13.5 ± 5.8	9.8 ± 3.9	4.8 ± 0.2[ac]
	female	20.1 ± 6.9	21.1 ± 6.5	12.4 ± 5.9[ac]	7.1 ± 3.3[ac]
Mid-arm muscle circumference, *cm*	male	27 ± 2	28 ± 2	24 ± 2	21 ± 2[bc]
	female	24 ± 2	25 ± 3	22 ± 3[c]	19 ± 2[ac]
Hand grip strength, *kg*	male	49 ± 10	34 ± 12[a]	24 ± 9[b]	12 ± 11[bc]
	female	27 ± 5	22 ± 9	13 ± 7[b]	11 ± 6[bc]
Body fat, *% of body weight*	male	20 ± 5	26 ± 5	23 ± 6	10 ± 2[ac]
	female	35 ± 7	36 ± 7	29 ± 5	24 ± 5[ac]

Statistically significant differences between patients and controls are marked [a] $P < 0.05$; [b] $P < 0.01$, and between patient groups I and group II and III are marked [c] $P < 0.05$

Table 3. Biochemical characteristics of 128 hemodialysis (HD) patients and 44 controls (mean ± SD)

Dialysis-free day	Controls $N = 44$	Group I $N = 46$	Group II $N = 65$	Group III $N = 17$
Serum creatinine, *μmol/liter*	84 ± 10	746 ± 196	694 ± 206	526 ± 195[c]
Serum urea, *mmol/liter*	5 ± 1	18 ± 5	21 ± 7	19 ± 4
Standard bicarbonate, *mmol/liter*	25 ± 2	24 ± 2	24 ± 3	24 ± 2
Serum phosphate, *mmol/liter*	1.0 ± 0.4	1.9 ± 0.4[b]	1.8 ± 0.5[b]	1.8 ± 0.5[b]
Serum cholesterol, *mmol/liter*	5.2 ± 1.1	5.6 ± 1.3	5.4 ± 1.5	5.4 ± 1.5
Serum triglycerides, *mmol/liter*	1.2 ± 0.2	1.7 ± 0.8	1.4 ± 0.6	1.3 ± 0.7
Serum total protein, *g/liter*	73 ± 2	76 ± 8	76 ± 7	71 ± 6
Serum albumin, *g/liter*	42 ± 4	35 ± 3[b]	32 ± 5[cd]	30 ± 5[cd]
Elevated serum CRP *>20 mg/liter*		17%	29%	64%[d]
Plasma IGF-1, *ng/ml*	182−389	221 ± 94	160 ± 104[d]	131 ± 89[d]
Plasma C3, *ng/ml*	0.5−0.85	0.60 ± 0.1	0.59 ± 0.1	0.63 ± 0.11
Serum transferrin, *mmol/liter*	2.1−3.6[a]	2.3 ± 0.6	2.0 ± 0.5	2.0 ± 0.4
Blood hemoglobin, *g/liter*	139 ± 9	102 ± 2[b]	97 ± 14[b]	96 ± 18[b]
Blood lymphocytes, *10^9/liter*	1.9 ± 0.7	1.8 ± 0.9	1.6 ± 0.5	1.9 ± 1.4

[a] Normal range of serum transferrin and IGF-1 of the clinical laboratories.

Statistically significant differences between patients and controls are marked [b] $P < 0.05$; [c] $P < 0.01$ and between patients group I and patient group II and III are marked [d] $P < 0.05$

Predictors of malnutrition as evaluated by SGNA

To analyze this, we performed logistic regression analysis, entering all variables, which were correlated with SGNA by univariate analysis (Table 6), with the presence of malnutrition (belonging to groups II + III) or not (belonging to group I) as outcome variable. The results, presented in Table 7, show that %A/DBW, HGS and S_{Alb} predicted malnutrition to about the same extent, MAMC as a predictor did almost reach statistical significance, whereas all the other variables were non-significant ($P > 0.2$).

Influence of cardiovascular disease

Patients with cardiovascular disease (CVD) were older and malnutrition was commoner than in patients without CVD, and they had lower HGS, S_{Cr}, S_{Alb}, p-IGF-1 and hemoglobin (Tables 8 and 9).

Predictors of serum albumin

Stepwise multiple regression analysis was used to find statistically significant independent predictors of S_{Alb} in the HD patients (Table 10). Nutritional status (SGNA) was the strongest predictor, followed by s-cholesterol, protein intake as assesed by nPNA, age, S_{CRP} and sex. The regression model could explain 37% of the variation in S_{Alb}.

The 36 patients who did not participate in this study comprised 19 males, 17 females, aged 56 (26 to 79) years. Five patients (13%) were diabetics. Absolute body weight was 65 ± 14 kg, nPNA was 1.14 ± 0.33 g/kg, Kt/V_{urea} was 1.41 ± 0.28. They did not differ significantly from the study population regarding age and sex distribution, percent diabetics, body wt, time on dialysis, nPNA and Kt/V_{urea}.

DISCUSSION

In this study, we intended to include all patients on maintenance HD who were treated at Huddinge University Hospital and its satellite units, and who had been dialyzed for more than two weeks. However, we failed to recruit 36 patients, representing 22% of the population, who refused to participate or were not referred by the staff. Nevertheless, we believe that the population studied was representative of the whole population, since the

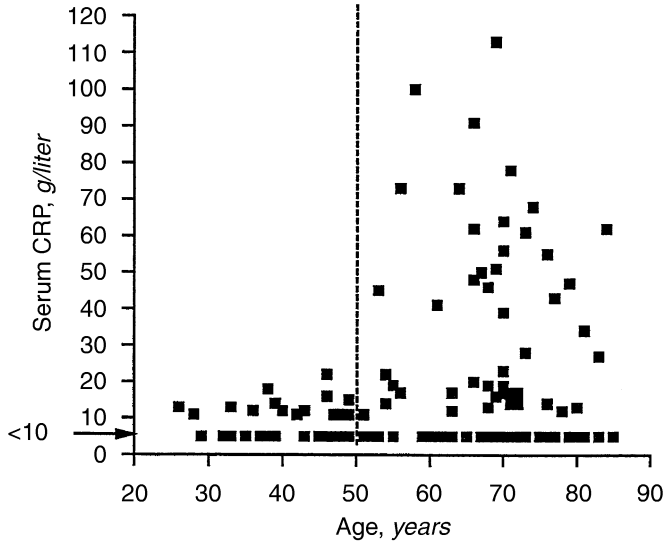

Fig. 2. Relationship between age and serum C-reactive protein (S_{CRP}). All patients except one with serum CRP > 20 mg/liter were over 50 years of age.

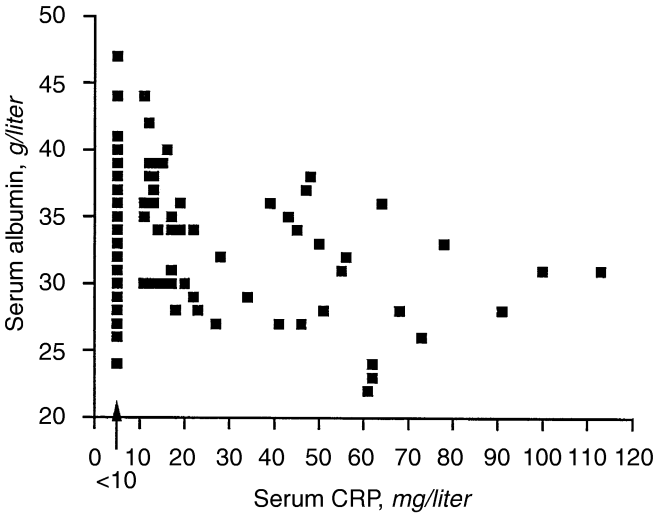

Fig. 3. Relationship between serum C-reactive protein (S_{CRP}) and serum albumin. Twenty-five of 28 patients with $S_{CRP} > 20$ g/liter had serum albumin (S_{Alb}) < 35 g/liter. For S_{CRP} values ≥ 10 mg/liter, there was a significant correlation between (log) S_{CRP} and S_{Alb} ($r = 0.48$, $P < 0.0001$).

patients who did not participate had about the same age and gender distribution, diagnoses of renal disease and dialysis data.

The high proportion of elderly patients and those with CVD may indirectly be a consequence of the efficient renal transplantation program in operation for many years in Sweden, no less than 55% of the total patient population on renal replacement therapy having a functioning renal graft [28]. Since patients who are given transplants tend to be younger and have less severe medical complications, this will result in a higher proportion of elderly patients and patients with CVD and other co-morbid conditions on maintenance dialysis.

In our primary analysis of the incidence of protein-energy malnutrition, we used SGNA, which gives an overall assessment of the degree of malnutrition, but does not include more sophisticated anthropometric measurements or biochemical parameters. Subjective global nutritional assessment has been shown to be a useful and reliable tool for clinical assessment of nutritional status in post-traumatic patients [20, 21], but to our knowledge has been applied in only a few studies of patients with renal failure [5, 7, 29]. In general, the grouping of patients according to SGNA seems to accord with anthropometric measurements such as body wt, fat mass, arm muscle circumference and hand-grip strength, as well as with biochemical parameters, such as S_{Alb} and p-IGF-1, all of which were gradually more reduced in groups II and III patients than in group I. Logistic regression analysis revealed that two anthropometric variables (%A/DBW and HGS) and one biochemical variable (S_{Alb}) predicted malnutrition independently and to about the same extent. Other variables which were correlated with SGNA, such as BFM, p-IGF-1 and S_{Cr}, did not reach significance as independent predictors, presumably because they covariated with the most predictive ones.

Table 4. Co-morbid conditions in 28 HD patients with serum C-reactive protein >20 mg/liter

	S_{CRP} >20 mg/liter
Infection and sepsis	17
Cardiovascular diseases	2
Gastrointestinal diseases	5
Malignant tumor	4

Table 5. Plasma free amino acid concentrations μmol/liter (mean ± SD) in 118 hemodialysis patients and 44 controls

	Controls $N = 44$	Group I $N = 44$	Group II $N = 58$	Group III $N = 16$
Essential AA				
Histidine	83 ± 13	81 ± 16	74 ± 16	72 ± 15[b]
Isoleucine	67 ± 17	59 ± 16	56 ± 16[b]	51 ± 14[b]
Leucine	134 ± 47	103 ± 26[c]	91 ± 29[c]	82 ± 20[c]
Lysine	178 ± 42	194 ± 49	178 ± 50	188 ± 58
Methionine	33 ± 10	24 ± 6[b]	20 ± 5[b]	21 ± 6[b]
Phenylalanine	52 ± 10	67 ± 18	59 ± 15	62 ± 16
Threonine	127 ± 30	118 ± 31	114 ± 37	111 ± 47
Tryptophan	46 ± 13	27 ± 9[c]	23 ± 7[c]	27 ± 11[c]
Tyrosine[a]	59 ± 20	47 ± 18[b]	46 ± 14[b]	53 ± 20
Valine	222 ± 48	187 ± 43[c]	171 ± 53[c]	163 ± 11[c]
Non-essential AA				
Alanine	312 ± 90	349 ± 94	311 ± 111	305 ± 99
Arginine	84 ± 20	100 ± 27[b]	96 ± 29	85 ± 35
Asparagine	50 ± 12	52 ± 11	50 ± 14	53 ± 16
Citrulline	30 ± 9	109 ± 29[c]	105 ± 34[c]	95 ± 36[c]
Glutamic acid	33 ± 15	43 ± 24	47 ± 25[b]	54 ± 35[c]
Glutamine	638 ± 89	651 ± 92	641 ± 108	643 ± 135
Glycine	246 ± 75	302 ± 134	275 ± 79	324 ± 162
Ornithine	62 ± 14	82 ± 31[b]	77 ± 21[b]	80 ± 31
Serine	122 ± 29	82 ± 18[c]	85 ± 19[c]	92 ± 27
Taurine	50 ± 14	44 ± 21	40 ± 16	42 ± 25
Sums of amino acids				
Total AA	2635 ± 358	2693 ± 318	2519 ± 408	2615 ± 542
Non essential AA	1677 ± 252	1725 ± 238	1632 ± 285	1685 ± 400
Essential AA	907 ± 160	831 ± 184	808 ± 180[c]	817 ± 156[c]
BCAA	424 ± 106	351 ± 78[c]	319 ± 93[c]	301 ± 56[c]

[a] Plasma tyrosine is considered to be essential in chronic uremic patient. Statistically significant differences between patients and controls are marked [b] $P < 0.05$; [c] $P < 0.01$

Table 6. Spearman rank correlation matrix for 14 variables

Variable	SGNA score	Age	Sex M/F	%A/DBW	HGS	MAMC	%BFM	nPNA	Kt/V_{urea}	S_{Alb}	p-IGF-1	S_{Cr}	ΣBCAA
Age	0.27[b]												
Sex M/F	0.15	0.07											
%A/DBW	−0.61[c]	−0.15	−0.20										
HGS	−0.46[c]	−0.54[c]	0.00	0.23[a]									
MAMC	−0.64[c]	−0.18	−0.08	0.73[c]	0.36[c]								
%BFM	−0.37[c]	0.04	0.43[c]	0.52[c]	0.03	0.50[c]							
nPNA	−0.01	−0.19[a]	0.21[a]	−0.04	0.24[b]	0.07	−0.00						
Kt/V_{urea}	0.06	−0.03	0.34[c]	−0.33[c]	0.03	−0.12	0.10	0.37[c]					
S_{Alb}	−0.40[c]	−0.32[c]	−0.12	0.00	0.42[c]	0.24[b]	−0.09	0.20[a]	0.13				
p-IGF-1	−0.36[c]	−0.49[c]	0.06	0.24[b]	0.56[c]	0.34[c]	0.12	0.34[c]	0.03	0.39[c]			
S_{Cr}	−0.30[b]	−0.22[a]	−0.21[a]	0.36[c]	0.15	0.31[c]	−0.04	0.10	−0.35[c]	0.10	0.36[c]		
ΣBCCA	−0.23[a]	−0.13	−0.24[b]	0.27[b]	0.08	0.32[c]	0.13	0.21[a]	0.00	0.16	0.28[b]	0.04	
S_{chol}	−0.09	0.02	0.30[b]	−0.03	0.19[a]	0.15	0.27[b]	0.18	0.29[c]	0.30[b]	0.10	0.04	0.02

The anthropometric variables, hand grip strength (HGS), mid-arm muscle circumference (MAMC) and body fat mass (%BFM), were entered into the analysis as percentage of the controls; % A/DBW, actual body weight in percent of desirable body weight, ΣBCAA, sum of the plasma concentrations of the branched chain amino acids (isoleucine, leucine and valine). Abbreviations are: BFM, body fat mass; nPNA, protein equivalence of nitrogen appearance; Kt/V_{urea}, dialyzer + renal urea clearance, dialysis time and volume obtained by urea kinetic modeling; S_{Alb}, serum albumin; p-IGF-1, plasma insulin-like growth factor-1; S_{Cr}, serum creatinine; ΣBCAA, branched chain amino acids that are metabolized mainly in muscle tissue.
[a] $P < 0.05$, [b] $P < 0.01$ and [c] $P < 0.001$

Table 7. Logistic regression analysis of anthropometric and biochemical predictors of malnutrition according to SGNA (groups II+III *viz* group I) in HD patients, omitting variables for which $P > 0.1$

	Estimate	χ^2	*P* value
Intercept	−40.42	13.64	0.0002
%HGS	0.06	6.39	0.012
%A/DBW	0.11	6.01	0.014
Serum albumin, *g/liter*	0.31	6.00	0.014
%MAMC	0.11	3.28	0.070
Total r^2 $r = 0.56$			

The anthropometric variables, hand grip strength (HGS) and mid-arm muscle circumference (MAMC) were entered into the analysis as percentage of the controls. Abbreviation is: %A/DBW, absolute body weight in percent of desirable body weight.

Table 8. Statistical comparison of younger and elderly hemodialysis patients

	≤ 65 years	> 65	*P*
Male/female	35/28	41/24	
Plasma IGF-1, *ng/ml*	219 ± 94	138 ± 97	0.0001[a]
Serum albumin, *g/liter*	34.5 ± 4.9	31.7 ± 3.9	0.0002[a]
% HGS	70.2 ± 24.5	45.2 ± 23.0	0.001[a]
% MAMC	97.8 ± 10.7	92.6 ± 11.7	0.01[a]
Percent malnourished (SGNA)	46%	68%	0.013[b]
nPNA	1.16 ± 0.24	1.06 ± 0.21	0.017[a]
Kt/V_{urea}	1.37 ± 0.26	1.37 ± 0.27	0.95[a]

Abbreviations are in the **Appendix.**
[a] Statistical significance was tested with Student's *t*-test
[b] Statistical significance was tested with Chi-squared test

Table 9. Statistical comparison of hemodialysis patients with and without cardiovascular diseases (CVD)

	No CVD	CVD	*P*
Male/female	34/17	42/35	
Percent malnourished (SGNA)	33%	73%	0.0001[a]
Age, *years*	56 ± 16	64 ± 12	0.0025[b]
Serum creatinine, *μmol/liter*	756 ± 211	648 ± 201	0.007[b]
Serum albumin, *g/liter*	34.4 ± 4.8	32.3 ± 4.4	0.01[b]
Blood hemoglobin, $g*liter^{-1}$	103 ± 15	96 ± 15	0.01[b]
%HGS	64.2 ± 29.1	52.5 ± 23.9	0.02[b]
Plasma IGF-1, *ng/ml*	200 ± 111	162 ± 97	0.05[c]
Serum C-reactive protein, *mg/liter >20*	15.7%	25.9%	0.16[a]
nPNA	1.12 ± 0.23	1.11 ± 0.22	0.97[b]
Kt/V_{urea}	1.39 ± 0.27	1.35 ± 0.26	0.38[b]

[a] Statistical significance was tested with Chi-squared test
[b] Statistical significance was tested with Student's *t*-test
[c] Statistical significance was tested with non parametric Mann-Whitney test

Evaluated by SGNA, 64% of our patients had signs of protein-energy malnutrition, which, however, was mild in most of them, only 12% being classified as moderately malnourished and 2 patients (< 2%) as severely malnourished. Nevertheless, the total incidence of malnutrition was higher than in most studies previously reported [7, 30], which raises the question whether this can be explained by some special features in our HD population.

One factor may be the relatively high age, with no less than 50% of the patients above the age of 65 years. It is well known that senescence *per se* involves a gradual involution of body cell mass [31, 32]. The observation that elderly patients were more frequently malnourished than younger ones according to SGNA, and had lower body wt, HGS, MAMC, S_{Alb} and p-IGF-1 (Table 8), accords with this view. The protein intake, estimated as nPNA, was also significantly lower in the elderly than in the younger patients, which confirmed earlier results showing an inverse correlation between nPNA and age [33].

Several co-morbidity factors may also have influenced the nutritional status either by causing a reduced nutritional intake or by promoting catabolism [12]. Thus, diabetes mellitus was more frequent among patients in group III than in the other two groups. There was also a high prevalence of CVD in the whole patient population (77%), and especially among the malnourished patient groups and the elderly patients. Another association between malnutrition and co-morbidity is evident from our observation that markedly elevated S_{CRP} (> 20 mg/liter), which in most cases was caused by infections and almost exclusively observed in patients above 50 years of age (Fig. 2), was more common in malnourished patients than in patients with normal nutrtional status.

Table 10. Forward stepwise multivariate regression analysis of predictors of serum albumin in hemodialysis patients

	Estimate	Standard error	*P* value
Intercept	32.54	0.41	<0.0001
SGNA *normal and malnourished*	1.46	0.35	<0.0001
Serum cholesterol *>5 and ≤5 mmol/liter*	1.42	0.37	0.0007
nPNA groups *<1.1 and ≥1.1 g/kg*	0.96	0.34	0.005
Age groups *<65 years and ≥65 years*	0.94	0.36	0.009
CRP groups *<20 and ≥20 mg/liter*	0.99	0.41	0.016
Sex, *female and male*	0.81	0.37	0.029

All variables that were significantly correlated with serum albumin (Table 6) were included into the initial model. Total r^2 adjusted to r = 0.37. Abbreviations are in the **Appendix.**

It has recently been reported that hypoalbuminemia is associated with presence of and *de novo* development of cardiac disease in HD and CAPD patients [34]. It is possible that the relationship is inverse, that is, that cardiac disease leads to malnutrition and hypoalbuminemia. Several studies show that patients having chronic cardiac failure without renal disease may develop weight loss and other signs of malnutrition, a condition called cardiac cachexia [35]. Cardiac failure patients have increased resting metabolic rate [36] and fat malabsorption [37]. There is evidence that tumor necrosis factor and other cytokines are major pathogenetic factors in the development of cardiac cachexia [38]. These factors may also elicit an acute phase response, resulting in, among others, reduced synthesis of S_{Alb} [39].

The patients in this study had mean Kt/V_{urea} values in the range of 1.34 to 1.37 with no difference between the three groups that is, the average dose of dialysis was at a level considered to be adequate at the time when this study was performed [40]. We found a significant correlation between Kt/V_{urea} and nPNA, confirming earlier observations by several groups [33, 41, 42]. Such a correlation has been interpreted to mean that the intake of protein depends on the dose of dialysis, presumably because underdialyzed patients suffer from anorexia due to the influence of uremic toxicity. However, there is also support for the view that the correlation between Kt/V_{urea} and nPNA mainly reflects a mathematical coupling because the calculations of respective equations have components in common [42].

The mean nPNA was relatively high (1.1 to 1.2 g/kg), with no difference between the groups, suggesting that the protein intake was adequate. However, it has been argued that referring PNA to actual body wt or to "normalized" body wt (nPNA) may be grossly misleading since, by so doing, malnourished patients with a reduced body cell mass may appear to have an adequate or high protein intake although the intake is low in relation to the requirements [43]. It was therefore recommended that PNA should be referred to the desirable body wt (DBW), or ideal body wt, which may better reflect the protein intake in relation to the needs. When PNA was referred to DBW in the present study, some of the malnourished patients had values far below those with normal nutritional status (Fig. 1), being as low as 0.4 g/kg in some of them thus suggesting that low protein intake may, indeed, have been of important for the development of malnutrition. Kt/V_{urea}, normalized to DBW, was also lower in the malnourished groups than in patients with normal nutritional status. Considering that the nature of uremic toxicity is still enigmatic, urea serving at best as a "surrogate" uremic toxin, it is questionable whether generation and removal of urea really reflects the behavior of clinically more important uremic toxins. Lacking such information, we cannot rule out that low Kt/V_{urea}, normalized to DBW, may reflect underdialysis, which leads to suppression of food intake.

Among the biochemical parameters, S_{Alb} is most frequently used to assess protein malnutrition, based on the concept that the level of S_{Alb} reflects the visceral protein status. However, this is only partly true since there are many other factors which influence the generation, distribution and catabolism of albumin, such as albumin synthesis inhibition, albumin degradation, albumin losses from the body, dilution by fluid overload and exchange between intravascular and extravascular compartments [44]. Serum albumin also decreases with age in apparently healthy subjects [27].

We observed a reduction in S_{Alb} in all three groups of patients, which decreased in proportion to the degree of malnutrition. In the stepwise regression analysis, the strongest independent predictor of the S_{Alb} level was the nutritional status as evaluated by the SGNA. Serum albumin was also correlated with nPNA (an indicator of protein intake) and S_{Chol} (an indicator of energy intake), suggesting that adequate nutritional intakes of protein and energy are essential for maintaining the visceral protein stores. Serum CRP was also a significant independent predictor of S_{Alb}. This accords with earlier observations in HD patients that albumin generation is reduced during the acute phase response and that S_{Alb} is inversely correlated with serum concentrations of CRP and α_2-macroglobulin [39]. The conclusion that non-nutritional factors influence S_{Alb} in HD patients is supported by our observation that S_{Alb} was significantly decreased in patients classified as having a normal nutritional status, compared to age-matched controls. An independent factor that influences S_{Alb} in HD patients is albumin leakage through the dialysis membranes, which has been observed with polysulfone dialyzers, after repeated reuses using bleach as the disinfectant [45]. In our study this was not a factor of importance, since none of the dialyzers was reused. Liver disease may also reduce albumin synthesis, but it was probably not important in this study, since only two patients had increased serum aspartate aminotransferase levels.

Plasma IGF-1 has been introduced as an indicator of nutritional status in renal failure patients. This correlates significantly with other biochemical and anthropometric markers of malnutrition and has been thought to be a better marker of malnutrition than other serum proteins [46, 47]. In the present study, p-IGF-1 was within normal range in the group I patients but gradually decreased in the group II and group III patients, suggesting that p-IGF-1 levels distinguished between normal and malnourished patients and reflected the degree of malnutrition. We should note that MAMC and HGS were more strongly correlated with p-IGF-1 than with S_{Alb}. The results suggest that p-IGF-1 may provide additional information as a nutritional marker, by reflecting the somatic (muscle) protein stores more closely than S_{Alb}.

In several earlier studies of nutritional status in HD patients low serum transferrin has been shown to be a useful marker of malnutrition. However, in the present study serum transferrin concentrations failed to distinguish between patients with normal nutritional status and the malnourished patient groups. The reason for this is presumably that a large proportion of the patients were treated with rhEPO and i.v. or oral iron, which may independently modify serum transferrin [48, 49].

We observed low concentrations of all essential amino acids,

except lysine and phenylalanine, in one or more of the patient groups. However, there was a trend towards decreasing values only for the BCAA, the degree of malnutrition being significant for leucine and the sum of concentration of BCAA. An earlier study [1] reported that valine appears to be the amino acid in plasma which best predicted the nutritional status; our results suggest that leucine may be at least as good a predictor as valine. However, the relatively small differences in mean values and the large overlap between the groups argue against these amino acids as sensitive indicators of the nutritional status. It should also be emphasized that for each free amino acid the plasma pool represents only a small fraction of the total body content. For most amino acids the intracellular concentration in skeletal muscle (the largest pool of free amino acids immediately available for protein synthesis) is higher than in plasma [50]. Several studies showed that in patients with renal failure the plasma concentrations of several amino acids do not reflect the intracellular concentrations in the muscle cells [51]. Therefore, one may question whether it is worthwhile to use plasma amino acid determinations for assessment of malnutrition, especially since the methods are expensive and time consuming.

Among factors causing protein catabolism and malnutrition in renal failure patients, metabolic acidosis has attracted much interest in recent years. It has become increasingly evident that metabolic acidosis, rather than uremia *per se*, may be an important stimulus for net protein catabolism by stimulating BCAA catabolism and proteolysis in skeletal muscle [52–55].

Earlier studies have shown no apparent association between total CO_2 or plasma bicarbonate levels and nutritional status as assessed by S_{Alb} [56, 57]. Only one study of CAPD patients reported that the increases in body wt and mid-arm circumference were greater in a group with fully corrected acidosis than in group with lower plasma bicarbonate levels [58]. In the present study, we observed no significant correlation between standard blood bicarbonate and any of the nutritional variables recorded. However, it should be emphasized that the acid-base balance was well controlled in most of the patients, only 16% having a predialysis standard bicarbonate $\leq$ 21 mmol/liter. Therefore, it cannot be excluded that a higher degree of acidosis may have a harmful effect on nutritional status by enhancing muscle proteolysis. Nevertheless, our observations of no association between blood bicarbonate and any of the anthropometric and biochemical variables recorded strongly suggest that metabolic acidosis was not an important factor for the development of protein malnutrition in our patients.

In summary, a high proportion of HD patients in this study showed signs of malnutrition, which was mild in the majority of patients. Clinical factors associated with malnutrition were high age, presence of cardiovascular disease and diabetes mellitus. The S_{Alb} level was influenced not only by nutritional status and protein intake but also independently by age, S_{CRP} and sex. Plasma IGF-1 levels also reflected the presence and severity of malnutrition and appeared to be more closely associated than S_{Alb} with indices of somatic protein mass. Elevated S_{CRP}, which mainly reflected the presence of infection/inflammation, was more common in elderly than in younger patients. Plasma amino acid levels, with the possible exception of the BCAA, seem to be poor predictors of malnutrition.

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APPENDIX

Abbreviations used in this article are: ABW, absolute body weight; ANOVA, analysis of variance; ΣBCAA, sum of concentrations of branched-chain amino acids; BFM, body fat mass; CVD, cardiovascular disease; DBW, desirable body weight; HD, hemodialysis; HGS, hand-grip strength; IGF-1, insulin-like growth factor-1; Kt/V_{urea}, dialyzer + renal urea clearance, dialysis time and volume obtained by urea kinetic modelling; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; nBW, normalized body weight; nPNA, protein equivalence of nitrogen appearance; p-IGF-I, plasma insulin-like growth factor-1; S_{Alb}, serum albumin; S_{CRP}, serum C-reactive protein; S_{Cr}, serum creatinine SGNA, subjective global nutritional assessment; TSF, triceps skinfold thickness.

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