IL-6 Levels, Nutritional Status, and Mortality in Prevalent Hemodialysis Patients

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Summary

Background and objectives The influence of serum IL-6 levels on nutritional status in chronic hemodialysis (HD) patients remains to be elucidated. The present report describes a prospective longitudinal study of IL-6 levels and nutritional parameters to determine whether high IL-6 levels are independently associated with nutritional status over time in a cohort of prevalent hemodialysis patients.

Design, setting, participants, & measurements 85 clinically stable hemodialysis patients (37.6% women), with a mean age of 66.5 ± 10.6 years, were studied after exclusion of patients with BMI < 20 kg/m² and/or serum albumin < 35 g/L. IL-6, dietary energy and protein intake, and biochemical markers of nutrition and body composition (anthropometry and bioimpedance analysis) were measured at baseline and at 6, 12, 18, and 24 months following enrollment. Observation of this cohort was continued over 2 additional years.

Results IL-6 levels increased with time in both unadjusted (linear estimate: 2.57 ± 0.44 pg/ml per 2 yrs; P = 0.001) and adjusted models (linear estimate: 2.35 ± 0.57 pg/ml per 2 yrs; P = 0.049). Significant reductions of daily energy intake, laboratory markers (albumin, transferrin, cholesterol, creatinine), and body composition (fat mass) with higher IL-6 levels were observed over the duration of the longitudinal observation period. However, none of the studied parameters were associated with changes in IL-6 levels over time (IL-6-by-time interactions were NS). Furthermore, cumulative incidences of survival were correlated with the baseline serum IL-6 levels (P = 0.004 by log-rank test). Finally, for each pg/ml increase in IL-6 level, the hazard ratio for death from all causes was 1.06 (95% CI 1.01 to 1.10) after adjustment for demographic and clinical parameters.

Conclusions Our results suggest that higher serum IL-6 levels are associated with all-cause mortality without additional changes in clinical and laboratory markers of nutritional status in clinically stable HD patients.

Introduction

The majority of chronic hemodialysis (HD) patients have elevated serum levels of inflammatory markers (1,2) that are powerful predictors of mortality in this population (2–7). A generalized increase in the inflammatory response in patients with ESRD may occur via decreased clearance of proinflammatory cytokines, volume overload, oxidative and carbonyl stress, patient-related mechanisms (underlying disease and comorbidities), as well as factors related to dialysis technique. These mechanisms of possible causes of inflammation in ESRD patients are discussed elsewhere (8–10). Among the various cytokines, IL-6 was found to be most closely related to mortality (3,4,6,7) and to be associated with more causes of inflammation than other cytokines and C-reactive protein (CRP) (11,12). While an experimental study by Ling et al. (13) suggested that protein-energy wasting (PEW) produces changes in inflammation-related protein characteristics of a low-grade systemic inflammatory response, clinical studies (14–16) found inflammation, PEW, and cardiovascular morbidity to be interrelated in HD patients, each additionally contributing to the high mortality in HD patients. Therefore, inflammation, as manifested by high levels of IL-6, has been reported as a possible link between PEW and increased cardiovascular morbidity and mortality in chronic HD patients (14,15). Moreover, several investigators suggested that PEW is a consequence of chronic inflammatory processes in patients with renal insufficiency (14,15,17,18). The pathophysiological basis of inflammatory cytokines, and particularly of IL-6-induced PEW, may be increased protein catabolism (19,20) and/or resistance to the anabolic effect of growth hormone, which may contribute to the loss of strength and muscle mass (21); in addition, inflammation may affect appetite and eating behavior (22,23). It was recently suggested that interactions...
between inflammatory markers and sTWEAK (soluble TNF-like weak inducer of apoptosis) affect the nutritional status of prevalent HD patients; thus, significant reductions in markers of PEW (IGF-1 and handgrip strength) associated with high levels of both IL-6 and sTWEAK may provide an additional link between inflammation and PEW (24). The malignant form of PEW, essentially caused by chronic inflammation in the HD population, is associated with pronounced hypoalbuminemia, markedly increased resting energy expenditure, oxidative stress, and poor clinical outcome, and has been termed as “malnutrition type 2” by Stenvinkel et al. (25). However, clinical data suggesting a significant role for IL-6 in mediating PEW in ESRD patients are available only from cross-sectional analyses (17,18,26,27) or based on similarity with the pathophysiology of PEW in cancer cachexia (15,25). Longitudinal studies designed to determine the impact of inflammation on nutritional parameters in a prevalent dialysis cohort are still lacking. We tested the hypothesis that high IL-6 levels, in the absence of any objective markers of PEW at baseline, might independently lead to anorexia and PEW in prevalent hemodialysis patients. To this end, we performed prospective longitudinal measurements of IL-6 levels and various nutritional markers in prevalent hemodialysis patients after exclusion of patients with PEW at baseline. Furthermore, we evaluated whether nutritional status was associated with longitudinal changes in IL-6 levels, and, in addition, whether observed changes in nutritional parameters could be related to survival of our cohort.

**Materials and Methods**

**Patients**

This prospective observational study was approved by the Ethics Committee of Assaf Harofeh Medical Center (Zerifin, Affiliated to the Sackler Faculty of Medicine Tel Aviv University, Israel). Informed consent was obtained before any trial-related activities. Patients were eligible for entry when they had been on HD therapy for at least 3 months and were 18 years or older, with no clinically active cardiovascular or infectious diseases on entry. To this end, we performed prospective longitudinal measurements of IL-6 levels and various nutritional markers in prevalent hemodialysis patients after exclusion of patients with PEW at baseline. Furthermore, we evaluated whether nutritional status was associated with longitudinal changes in IL-6 levels, and, in addition, whether observed changes in nutritional parameters could be related to survival of our cohort.

**Anthropometric Measurements**

BMI, triceps skinfold thickness (TSF), mid-arm circumference (MAC), and calculated mid-arm muscle circumference (MAMC) were measured as anthropometric variables. TSF was measured with a conventional skinfold caliper using standard techniques. Mid-arm circumference was measured with a plastic measuring tape. MAMC was estimated as follows:

\[
MAMC = \left(\frac{\text{Patient's actual weight} - \text{SBW}}{0.25}\right) + \text{SBW}.
\]

Standard body weight (SBW) was determined by the National Health and Nutrition Examination Survey II (NHANES II) population medians for age, gender, frame size, and stature (29). Dietary protein intake was also estimated by protein catabolic rate (PCR) calculation from the patient’s urea generation rate by urea kinetics modeling (30). Single-pool model urea kinetics was used to estimate the normalized PCR (nPCR).

**Body Composition Analysis**

Body composition was determined by body impedance analysis (B.I.A. Nutriguard-M, Data-Input, Frankfurt, Germany). On the day of blood collection, patients underwent BIA measurement at approximately 30 minutes postdialysis. BIA electrodes were placed on the same body side used for anthropometric measurements. The multifrequency
technique was used. Recently, both BIA and near-infrared interactance were validated as reliable tests for estimation of total body fat percentage in maintenance hemodialysis patients, using DEXA as the reference test (32). Fat-free mass (FFM) was calculated using the approach of Kyle et al., validated by DEXA on 343 healthy adult subjects (33):

\[ \text{FFM} = -4.104 + (0.518 \times \text{height}^2)/\text{resistance} + (0.231 \times \text{weight}) + (0.130 \times \text{reactance}) + (4.229 \times \text{gender: men} = 1, \text{women} = 0). \]

Phase angle (PA) has been shown to provide a BIA prognostic index of morbidity and mortality (34).

**Laboratory Evaluation**

Blood samples were taken in a nonfasting state before a midweek hemodialysis session. Complete blood count, creatinine, urea, albumin, Transferrin, and total cholesterol were measured by routine laboratory methods. IL-6 levels were measured in plasma samples using commercially available ELISA kits (R&D System, Minneapolis, MN) according to the manufacturer’s protocol. The mean minimal detectable level for IL-6 was 0.7 pg/ml; the intra-assay and interassay coefficients of variation were 4.2% and 6.4%, respectively.

**Statistical Analysis**

Data are expressed as mean ± SD, median, and interquartile range (Q1 to Q3) for variables that did not follow a normal distribution, or frequencies, as noted.

Repeated-measures ANOVA was performed by using the MIXED model. Only patients with ≥ 2 study visits were included in the analyses. Base models were adjusted for age, gender, diabetes status, dialysis vintage, and history of cardiovascular diseases. F tests were used to assess the significance of the fixed effects, and P values of less than 0.05 were considered significant. To evaluate whether IL-6 influenced the trends in the various dependent variables, we included in each base model terms for individual “IL-6-by-time” interactions.

Nutritional characteristics at baseline and on all scheduled visits were compared between the patients who were alive/censored versus those who died using a two-sided t test for continuously distributed data. Since the IL-6 levels were not normally distributed, median scores were used for comparisons using the nonparametric Mann–Whitney U-test.

The cutoff for the most accurate discrimination of mortality risk for IL-6 was derived using standard receiver operating characteristic (ROC) curves. Survival analyses were performed using the Kaplan–Meier survival curve and the Cox proportional hazard model. The univariate and multivariate Cox regression analyses are presented as hazard ratios with their confidence intervals (CI). All predictors (except for categorical ones) were used as continuous variables.

All statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL).

**Results**

The baseline characteristics of the cohort are shown in Table 1. The 85 clinically stable, prevalent HD patients participating in this study included 38% women; over half of the participants (54%) had diabetes mellitus (DM), and nearly the same proportion had a history of cardiovascular disease, including myocardial infarction, coronary artery procedures such as angioplasty or surgery, previous cerebrovascular accident, or peripheral vascular disease. The main objective nutritional characteristics (laboratory and clinical parameters) at baseline were consistent with satis-
factory nutritional status of the study participants. Postdiagnosis hydration status of our cohort was normal according to the extracellular water to total body water ratio (ECW/TBW). Only dietary intake based on 3-day self-completed food diaries was lower than the recommended daily energy and protein intake norms for hemodialysis patients.

During the longitudinal part of the study, IL-6 levels increased with time in both unadjusted (linear estimate: 2.57 ± 0.44 pg/ml per 2 yrs; \( P = 0.001 \)) and adjusted (for age, gender, DM status, dialysis vintage, and history of CV disease) models (linear estimate: 2.35 ± 0.57 pg/ml per 2 yrs; \( P = 0.049 \)) (Figure 1).

Linear mixed models were used to study the effects of longitudinal IL-6 changes on changes in nutritional parameters (slopes) over 24 months, including fixed parameters such as age, gender, diabetes status, dialysis vintage, and previous cardiovascular events (Table 2). Longitudinally, a 1 pg/ml increase in IL-6 over time, controlling for fixed factors, was associated with a 0.1588 kcal/kg per d reduction in daily energy intake. The effect of inflammation, manifested by higher IL-6 levels, on acute phase reactants was confirmed: On average, serum albumin was lower by 0.06 g/L for every 1 pg/ml increase in IL-6 (\( P < 0.001 \)). Analogous associations were observed between longitudinal changes in IL-6 levels and other laboratory markers of the acute phase: transferrin, cholesterol, and TLC (Table 2). Changes in serum creatinine levels were also inversely related to changes in IL-6 levels. From body composition parameters, only fat mass and phase angle were observed to be associated significantly with inflammation: Every 1-pg/ml increase in IL-6 was associated with reductions in fat mass (linear estimate: \(-0.0314 \text{ kg} [\text{CI: } -0.0509; -0.0117], P = 0.002\) and phase angle (linear estimate: \(-0.0054^\circ [\text{CI: } -0.0107; -0.0001], P = 0.045\). Of interest, IL-6-by-time interactions were NS. Thus, despite the significant longitudinal changes in dietary intake, laboratory nutritional markers, and body composition parameters, IL-6 did not correlate with the change over time of any of these indicators of nutritional status over 2 years of follow-up.

Table 3 summarizes data concerning serum IL-6, and laboratory and clinical nutritional parameters, of patients who died during follow-up (36.1 ± 18.8 months) versus those alive/censored, collected over the course of 24 months. The patients who died had significantly greater serum levels of IL-6 and narrower phase angle on all five scheduled visits along 2 years of longitudinal observation. Changes of IL-6 levels over time in patients who died during follow-up versus those alive, adjusted for demographic and clinical parameters, are shown in Figure 2. Dietary intake indicators and TSF were lower only on the fourth visit (18-month measurements), and serum albumin was lower only on the fifth visit (24-month measurements) in patients who died compared with those alive/censored. The remaining laboratory and clinical nutritional parameters did not significantly differ between the two groups on any of the five visits.

The ROC curve confirmed serum IL-6 levels as a reliable marker of all-cause mortality in hemodialysis patients (area under the curve, 0.68 [0.56 to 0.80]; \( P = 0.005 \); Figure 3a). The ROC curve allowed us to define a cutoff value for serum IL-6 (6.605 pg/ml), with a sensitivity of 66% and specificity of 66%. Patients with a baseline IL-6

![Figure 1](image_url)  
**Figure 1.** Box and whisker plots of IL-6 levels at baseline (month 0) and at 6-month intervals in the study population. IL-6 levels increased significantly with time in both univariate (crude) analysis, linear estimate, 2.57 ± 0.44 pg/ml per 2 yrs, \( P = 0.001 \); and after adjustments for age, gender, diabetes status, dialysis vintage, and past cardiovascular disease, linear estimate, 2.35 ± 0.57 pg/ml per 2 yrs, \( P = 0.049 \).
level less than the cutoff value had significantly better survival than patients with a baseline IL-6 level greater than the cutoff value (Figure 3B).

Results of the different multivariate models are listed in Table 4. In the first model including age, gender, diabetes status, dialysis vintage, and past cardiovascular disease, and IL-6 as a continuous variable. The model takes into account every measurement of IL-6 and presents nutritional variables at each time point separately for each patient. Regression coefficients indicate mean longitudinal change in outcome variables associated with a 1-ppg/ml longitudinal increase in IL-6, controlling for fixed factors. DEI, daily energy intake; DPI, daily protein intake; nPNA, normalized protein nitrogen appearance; TLC, total lymphocyte count; EPO, erythropoietin; BMI, body mass index; TSF, triceps skinfold thickness; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; FM, fat mass; FFM, fat-free mass; DM, diabetes mellitus; CV, cardiovascular.

All nutritional variables presented in the table were modeled separately as dependent variables, whereas independent variables included fixed factors (such as age, gender, diabetes status, dialysis vintage, and past cardiovascular disease), and IL-6 as a continuous variable. The model takes into account every measurement of IL-6 and presents nutritional variables at each time point separately for each patient. Regression coefficients indicate mean longitudinal change in outcome variables associated with a 1-ppg/ml longitudinal increase in IL-6, controlling for fixed factors. DEI, daily energy intake; DPI, daily protein intake; nPNA, normalized protein nitrogen appearance; TLC, total lymphocyte count; EPO, erythropoietin; BMI, body mass index; TSF, triceps skinfold thickness; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; FM, fat mass; FFM, fat-free mass; DM, diabetes mellitus; CV, cardiovascular.

Table 2. Associations of longitudinal IL-6 changes with changes in nutritional parameters (slopes) over 24 months, based on a mixed-effects model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>F</th>
<th>P</th>
<th>P*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
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<tr>
<td>Dietary intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ DEI (kcal/kg per d)</td>
<td>-0.16</td>
<td>-0.31</td>
<td>-0.01</td>
<td>6.186</td>
<td>0.04</td>
</tr>
<tr>
<td>Δ DPI (g/kg per d)</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.003</td>
<td>3.513</td>
<td>0.06</td>
</tr>
<tr>
<td>Δ nPNA (g/kg per d)</td>
<td>-0.001</td>
<td>-0.002</td>
<td>0.002</td>
<td>0.004</td>
<td>0.95</td>
</tr>
<tr>
<td>Biochemical markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Albumin (g/L)</td>
<td>-0.06</td>
<td>-0.08</td>
<td>-0.04</td>
<td>37.404</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ Transferrin (mg/dl)</td>
<td>-0.32</td>
<td>-0.55</td>
<td>-0.08</td>
<td>8.073</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ Creatinine (mg/dl)</td>
<td>-0.01</td>
<td>-0.02</td>
<td>0.002</td>
<td>6.773</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ Cholesterol (mg/dl)</td>
<td>-0.54</td>
<td>-0.81</td>
<td>-0.25</td>
<td>14.850</td>
<td>0.001</td>
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<tr>
<td>Δ TLC (∗10^3/ml)</td>
<td>-0.005</td>
<td>-0.008</td>
<td>0.003</td>
<td>18.650</td>
<td>0.001</td>
</tr>
<tr>
<td>EPO dose (∗10^4 U/week)</td>
<td>-0.04</td>
<td>-0.14</td>
<td>0.06</td>
<td>0.598</td>
<td>0.44</td>
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<tr>
<td>Anthropometric measurements</td>
<td></td>
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<tr>
<td>Δ BMI (kg/m^2)</td>
<td>-0.19</td>
<td>-0.04</td>
<td>0.003</td>
<td>3.045</td>
<td>0.08</td>
</tr>
<tr>
<td>Δ TSF (mm)</td>
<td>-0.01</td>
<td>-3.57</td>
<td>3.57</td>
<td>25.515</td>
<td>0.97</td>
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<tr>
<td>Δ MAC (cm)</td>
<td>-0.006</td>
<td>-0.02</td>
<td>0.003</td>
<td>1.637</td>
<td>0.20</td>
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<tr>
<td>Δ MAMC (cm)</td>
<td>0.001</td>
<td>-0.009</td>
<td>0.01</td>
<td>0.011</td>
<td>0.92</td>
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<tr>
<td>Bioimpedance analysis</td>
<td></td>
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<tr>
<td>Δ FM (kg)</td>
<td>-0.03</td>
<td>-0.05</td>
<td>-0.01</td>
<td>9.933</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ Body fat (%)</td>
<td>-0.03</td>
<td>-0.10</td>
<td>0.04</td>
<td>0.647</td>
<td>0.42</td>
</tr>
<tr>
<td>Δ FFM (kg)</td>
<td>0.0001</td>
<td>-0.17</td>
<td>0.17</td>
<td>0.0001</td>
<td>0.10</td>
</tr>
<tr>
<td>Δ Phase angle (°)</td>
<td>-0.005</td>
<td>-0.011</td>
<td>-0.001</td>
<td>4.638</td>
<td>0.05</td>
</tr>
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</table>

All nutritional variables presented in the table were modeled separately as dependent variables, whereas independent variables included fixed factors (such as age, gender, diabetes status, dialysis vintage, and past cardiovascular disease), and IL-6 as a continuous variable. The model takes into account every measurement of IL-6 and presents nutritional variables at each time point separately for each patient. Regression coefficients indicate mean longitudinal change in outcome variables associated with a 1-ppg/ml longitudinal increase in IL-6, controlling for fixed factors. DEI, daily energy intake; DPI, daily protein intake; nPNA, normalized protein nitrogen appearance; TLC, total lymphocyte count; EPO, erythropoietin; BMI, body mass index; TSF, triceps skinfold thickness; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; FM, fat mass; FFM, fat-free mass; DM, diabetes mellitus; CV, cardiovascular. *P for trend for IL-6-by-time interactions.
inflammation were found in continuous ambulatory peritoneal dialysis (CAPD) patients by Dong et al. (36). However, results of longitudinal studies were not unequivocal: While Kaysen et al. (37) demonstrated that markers of inflammation and dietary protein intake expressed as nPCR (normalized protein catabolic rate) exerted competing effects on serum
albumin and creatinine in 364 hemodialysis patients, Johansen et al. (38) did not find a modulating effect of CRP and IL-1β on dietary energy and protein intake over time in a smaller cohort.

Many studies relied on assumptions about the role of inflammation in the modification of nutritional status of chronic hemodialysis patients based on cross-sectional findings (1,17,18,39–41), but not all them were able to provide clinical evidence supporting this link between PEW and nutritional markers in HD patients (40,41). A few studies have attempted to follow HD patients longitudinally to determine whether nutritional status is associated with inflammation over time. Analyzing laboratory data obtained from patients in the HEMO study, Kaysen et al.

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**Figure 2.** | Longitudinal changes of IL-6 levels in patients who died during follow-up versus those alive: univariate analysis (A) and after adjustments for age, gender, diabetes status, dialysis vintage, and past cardiovascular disease (B). Data presented as medians with 95% confidence intervals. * P < 0.05.
Figure 3. (A) Receiver operating characteristic curve of IL-6 levels; fraction of true-positive (sensitivity) and false-positive (1 – specificity) results for serum IL-6 level as a marker of all-cause mortality. Calculated area under the curve was 0.68, with 95% CI 0.56 to 0.80 (P = 0.005). (B) Kaplan–Meier survival curves of surviving patients comparing subgroups with baseline serum IL-6 levels less or greater than the cutoff value (6.605 pg/ml). Log-rank test, P = 0.004.

Patients at risk:

| Above cut-off | 40 | 38 | 28 | 21 | 17 | 11 | 7 |
| Below cut-off  | 45 | 44 | 32 | 29 | 24 | 22 | 19 |
(38) found CRP levels associated with serum albumin and creatinine concentrations. During a year of longitudinal observation on 54 HD patients by Johansen et al. (38), CRP influenced the change in albumin, and IL-1β modulated the change of phase angle over time. Nevertheless, no significant changes over time in body composition, or other serum biochemical markers of nutrition, were found in this study (38). Although the principal biomarker of inflammation measured in our study (IL-6) was different from those used in previous longitudinal studies (CRP, IL-1β, and IL-1 receptor antagonist), the discrepancies between our results and theirs may also be caused by differences in population characteristics (note that we excluded patients with BMI less than 20 kg/m² and/or albumin levels less than 35 g/L), sample size, and observation time. Additionally, a decrease in the levels of most laboratory nutritional markers (such as albumin, cholesterol, or transferrin) was interpreted as a negative acute-phase response to inflammatory stimuli in several of the above studies (26,37,39,42) and not necessarily as a decline in nutritional status.

Although over the duration of our longitudinal observation, we observed the elevation of IL-6 to be associated with lower dietary intake, laboratory markers of decreased nutritional adequacy (deceased albumin, cholesterol, transferrin, TLC, and creatinine), and changes in body composition parameters (fat mass), this disparity did not appear to widen over the 2 years of follow-up. Thus, IL-6 did not associate with the changes in nutritional markers over time in our population. This finding can be explained in several ways. First, inflammation occurs episodically in hemodialysis patients (43), and variation in CRP levels in prevalent HD patients was found as predicted partly by intercurrent events (44,45); therefore, the presence of chronic inflammation at a given time of observation, measured by serum IL-6 levels, may be overestimated. Second, the level of chronic inflammation in HD patients may vary over time, even during a period free of clinically apparent inflammatory events, as shown by Tsirpanlis et al. (46). Furthermore, the variability of inflammatory marker levels over time in hemodialysis patients may additionally be influenced by patient-related factors (residual renal function, genetic determinants) or dialysis-specific factors such as membrane bio-incompatibility, dialysate backflow, endotoxemia, and the intermittent nature of hemodialysis (47). Therefore, the strength of the influence of inflammation on nutrition in any patient may vary over time as well. Third, our study included limited follow-up. It is possible that certain elements of nutritional status, including body composition, might have changed appreciably if follow-up was continued over 2 years in surviving patients. Finally, since we observed significantly greater phase angle, as well as a trend toward greater dietary intake, TSF, and fat mass levels in patients who remained alive until the end of the study period (Table 3), and increasing mortality burden in patients with higher IL-6 levels (Tables 3 and 4, Figure 3), it is possible that the patients with higher levels of inflammation are prone to developing PEW, but their suboptimal dietary state does not reach detectable levels before death.

Of interest is the observation that IL-6 levels increased with time in our cohort. Bossola et al. (48) found stable levels of CRP over 3 years of observation in a cohort of prevalent hemodialysis patients. In contrast, Kaysen et al. (43) showed that the levels of CRP and other acute-phase proteins varied considerably over time in 37 participants of the HEMO study. An explanation of the increasing levels of the IL-6 in our cohort would require identification of the factors responsible for the inflammation in HD patients (8–10), but our study was not designed to answer this question.

Some limitations of the present study should be considered. First, this study is based on a relatively small sample size and represents selected group of prevalent HD patients (survivors) with serum albumin >35 g/L and/or BMI >20 kg/m², limiting the ability of our findings to be generalized. Therefore, we may have lacked the sensitivity to detect subtle influences of inflammation on the outcome variables. Second, this study used only an observational

<table>
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<tr>
<th>Table 4. Cox proportional hazard ratios for death</th>
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<td></td>
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<tr>
<td>Age (1 yr ↑)</td>
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<tr>
<td>Gender (men versus women)</td>
</tr>
<tr>
<td>DM (yes versus no)</td>
</tr>
<tr>
<td>History of CVD (yes versus no)</td>
</tr>
<tr>
<td>Dialysis vintage (1 mo ↑)</td>
</tr>
<tr>
<td>Albumin (1 g/L ↑)</td>
</tr>
<tr>
<td>FFM (1 kg ↑)</td>
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<tr>
<td>FM (1 kg ↑)</td>
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<tr>
<td>IL-6 (1 pg/ml ↑)</td>
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Model 1 includes age (per year), gender, CVD in the past, dialysis vintage, DM status, and basal albumin levels. In model 2, body composition parameters (FFM and FM) are added, and in model 3, IL-6 levels (per increase in 1 pg/ml) are added. CI, confidence interval; HR, hazard ratio; IL-6, interleukin-6; FM, fat mass; FFM, fat-free mass; DM, diabetes mellitus; CVD, cardio vascular disease.
approach, without manipulation of exposure factors, and, therefore, no definitive cause-and-effect relationship can be derived for any of the risk factors analyzed. Dietary intake assessed by 3-day food records is another limitation of the study, as results can be subjective and incomplete, and can vary considerably from day to day as a result of dialysis treatment sessions and associated disturbances in food intake. Furthermore, we did not evaluate residual renal function, which may itself have an impact on nutritional status and inflammation of our patients. Finally, although IL-6 is the best indicator of an inflammatory response (6), we measured only a single inflammatory marker, and, thus, our findings related to inflammation cannot be extrapolated to other markers. Nevertheless, the present study has the advantage of providing long-term longitudinal data on the relationship between serum concentrations of IL-6 and nutritional parameters in prevalent HD patients.

In summary, we showed that chronic inflammation, as measured by higher serum IL-6 levels, is associated with all-cause death without association with changes in clinical and laboratory markers of nutritional status in clinically stable HD patients. Nevertheless, the observational approach of the study and the strong associations between IL-6 and nutritional markers across visits does not allow us to exclude on the possibility that the effects of IL-6 are mediated through changes in nutritional status over time. Our data further support the concept of “malnutrition type 2” suggested by Stenvinkel et al. (25); the high rate of all-cause mortality may occur before signs of clinical PEW can be detected. While results from this observational study cannot provide definitive proof, they suggest that early detection of inflammation by elevated laboratory markers is of utmost importance, so that this condition may be appropriately managed, even in seemingly well-nourished prevalent HD patients.

Disclosures
None.

References


Received: February 20, 2011 Accepted: May 30, 2011

Published online ahead of print. Publication date available at www.cjasn.org.