Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients¹–⁴

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ABSTRACT

Background: Cross-sectional studies have shown an association between the duration (y) of dialysis and nutritional status, providing evidence of wasting.

Objective: The aim was to determine the extent, pace, determinants, and optimal methods of assessing wasting in patients undergoing hemodialysis.

Design: Laboratory variables, body composition, and physical activity, function, and performance were tested 4 times over 1 y in 54 hemodialysis patients. Changes in repeated measures were evaluated, with adjustment for baseline differences by age, sex, race, diabetes status, and dialysis vintage (ie, time since initiation of dialysis).

Results: No significant changes in body weight, fat mass, lean body mass, or laboratory variables were observed. Phase angle, a bioelectrical impedance analysis–derived variable related to body cell mass, decreased significantly (linear estimate: −0.043°/mo, or ≈0.5°/y; P = 0.001). Physical activity measured by accelerometry declined 3.4%/mo (P = 0.01). The Maximum Activity Score of the Human Activity Profile (HAP) also declined significantly (linear estimate: −0.50/mo, or ≈6 points/y; P = 0.025). Higher interleukin 1β (IL-1β) concentrations were associated with a narrower phase angle (P = 0.004) and with a more rapid decline in phase angle with time (time × IL-1β interaction, P = 0.01); similar effects of IL-1β on physical activity were observed. Dietary protein and energy intakes were associated with changes in the HAP.

Conclusions: Evidence of adverse changes in body composition and physical activity, function, and performance and of a modest influence of inflammation and dietary intake on these changes was observed in this cohort. Tools such as bioelectrical impedance analysis, accelerometry, and the HAP may be required to identify subtle changes. Am J Clin Nutr 2003;77:842–6.

KEY WORDS  End-stage renal disease, hemodialysis, nutritional status, physical activity, physical performance, physical function, inflammation, longitudinal study

INTRODUCTION

Numerous reports have documented a high prevalence of protein-calorie malnutrition and poor physical functioning in patients receiving hemodialysis (1, 2), and indexes of nutritional status and physical functioning have been linked to mortality in this population (3–5). Some potential factors widely thought to contribute to poor nutritional status and physical functioning include decreased protein or energy intake, chronic inflammation, physical inactivity, concurrent acute or chronic conditions or illnesses, and the catabolic stimulus of dialysis itself (6). Because these processes are generally chronic, it would be expected that a progressive decline in nutritional status, or wasting, should be observed when they are operative. However, there have been few attempts to follow patients longitudinally to determine whether wasting is occurring and, if so, whether one can identify factors associated with wasting. Barriers to the performance of longitudinal studies have included the lack of consensus about which variables should be followed, the paucity of information about which measures might be most sensitive to change, and the expense, effort, and time associated with these studies. Specifically, it is not clear whether those measures most predictive of mortality would be most informative in longitudinal analyses.

A recent cross-sectional analysis of the association between dialysis vintage (ie, time since initiation of dialysis) and nutritional status included information derived from bioelectrical impedance analysis as well as from traditional biochemical indicators and provided some informative data (7). Generally, body-composition indexes were more closely linked with vintage than were biochemical measures. Body weight, estimated total body water, estimated body cell mass, and phase angle were all lower among patients with longer vintage, with the largest relative differences observed for phase angle. However, it is difficult to draw conclusions about the change in body composition with time from a cross-sectional study because of confounding and selection and lead-time bias.

The goal of the current study was to make prospective longitudinal measurements of nutritional status (body composition and

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biochemical indexes) and of physical activity, function, and performance to determine whether nutritional and functional status decline over time in patients receiving dialysis. In addition, food intake and markers of inflammation were measured to determine whether any observed changes could be related to inadequate protein or energy intake or to ongoing inflammation.

SUBJECTS AND METHODS

Subjects

Fifty-four men and women living in the community and undergoing hemodialysis 3 times/wk at the outpatient dialysis units at San Francisco General Hospital, the University of California, San Francisco–Mt Zion Medical Center, and the San Francisco Veterans Affairs Medical Center participated in the study. All subjects gave written informed consent for participation. The study protocol was approved by the appropriate committees on human research. Results of the baseline physical activity, function, and performance tests for a subset of these subjects were reported previously (8–10).

Measurements

Study measurements were performed at baseline and 4, 8, and 12 mo from enrollment during a visit to the General Clinical Research Center at San Francisco General Hospital on a midweek day between dialysis treatments. Specifically, body-composition measures included body weight, phase angle derived from bioelectrical impedance analysis (RJL Systems, Detroit), and fat and fat-free mass by dual-energy X-ray absorptiometry (Lunar, Madison, WI). Phase angle is calculated as the arctangent of reactance over resistance and is related to body cell mass and to the distribution of fluid between intracellular and extracellular compartments (11). Biochemical indexes of nutritional status included serum albumin, creatinine, and total cholesterol concentrations. Physical functioning was assessed by 2 questionnaires [the Human Activity Profile (HAP) and the Physical Functioning and Physical Component Scores on the 36-item, short-form questionnaire of the Medical Outcomes Study] and 3 physical-performance tests (gait speed, stair-climbing time, and chair-rising time) as described elsewhere (9, 10). The HAP consists of a list of 94 activities ranked in ascending order of the level of energy required to perform each activity (12). Subjects are asked to assign each activity to 1 of 3 categories: 1) “still doing this activity,” 2) “have stopped doing this activity,” or 3) “never did this activity.” The Maximum Activity Score is the numeral identifying the activity with the highest oxygen-consumption requirement that the subject still performs. The Adjusted Activity Score is the difference between the Maximum Activity Score and the number of activities the subject has stopped performing, which gives a better estimate of the range of activities performed and of the presence of impairment.

Blood was drawn at each study visit and stored for analysis of inflammatory markers. Enzyme-linked immunosassay was used to measure the following inflammatory markers at the end of the study: C-reactive protein (CRP; detection range: 1–50 μg/mL; Hemagen Diagnostics, Columbia, MD), interleukin 1β (IL-1β; detection range: 3.9–250 pg/mL; R & D Systems, Minneapolis), IL-1-receptor antagonist (detection range: 46.9–3000 pg/mL; R & D Systems, Minneapolis), and tumor necrosis factor α (detection range: 15.6–1000 pg/mL; Biosource International, Camarillo, CA).

Nutritional intake was assessed by using the Block–National Cancer Institute 110-item food frequency questionnaire (13). Subjects were asked to report their usual food intake during the previous year. The questionnaire was described in detail previously, as were its validity and reproducibility (13–15). With the use of software developed for the survey instrument, the frequency of consumption of each food was multiplied by the nutrient content of the reported portion sizes to generate average daily intakes of protein and energy. Food-frequency information was collected only at the initial study visit.

Statistical analysis

Continuous variables were described as means ± SDs or medians and interquartile ranges; categorical variables were described as proportions. Inflammatory markers were log transformed to attenuate the influence of very high values on inference testing. Repeated-measures analysis of variance was performed by using the MIXED model with an unstructured covariance matrix (16). The MIXED model was chosen for its flexibility, because it allowed us to incorporate all available data. We applied an unstructured variance-covariance matrix to obviate assumptions of particular data structure that might otherwise have been required and to ensure that P values were conservatively estimated. Model fit was assessed by using Akaike’s information criteria. Only patients with ≥2 study visits were included in the analyses.

Time was the main independent variable of interest; in other words, we focused on the association between time and all dependent variables to evaluate for the presence of wasting. Base models were adjusted for age, sex, race, diabetes status, and dialysis vintage, because these factors were correlated with many of the dependent variables tested in the analyses. To evaluate whether (and to what degree) inflammation influenced the trends in dependent variables, we included in each base model terms for individual inflammatory markers and the time × inflammatory marker interaction. The latter terms tested whether the trend observed was dependent on the concentration of the inflammatory markers. In other words, if the serum albumin concentration tended to decrease over time, the time × CRP interaction term would evaluate whether the downward trend in albumin was dependent on the CRP concentration. Finally, estimates of dietary protein (g/d) and energy (kcal/d) intakes over the year before study enrollment were assessed individually by adding them to the base model. All analyses were conducted by using SAS 8.0 (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the cohort are shown in Table 1. The sex and racial distribution of the subjects is representative of the dialysis population in the San Francisco Bay area. However, the requirement that subjects make a study visit on a nondialysis day yielded a younger, healthier, and higher-functioning group of study subjects than the total available population in the 3 dialysis units or than the population in other studies of unselected dialysis patients (5). Forty-one patients completed the 4-mo visit, 35 completed the 8-mo visit, and 31 completed the 1-y follow-up. Reasons for withdrawal from the study included transfer to a nonstudy dialysis facility (n = 5), change to peritoneal dialysis (n = 3), transplantation (n = 3), death (n = 4), and voluntary withdrawal—usually for medical reasons (n = 8).
When acute phase reactants and cytokines were added to the models, some interesting associations were observed. The effect of CRP on serum albumin concentrations was confirmed (17, 18). On average, serum albumin was lower by 0.03 g/dL for every unit increase in log CRP ($P = 0.042$). In addition, CRP modulated the change in albumin over time, with albumin tending to rise when CRP was low and decline when CRP was high (time $\times$ log CRP interaction, $P = 0.007$). The strong association between body fat mass and serum leptin concentration was also confirmed. For every unit increase in log serum leptin concentration, body fat mass was higher by 5.31 g ($P < 0.0001$). Higher IL-1$\beta$ concentrations were associated with a narrower phase angle ($P = 0.004$) and with a more rapid decline in phase angle with time (time $\times$ log IL-1$\beta$ interaction, $P = 0.01$). For example, the model would predict that a patient with a phase angle of 5° and an undetectable IL-1$\beta$ concentration would experience an 11.4% reduction in phase angle to 4.43° per 1 y.

A similar patient with an IL-1$\beta$ concentration of 5.0 pg/mL would be expected to decrease his or her phase angle by 14.6% to 4.27° over the same time period. Higher IL-1$\beta$ concentrations were also associated with lower physical activity. As with fat mass, expected associations between physical activity and leptin were observed. On average, physical activity was lower by >17 000 arbitrary units with each log increase in leptin concentration ($P = 0.0015$). Although physical activity tended to decline over time, it tended to decline less so among subjects with higher serum leptin concentrations (time $\times$ leptin interaction, $P = 0.04$).

The associations of protein and energy intakes with changes in outcome variables were also modeled. Dietary protein and energy...
intakes were not significantly associated with changes in any measure of body composition or in any laboratory marker of nutritional status. However, dietary protein and energy intakes were associated with changes in measures of physical function, especially the HAP. Although the Maximum Activity Scores tended to decline overall, the rate of decline was attenuated with increased dietary protein (time × protein interaction, \( P < 0.00001 \)) and energy intake (time × energy interaction, \( P = 0.009 \)). The Adjusted Activity Score and other tests of physical activity, function, and performance showed qualitatively similar associations with dietary intake (data not shown), albeit with lesser degrees of statistical significance.

**DISCUSSION**

The results of this analysis showed adverse changes in body composition and physical activity and function over time and support the hypothesis that end-stage renal disease is associated with wasting and physical decline. However, changes were detected only in phase angle, the Maximum Activity Score of the HAP, and physical activity by accelerometry. The small size of the study could have precluded detection of changes in other measures of body composition or physical function or performance. Nevertheless, these results suggest that phase angle and HAP scores are sensitive ways to monitor changes in these areas. A decline in phase angle indicates that a change in body composition, specifically the loss of body cell mass, may occur even in the absence of a change in weight or lean body mass. A likely explanation for such a finding in a dialysis population is that there is an increase in extracellular fluid that is proportional to a decrease in body cell mass. In other words, dry weight may not have been fully adjusted in response to changes in body composition. Furthermore, changes in phase angle may have clinical significance because an association between phase angle and mortality in patients with end-stage renal disease was shown previously (19). Likewise, a decline in the Maximum Activity Score of the HAP indicates that patients are currently performing fewer taxing activities, even in the absence of a change in the more narrow range of activities included in physical-performance testing. The Maximum Activity Score of the HAP was previously shown to be closely associated with physical activity and physical functioning (9), and in this study the changes in Maximum Activity Score parallel the observed decrease in physical activity measured by accelerometry. Therefore, we believe that the current study has identified phase angle, the HAP, and accelerometry as sensitive ways to detect changes in body composition, physical functioning, and physical activity in the dialysis population.

Markers of inflammation were associated with some measures of nutritional status or body composition and in some cases with the changes in these variables over time. However, inflammatory markers were not associated with measures of, or changes in, physical function. It is possible that alteration of function could be a late consequence of malnutrition and, thus, is less likely related to rapidly changing concentrations of inflammatory markers. Although the principal cytokines measured here were IL-1β and IL-1 receptor antagonist, these are released by the same processes that initiate the release of tumor necrosis factor α (20). The half-lives of these cytokines are short and their serum concentrations may underestimate the biologic events accompanying their release because they act locally.

The change in phase angle and its modulation by IL-1β may reflect a reduction in muscle mass influenced by inflammation in this population. Reactance reflects the stored charge on cell membranes, and may diminish with a reduction in viable cell number or size. Inflammation causes wasting of muscle mass through a ubiquitin-mediated process (21, 22). Although the recovery of visceral proteins (specifically albumin) after inflammatory events occurs fairly quickly, regeneration of lost somatic proteins, specifically muscle, is less well assured. Although inflammation occurs episodically in hemodialysis patients (23), patients who have evidence of inflammation at one point in time are more likely to experience inflammation later.

The small size of the study did not allow assessment of more complex (eg, 3-way) interactions and may have resulted in the failure to detect more subtle changes over time or the influence of inflammatory markers on changes in other measures of body composition or physical function and performance. However, the confirmation of known associations, such as those between serum albumin and CRP (17, 18) and between body fat and serum leptin (24, 25), suggests that the analytic approach was valid and the novel findings described here are likely to be correct.

Protein and energy intakes were not associated with measures of body composition or nutritional status but were associated with several measures of physical function. The lack of a direct relation between intake and nutritional status could reflect the modulating influence of inflammation. The associations of serum albumin and creatinine concentrations with CRP concentrations lend some support to this construct. The association between intake and physical function could be mediated by the energy requirements of physical activity. For example, greater energy expenditure through physical activity is associated with better physical functioning and with greater energy intake to preserve energy balance.

The study has several important limitations. First, the sample size was relatively small, and as noted above, we may have lacked the sensitivity to detect subtle changes in the natural history of disease or subtle influences of inflammation or intake on these changes. Second, the sample was somewhat healthier and more fit than was the general population with end-stage renal disease because of the rigors of testing; studying a less able-bodied sample might have identified more abnormalities. Third, there was limited follow-up. It is possible that certain elements of nutritional status, including body composition, might not change appreciably within 12 mo but would do so over 24 or 36 mo. This delay in identification of wasting may be more pronounced given the general good health of the cohort. We previously showed that the relation between body composition and dialysis vintage was rather subtle, except among patients dialyzed for >5 y (7). Finally, because we only studied hemodialysis patients, these results may not be generalizable to patients receiving peritoneal dialysis or to those who have undergone kidney transplantation. The body composition (and physical function) of these populations may be greatly affected by excess calories derived from peritoneal dialysate and the use of glucocorticoids, respectively.

In summary, we showed that wasting and physical decline occur in hemodialysis patients and that some measures of body composition and physical activity and function appear to be more sensitive to change than others. Bioelectrical impedance analysis and HAP testing are easily performed and may be particularly useful for evaluating interventions to improve or prevent the decline of body composition and physical function in hemodialysis patients. Larger cohort studies and intervention trials will be required to better understand the natural history of body-composition changes and impaired physical function in
hemodialysis patients and methods to maintain and improve body composition and physical function.

KLJ and GMC were involved in the study design, in obtaining funds for the study, in the data analysis, and in writing the manuscript; GAK helped interpret the results and write the manuscript; BSY helped develop and execute the data-analysis plan and reviewed and approved the manuscript; MdS collected the data and reviewed and approved the manuscript; and AMH was involved in formulating the data-analysis plan and reviewed and approved the manuscript. None of the authors had any financial or personal interest in any company or organization sponsoring the research, including advisory board affiliations.

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