Nephrol Dial Transplant (2005) 20: 2765–2774
doi:10.1093/ndt/gfi132
Advance Access publication 4 October 2005

Original Article

Nephrology Dialysis Transplantation

Self-reported appetite, hospitalization and death in haemodialysis patients: findings from the Hemodialysis (HEMO) Study

Jerrilynn D. Burrowes[1], Brett Larive[2], Glenn M. Chertow[3], David B. Cockram[4], Johanna T. Dwyer[5,6], Tom Greene[2], John W. Kusek[7], June Leung[6] and Michael V. Rocco[8] for the HEMO Study Group

[1]Department of Nutrition, C.W. Post Campus of Long Island University, Brookville, NY, [2]Department of Biostatistics and Epidemiology, The Cleveland Clinic Foundation, Cleveland, OH, [3]Departments of Medicine, Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, [4]Ross Products Division, Abbott Laboratories, Medical and Regulatory Affairs, Columbus, OH, [5]Tufts University Schools of Medicine and Friedman School of Nutrition Science and Policy, Boston, MA, [6]Frances Stern Nutrition Center, Tufts-New England Medical Center, Boston, MA, [7]National Institute of Diabetes, Digestive and Kidney Disease, National Institutes of Health, Bethesda, MD and [8]Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Abstract

Background. Anorexia is an important cause of protein–energy malnutrition (PEM) in haemodialysis patients. We investigated whether self-reported appetite was associated with death and hospitalization in subjects enrolled in the Hemodialysis (HEMO) Study.

Methods. The HEMO Study was a 7-year, multicentre, randomized trial ($N = 1846$), which examined the effects of dialysis dose and membrane flux on mortality and morbidity. Three questions from the Appetite and Diet Assessment Tool (ADAT) were used to determine whether appetite had changed over time in the randomized treatment groups. The relations among ADAT scores, dietary protein and energy intakes, biochemical and anthropometric measures, and quality of life were assessed. We used Cox proportional hazards models to evaluate the relative risks of death and hospitalization associated with static and dynamic ADAT scores, adjusted for demographic factors, dose and flux assignments, and co-morbidity.

Results. The average length of follow-up was 2.84 years. After adjusting for demographic factors and randomized treatment assignments, there was a significant association between poorer self-reported appetite and death (RR 1.52, 95% CI 1.16–1.98); however, the association became non-significant with further adjustment for co-morbidity (RR 1.23, 95% CI 0.94–1.62). Poorer appetite was unequivocally associated with increased hospitalization rates (multivariable RR 1.35, 95% CI 1.13–1.61). The longitudinal effect of worsening appetite from baseline to 1 year was not associated with mortality or hospitalization rate after adjusting for co-morbidity.

Conclusions. The association between appetite and death was confounded by co-morbidity. Self-reported appetite was associated with hospitalization rate in haemodialysis patients and, thus, it may be a useful screening tool for this outcome. Patients who report poor or very poor appetites should be monitored, and they should receive more comprehensive nutritional assessments.

Keywords: anorexia; appetite; haemodialysis; malnutrition; morbidity; mortality

Introduction

The prevalence of protein-energy malnutrition (PEM) among maintenance haemodialysis patients varies from 30–75% as determined by conventional measures of nutritional status (e.g. dietary, anthropometric and clinical measures) [1–3]. PEM is important since it is associated with poor clinical outcomes [4,5]. Although alterations in protein and energy metabolism may contribute to PEM, anorexia, defined as diminished appetite resulting in inadequate nutrient intake, may be the single most important cause of PEM, since it also affects a substantial number of haemodialysis patients [3,6–9]. Early identification and initiation of interventions for diminished appetite in maintenance

Correspondence and off print requests to: Jerrilynn D. Burrowes, PhD, RD, Department of Nutrition, C.W. Post Campus of Long Island University, School of Health Professions and Nursing, 720 Northern Blvd., Brookville, NY 11548, UAS.
Email: jerrilynn.burrowes@liu.edu

haemodialysis patients may prevent or retard deteriorating nutritional status and the progression of PEM. A few prospective studies have examined the association between appetite and clinical outcomes in maintenance haemodialysis patients [3]. Using data from a randomized clinical trial of haemodialysis dose and membrane flux (the Hemodialysis [HEMO] Study), we investigated the associations among self-reported appetite, death and hospitalizations. We hypothesized that appetite would correlate with objective parameters of nutritional status (biochemical and anthropometric measures) and that poorer appetite would be associated with increased death and hospitalization rate.

Subjects and methods

Study design

The design, methods and primary outcomes of the HEMO Study have been published previously [10]. Briefly, the HEMO Study was a 7-year, prospective, multicentre, randomized, 2×2 factorial clinical trial sponsored by the National Institute of Diabetes, Digestive and Kidney Disease of the National Institutes of Health. The objective of the trial was to examine the effects of dialysis dose (standard equilibrated Kt/V [eKt/V] of 1.05 *vs* high eKt/V of 1.45) and membrane flux (low β_2 microglobulin clearance <10 ml/min *vs* high β_2 microglobulin clearance >20 ml/min) on mortality and morbidity in haemodialysis patients. Subjects were randomly assigned with equal allocation to the two dose and flux groups.

Study population

A total of 1846 subjects between the ages of 18 and 80 years were enrolled in the trial from March 1995 to October 2000. Subjects were on maintenance haemodialysis three times per week for at least 3 months. Subjects were excluded from the trial if they had either a serum albumin <26 g/l (as measured by nephelometry); a residual renal clearance of urea >1.5 ml/min normalized to 351 of estimated total body water; were unable to achieve an eKt/V >1.30 in ≤4.5 h on two of three consecutively monitored dialysis sessions targeting the high dose dialysis goal; had co-morbid medical conditions such as severe cardiac disease, active malignancies requiring chemotherapy or radiation therapy, known acquired immunodeficiency syndrome (AIDS); or were unable or unwilling to follow study procedures. The Institutional Review Boards at each of the 15 clinical centres approved the study protocol. Written informed consent was obtained from each study subject.

Outcomes

Death from any cause was the primary outcome. Among the secondary outcomes, we report the rate and duration of hospitalizations not related to vascular access.

Measures of nutritional status

Subjective assessment of appetite. The Appetite and Diet Assessment Tool (ADAT) was used to determine whether appetite changed over time in the randomized dialysis dose and/or membrane flux treatment groups [11]. The ADAT was administered at baseline, and annually thereafter to obtain information on the subjects' general level of appetite and eating habits on dialysis and non-dialysis treatment days. The first three ADAT questions were related to appetite. The responses to the first question, *During the past week, how would you rate your appetite?* adhered to a 5-point Likert scale: (1) *very good*, (2) *good*, (3) *fair*, (4) *poor* and (5) *very poor*. The second and third questions asked whether there had been a change in appetite in the past week and, if so, had appetite *increased*, *remained the same*, or *decreased*. We have previously shown that baseline responses to the first ADAT question were associated with decreased dietary energy and protein intakes and with other measures of nutritional status [9].

Evaluation of dietary intake. Dietary protein and energy intakes were assessed from 2-day diet diary-assisted recalls administered concurrently with the ADAT. Details of the methods used for collecting and analysing the diet recalls have been published elsewhere [12]. Dietary protein intake was also estimated from the equilibrated protein catabolic rate normalized to body weight (enPCR). The enPCR was calculated monthly from the urea generation rate using formal urea kinetic modelling. In stable, non-catabolic maintenance haemodialysis patients, enPCR estimates dietary protein intake.

Biochemical indices. Biochemical measures of nutritional status, including serum albumin (measured at baseline and monthly at a central laboratory by nephelometry) and serum creatinine, and total cholesterol (measured at baseline and biannually at the laboratory of each clinical centre) were analysed.

Anthropometric measures. Post-dialysis weight was measured after each dialysis session and averaged. Body mass index (BMI) was calculated from the mean post-dialysis weight and stature. If the subject had an amputation or was unable to stand, stature was estimated from knee height [13]. Upper arm and calf circumferences were used to assess lean body mass and were obtained, at baseline and annually, by trained and certified study dietitians using standard caliper-based methods.

Other clinical indicators

Health-related quality of life (HRQOL) was measured by the Medical Outcomes Study Short Form-36 (SF-36), a self-administered questionnaire that explores eight generic health constructs (physical functioning, role limitations caused by physical problems, bodily pain, general health perceptions, vitality, social function, role limitations caused by emotional problems, and general mental health) [14]. Only summary measures of the physical component scale (PCS), a measure of physical health, and the mental component scale (MCS), a measure of emotional function, were analysed.

Case-mix variables and co-morbidity indicators

Case-mix variables included age, gender, race (black *vs* non-black), diabetes and dialysis vintage (time since initiation of dialysis), the latter was modelled as two continuous variables for values above and below 10 years because the two ranges had shown very different patterns of risk in prior

modelling (unpublished data). To account for co-morbidity, eight individual disease severity (IDS) scores were modelled. These eight scores were subcomponents of the Index of Coexisting Disease (ICED) scores and were found to be more predictive of mortality at baseline than the ICED itself. The individual IDS scores included: arrhythmias and conduction problems, the maximum of ischaemic and other heart disease scores where ischaemic disease was modelled as present/absent, the maximum of the cerebral and peripheral vascular disease scores, congestive heart failure, respiratory disease, non-vascular nervous system disease, gastrointestinal disease and malignancy. Each score, if unmodified, had four categories ranging from no presentation to severe disease.

Statistical analysis

Continuous variables were described as means and standard deviations (SD), while categorical variables were presented as frequencies and percentages. Trends in the appetite assessment frequencies were compared among subgroups using Cochran–Mantel–Haenszel χ^2 tests. Cross-sectional differences among nutritional and other markers by appetite assessment category were assessed using ANOVA and additional pair-wise comparisons were conducted using Tukey's method. Differences among cross-sectional cohorts were tested using Student's *t*-test, χ^2 and Cochran–Mantel–Haenszel χ^2 tests, while differences between the IDS scores at baseline and 1 year were evaluated using generalized estimating equations [15].

We used proportional hazards (Cox) regression to examine the associations of level of appetite with survival [16,17]. Results were reported as relative risks (RR) with 95% confidence intervals (95% CI). Two general models were explored: one examined risks associated with baseline appetite assessment; the other explored how changes in appetite from the prior year might inform the relative risks for the cross-sectional scores. For the latter we used cross-sectional values from 1 year of follow-up controlling for their changes from baseline. Both model types controlled for the HEMO treatment assignments and case-mix variables listed previously. Additional models were adjusted for the eight IDS co-morbidity scores listed above. The RRs for appetite variables in each model described were tested for short- *vs* long-term effects using a cut-off of 1 year past the data collection times for the cross-sectional measures (baseline models: short-term effect, <1 year of follow-up, long-term effect, ≥1 year of follow-up; year-1-with-change model: short-term effect, <2 years of follow-up, long-term effect, ≥2 years of follow-up). In each analysis, subjects were censored for transplantation (baseline, $n = 194$; follow-up 1 year, $n = 116$) and transfer to non-participating facilities or change of dialysis modality (baseline, $n = 194$; follow-up 1 year, $n = 122$).

We also examined whether appetite affected the rate of non-vascular access related hospitalizations (number per year) using over-dispersed Poisson regression models [18]. We used the same general baseline and year-1-with-change models, again testing for additional effects of co-morbidity and for short- as opposed to long-term associations. Mean levels of changing appetite over time were assessed using informative censoring pattern-mixture models [12]. Two-tailed *P*-values < 0.05 were considered significant. Given the exploratory nature of the analysis, we did not adjust for multiple comparisons. Statistical analyses were conducted using SAS 8.0 (Cary, NC).

Results

Subject characteristics

Table 1 presents the demographic characteristics, randomized treatment assignment and nutrition indicators by self-reported appetite in the HEMO Study cohort at baseline. 215 subjects died and 176 were lost to follow-up [i.e. transferred ($n = 72$); transplanted ($n = 78$); administrative censoring ($n = 26$)] within the first year. Of the 1455 subjects remaining in the study 1 year after randomization, 100 did not complete the ADAT and were thus excluded from further analyses. Subjects who had completed the ADAT after 1 year of follow-up experienced a 38.5% mortality rate *vs* 55% in those who did not complete the assessment ($P = 0.0012$). No other significant differences were found between the two groups for the modelled factors as outlined in the section on case-mix and co-morbidity indicators. Compared with the entire baseline cohort, the 1355 subjects with ADAT completed at 1 year were older by an average of 2.4 years (95% CI 0.9–3.8) and showed improved appetite at 1 year (by 0.16 of one appetite category, 95% CI 0.03–0.28). A one category worsening in the appetite score (e.g. good to fair) was associated with decreases of 0.017 g/kg/day in adjusted protein intake (95% CI −0.038–0.039) and 0.55 kcal/kg/day in adjusted energy intake (95% CI −0.97–0.13). The 1 year cohort had less severe co-morbid medical conditions as measured by all the individual IDS scores, except malignancy (data not shown).

Clinical correlates of self-reported appetite at baseline

Over one-half of the subjects reported a very good and good appetite (57%) and few reported a very poor appetite (<2%) (Table 1). Consequently, the very poor and poor categories were combined in subsequent analyses (i.e. poor/very poor). Decreased appetite ratings during the preceding week were evident primarily among patients who reported poor or very poor appetites. A smaller percentage of men and subjects with diabetes reported very good appetite, as the proportion of each reporting their appetite as good was similar to those reporting poor/very poor appetites. The distribution of appetite ratings did not differ by randomized treatment assignment, race, age and dialysis vintage.

Table 1 also shows the mean values of the baseline nutrition indicators for the various appetite ratings. With poorer appetite ratings, we observed lower values for dietary energy and protein intakes, serum albumin, creatinine, post-dialysis body weight, and upper arm and calf circumferences. Table 2 shows the quality of life scores and the co-morbidity markers by appetite ratings. Lower values for both PCS and MCS scores

Table 1. Demographic characteristics, treatment assignment and nutrition indicators by self-reported appetite in the HEMO Study cohort at baseline[a]

Variable	Overall ($N=1846$)	Subjective assessment of appetite rating at baseline ($N=1846$)				
		Very good ($n=541$)	Good ($n=702$)	Fair ($n=440$)	Poor/very poor ($n=163$)	P-value[b]
HEMO cohort (%)	–	29.3	38.0	23.8	8.8	–
Appetite status						
changed in the past week (n missing = 7)	18.4	8.5	13.5	31.6	36.2	**<0.0001**
Increased (%)	6.9	6.3	5.8	8.9	8.0	
Decreased (%)	9.9	1.5	6.4	19.6	26.4	
Sex (% male)	43.8	49.2	56.7	62.3	61.4	**<0.0001**
Race (% black)	62.6	65.3	62.5	60.2	60.7	0.11
Diabetes (%)	44.6	38.1	45.9	50.0	46.0	**0.0014**
Dialysis vintage (years)	3.7 ± 4.4	3.81 ± 4.35	3.63 ± 4.22	3.84 ± 4.61	3.84 ± 4.30	0.82
Age (years)	57.6 ± 14.0	56.9 ± 14.0	58.0 ± 14.2	57.7 ± 13.8	58.2 ± 14.2	0.51
Treatment assignments						
Dialysis dose (% high)	50.2	47.9	49.7	52.7	49.1	0.30
Membrane flux (% high)	50.1	47.7	50.6	51.4	50.3	0.32
Nutrition status indicators						
Dietary protein intake (g/kg/day) (n missing = 2)	0.93 ± 0.35	0.95 ± 0.35[d]	0.95 ± 0.33[e]	0.92 ± 0.35[f]	0.83 ± 0.35[d,e,f]	**0.0007**
Dietary energy intake (kcal/kg/day) (n missing = 2)	22.7 ± 8.2	23.4 ± 8.44[d]	22.8 ± 7.93	22.2 ± 8.25	21.3 ± 8.40[d]	**0.020**
enPCR (g/kg/day)	1.03 ± 0.24	1.07 ± 0.23[d]	1.04 ± 0.23[e]	1.01 ± 0.23[d,f]	0.93 ± 0.25[d,e,f]	**<0.0001**
Serum albumin (g/l)[c]	36.2 ± 3.6	36.9 ± 3.3[d]	36.4 ± 3.6[e]	35.7 ± 3.8[d,e]	34.9 ± 3.7[d,e]	**<0.0001**
Serum creatinine (μmol/l) (n missing = 1)	910.5 ± 256.4	972.4 ± 259.9[d]	892.8 ± 251.9[d]	869.9 ± 249.3[d]	848.6 ± 242.2[d]	**<0.0001**
Serum total cholesterol (mmol/l) (n missing = 174)	4.50 ± 1.06	4.47 ± 1.05	4.55 ± 1.06	4.42 ± 1.07	4.50 ± 1.08	0.40
Body mass index (kg/m^2)	25.5 ± 5.28	25.7 ± 5.28	25.5 ± 5.38	25.3 ± 5.35	24.6 ± 4.54	0.11
Post dialysis body weight (kg)	69.2 ± 14.7	71.0 ± 14.3[d]	69.0 ± 15.3	67.5 ± 14.8[d]	66.8 ± 12.9[d]	**0.0003**
Upper arm circumference (cm) (n missing = 5)	30.1 ± 5.1	0.8 ± 4.79[d]	30.1 ± 5.23	29.8 ± 5.24[d]	28.9 ± 4.81[d]	**0.0002**
Calf circumference (cm) (n missing = 34)	33.3 ± 4.0	33.8 ± 3.82[d]	33.4 ± 4.28	32.9 ± 3.82[d]	32.7 ± 3.47[d]	**0.0005**

[a]Values reported are mean ± SD for continuous variables and percentages within appetite categories for all categorical variables; $P \leq 0.05$ was considered statistically significant.
[b]Frequency data were compared using Cochran–Mantel–Haenszel χ^2 tests; differences among means for the continuous variables were tested for using ANOVA; $P \leq 0.05$ was considered statistically significant.
[c]As measured by nephelometry.
[d,e,f]Means within a row with the same superscript symbols are significantly different, $P < 0.05$ (pair-wise comparisons by Tukey's simultaneous tests).

were observed with poorer appetite ratings. Pair-wise comparisons showed significant differences for most of the nutrition markers (Table 1) and QOL scores (Table 2). Table 2 also shows that self-reported appetite was associated with co-morbidity.

Change in self-reported appetite and effect of HEMO interventions (Dose and Flux)

The data were previously analysed based on the subjects' randomized treatment assignments [12]. Self-reported appetite rating increased from baseline to 3 years of follow-up by an average of 0.18 (95% CI 0.12–0.24). As reported previously, this change in appetite did not differ significantly in either the dialysis dose or membrane flux treatment groups (0.0003 ± 0.042, $P = 0.99$; -0.058 ± 0.042, $P = 0.17$, respectively).

Association of self-reported appetite with mortality

The percentage of subjects who died by appetite rating at baseline are shown in Table 3. A large number of deaths ($n = 792$) occurred over follow-up. Table 4 shows the results of two time-to-event models for self-reported appetite assessment measured at baseline; one of these models adjusted for co-morbidity whereas the other did not (models 2 and 1, respectively). In contrast to subjects who rated their appetite as very good, model 1 showed that subjects who reported a poor/very poor appetite at baseline experienced a 52% increased risk of mortality (95% CI = 16–98%) without adjusting for co-morbidity, but this result became non-significant after adjusting for co-morbidity (model 2). We also examined whether changes from previous appetite states might prove to be independently predictive and/or whether controlling for their effects might independently predict patient death after controlling for current appetite. To this end, we ran the year-1-with-change model adjusting for the same two sets of controls (model 3 – adjustment for case-mix and treatment only; model 4 – those plus an additional adjustment for co-morbidity at 1 year). The change in appetite assessment from baseline to 1 year was non-significant in both models 3 and 4. In model 3, the risk of mortality was increased in subjects with fair and poor/very poor appetites by 43% (95% CI 8–90%) and 69% (95% CI 17–144%),

Table 2. Quality of life and co-morbidity markers by self-reported appetite in the HEMO Study cohort at baseline[a]

Variable	Overall ($N=1846$)	Subjective assessment of appetite rating at baseline ($N=1846$)				
		Very good ($n=541$)	Good ($n=702$)	Fair ($n=440$)	Poor/very poor ($n=163$)	P-value[b]
Clinical indicators (mean ± SD)						
SF-36 physical health score (n missing = 128)	35.7 ± 10.1	37.9 ± 10.0[c]	35.9 ± 10.0[b,c,d]	34.6 ± 10.3[c,d]	31.2 ± 9.1[c,d,e]	**<0.0001**
SF-36 mental health score (n missing = 128)	51.6 ± 10.9	51.6 ± 10.8[c]	50.6 ± 10.4[d]	47.5 ± 11.3[c,d]	47.2 ± 11.2[c]	**<0.0001**
Co-morbidity indices (%) (n missing = 40)						
Congestive heart failure						
None	52.6	64.2	65.7	62.6	58.6	**0.0050**
Mild/moderate	46.8	34.3	33.3	35.6	39.0	
Severe	0.6	1.5	1.0	1.7	2.3	
Arrhythmias and conduction problems						
None	59.6	75.4	72.0	67.1	67.6	**<0.0001**
Mild/moderate	39.5	22.8	25.5	29.4	29.3	
Severe	0.95	1.7	2.5	3.5	3.1	
Ischaemic and other heart disease						
None	19.6	30.5	29.3	28.1	22.7	**0.013**
Mild/moderate	17.1	68.1	69.2	70.3	76.3	
Severe	2.4	1.4	1.5	1.6	1.1	
Cerebral and peripheral vascular disease						
None	58.8	68.7	68.1	64.3	60.1	**0.0034**
Mild/moderate	33.4	26.3	26.6	30.7	34.2	
Severe	7.8	5.0	5.3	5.0	5.8	
Respiratory disease						
None	80.5	88.0	85.0	85.3	84.2	**0.043**
Mild/moderate	19.3	11.7	14.4	14.2	15.5	
Severe	0.2	0.3	0.6	0.4	0.4	
Non-vascular nervous system disease						
None	53.3	70.1	67.6	62.3	52.9	**<0.0001**
Mild/moderate	46.6	29.3	32.0	37.5	47.1	
Severe	0.1	0.7	0.3	0.2	0	
Gastrointestinal and hepatobiliary disease						
None	45.2	62.9	57.0	51.0	46.4	**<0.0001**
Mild/moderate	50.5	33.8	39.0	43.9	49.1	
Severe	5.4	3.3	3.9	5.1	4.5	
Malignancy						
None or >5 years since last treatment	93.6	95.1	95.6	95.4	95.9	0.87
Diagnosis <5 years	6.4	4.9	4.4	4.6	4.1	

[a]Values reported are mean ± SD for continuous variables and percentages within appetite categories for all categorical variables; $P \leq 0.05$ was considered statistically significant.
[b]Frequency data were compared using Cochran–Mantel–Haenszel χ^2 tests; differences among means for the continuous variables were tested using ANOVA; $P \leq 0.05$ was considered statistically significant.
[c,d,e]Means within a row with the same superscript symbols are significantly different, $P < 0.05$ (pair-wise comparisons by Tukey's simultaneous tests).

respectively; these risks became non-significant after adjusting for co-morbidity (model 4).

Time trends in relative risk of mortality

We assumed that the risks associated with differences in appetite might be relatively short-lived since appetite is transitory. At baseline, 18% of the subjects reported changes in appetite over the past week (Table 1). To confirm our hypothesis, we tested for short-term (<1 year of follow-up) *vs* long-term (≥1 year of follow-up) effects. Figure 1 shows the resulting mortality associations. Among the baseline models, which did not adjust for disease states, only long-term risks for the poor/very poor appetite category were significant in the absence of co-morbidity (53% increased risk compared with very good appetite patients at baseline, 95% CI 11–111%). For the year-1-with-change models, which omitted the effects of co-morbidity, patients with poor/very poor appetites experienced the highest risks in both the short- and the long-term. Patients with good and fair appetites also exhibited lesser risks and patients with a very good appetite had the lowest (Figure 1). However, these associations became non-significant after controlling for co-morbidity. Only long-term effects for the changes in appetite from baseline remained independently predictive of death (19% increased risk per category of worsening change, 95% CI 2–38%).

Morbidity (non-access hospitalizations)

The mean annual rate and duration of non-access related hospitalizations per year by appetite rating at baseline are shown in Table 3. Table 5 shows the relative risks for each additional non-access related hospitalization per year in the four models used previously in mortality analyses. In model 2, subjects

Table 3. Death and hospitalization rate by self-reported appetite in the HEMO Study cohort at baseline[a]

Variable	Overall ($N=1846$)	Subjective assessment of appetite rating at baseline ($N=1846$)				
		Very good ($n=541$)	Good ($n=702$)	Fair ($n=440$)	Poor/very poor ($n=163$)	*P*-value
Outcomes						
Died (%)[b]	42.8	39.2	44.6	43.0	46.6	0.19[d]
Hospitalization frequency (admissions/year)[c]	1.65 ± 2.56 (0.2, 1.0, 2.1)	1.52 ± 2.67 (0.2, 0.9, 1.9)	1.53 ± 2.01 (0, 0.9, 2.0)	1.99 ± 3.07 (0.2, 1.3, 2.5)	2.29 ± 3.26 (0.4, 1.5, 2.7)	[e]
Duration of hospitalizations (days/year)[c]	11.8 ± 24.5 (0.4, 4.5, 13.5)	10.8 ± 24.6 (0.2, 4.0, 11.8)	10.3 ± 18.9 (0, 3.8, 12.1)	16.2 ± 47.9 (0.5, 6.0, 17.0)	21.4 ± 46.6 (1.7, 6.6, 17.7)	**<0.0001**[f]

[a]Values reported are mean ± SD for continuous variables and percentages within appetite categories for all categorical variables.
[b]Deaths excluding patients who transferred away from participating HEMO facilities.
[c]Values in parentheses represent the 25th, 50th, and 75th percentiles.
[d]Differences in number of deaths by appetite category using a Cochrane–Mantel–Haenszel χ^2 test.
[e]Differences in hospital frequency by appetite category using over-dispersed Poisson regression model: good *vs* very good, $P=0.19$; fair *vs* very good, $P<0.0001$; poor/very poor *vs* very good, $P<0.0001$.
[f]Differences in hospital duration by appetite category using ANOVA (*P* for omnibus test given). Tukey pair-wise comparisons showed differences between these groups: poor/very poor and good; poor/very poor and very good; fair and good; fair and very good.

Table 4. Time to mortality models: effects of appetite assessment[a]

Self-reported appetite assessment Comparisons/effects	Baseline appetite assessment models				Year-1-with-change appetite assessment models			
	MODEL 1 case-mix and treatment group controls only		MODEL 2 additional controls for co-morbidity[b]		MODEL 3 case-mix and treatment group controls only		MODEL 4 additional controls for co-morbidity[b]	
	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value
Good *vs* very good appetite	1.15 (0.96, 1.38)	0.13	1.11 (0.93, 1.33)	0.26	1.10 (0.86, 1.41)	0.43	1.17 (0.87, 1.44)	0.39
Fair *vs* very good appetite	1.20 (0.98, 1.47)	0.085	1.08 (0.88, 1.33)	0.46	1.43 (1.08, 1.90)	**0.013**	1.20 (0.90, 1.60)	0.22
Poor/very poor *vs* very good appetite	1.52 (1.16, 1.98)	**0.0023**	1.23 (0.94, 1.62)	0.13	1.69 (1.17, 2.44)	**0.0049**	1.34 (0.92, 1.96)	0.13
Worsening appetite from baseline to 1 year (per category)	–	–	–	–	0.92 (0.83, 1.02)	0.13	0.99 (0.89, 1.10)	0.81

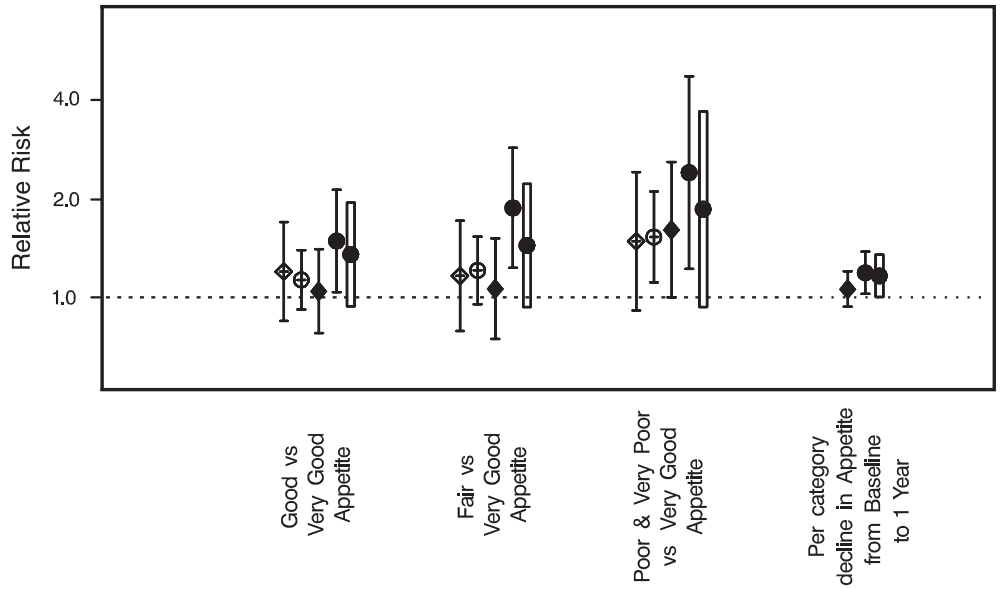
[a]All results adjusted for the effects of dose and flux treatment assignment, age, gender, black race, diabetic status and dialysis duration.
[b]Comorbidity indicators adjusted for in the analysis included arrhythmias and conduction problems, the maximum of ischaemic and other heart disease scores where ischaemic disease was modelled as present/absent, the maximum of the cerebral and peripheral vascular disease scores, congestive heart failure, respiratory disease, non-vascular nervous system disease, gastrointestinal disease, and malignancy.

who reported having fair and poor/very poor baseline appetites showed 20 and 35% increased risks, respectively, compared with the very good appetite category, even after adjusting for co-morbidity (95% CIs 15–37% and 13–61%, respectively). These relative risks remained significant although they were attenuated after adjustment for co-morbidity (model 1). The same comparisons proved significant in the year-1-with-change model after adjusting for co-morbidity (model 4). Risks for worsening appetite from baseline to 1 year (model 3) increased by 7% (95% CI 0–14%). However, the increased risk was no longer statistically significant after factoring in co-morbidity (model 4).

Time trends in relative risk of hospitalization

Short-term (<1 year of follow-up) and long-term (≥1 year of follow-up) morbidity risks were also calculated for the rates of an additional non-access related hospitalization among patients with good, fair, and poor/very poor appetites compared with those with a very good appetite. Figure 2 presents the resulting risks in the models with adjustment for co-morbidity. In the baseline model, effects were stronger among the fair and poor/very poor appetite patients who had increased risks (28%, 95% CI 7–54% and 49%, 95% CI 17–89%, respectively). Of the corresponding comparisons among the year-1-with-change models, only the effects of the fair *vs* very good appetite for the model adjusting for co-morbidity were significant (63% increased risk, 95% CI 9–143%). The protective effect over the entire follow-up period for worsening appetite from the prior year's value did not translate into significant effects over the short- or long-term.

Appetite may be influenced by the elaboration of cytokines and the acute phase response. We conducted companion analyses in a subset of 387 baseline and



Results adjusted for effects of age, gender, black race, presence of diabetes, dialysis vintage and HEMO flux and dose treatment assignments.
*IDS comorbidity adjustment factors included arrhythmias and conduction problems, congestive heart failure, respiratory disease, non-vascular nervous system disease, gastrointestinal disease, malignancy, the maximum of ischaemic and other heart disease scores where ischaemic disease was modelled as present vs absent and the maximum of the cerebral and peripheral vascular disease scores.

Fig. 1. Relative risks for mortality (and 95% CI) for comparing self-reported appetite categories by model and follow-up period (without adjusting for co-morbidity, except in one case). Relative risks shown for the baseline model with <1 year of follow-up (diamond) and ≥1 year of follow-up (circle); for the year-1-with-change model, 1–2 years of follow-up (solid diamond) and ≥2 years of follow-up (solid circle). Also shown is ≥2 years of follow-up adjusting for 1 year co-morbidity (concentric circles).

Table 5. Poisson regression models for rate of non-access related hospitalizations: effects of appetite assessment[a]

Self-reported appetite assessment comparisons/effects	Baseline appetite assessment models				Year-1-with-change appetite assessment models			
	MODEL 1 case-mix and treatment group controls only		MODEL 2 additional controls for co-morbidity[b]		MODEL 3 case-mix and treatment group controls only		MODEL 4 additional controls for co-morbidity[b]	
	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value
Good *vs* very good appetite	1.04 (0.92, 1.18)	0.53	1.01 (0.90, 1.14)	0.81	1.10 (0.94, 1.29)	0.25	1.10 (0.94, 1.29)	0.22
Fair *vs* very good appetite	1.28 (1.12, 1.43)	**0.0003**	1.20 (1.05, 1.37)	**0.0074**	1.37 (1.14, 1.66)	**0.0009**	1.29 (1.08, 1.55)	**0.0056**
Poor/very poor *vs* very good appetite	1.54 (1.29, 1.85)	**<0.0001**	1.35 (1.13, 1.61)	**0.0008**	1.83 (1.40, 2.38)	**<0.0001**	1.30 (1.02, 1.67)	**0.0373**
Worsening appetite from baseline to 1 year (per category)	–	–	–	–	1.07 (1.00, 1.14)	**0.049**	0.95 (0.89, 1.01)	0.124

[a]All results adjusted for the effects of dose and flux treatment assignment, age, gender, black race, diabetic status and dialysis duration.
[b]Comorbidity indicators adjusted for in the analysis included arrhythmias and conduction problems, the maximum of ischaemic and other heart disease scores where ischaemic disease was modelled as present/absent, the maximum of the cerebral and peripheral vascular disease scores, congestive heart failure, respiratory disease, non-vascular nervous system disease, gastrointestinal disease and malignancy.

487 1 year subjects in whom C-reactive protein (CRP) was obtained. Risks associated with poorer appetite were not materially changed by adjustment for CRP (data not shown).

Discussion

The substantial prevalence of PEM and its negative effects on the health of maintenance haemodialysis patients stimulated our interest in studying the effects of anorexia on survival and hospitalization in HEMO Study participants. We explored whether a relatively crude self-assessment of appetite might prove to be an independent risk factor for death and hospitalization. If true, this might have significant clinical implications for the treatment and prevention of PEM in the maintenance haemodialysis population.

Poor/very poor appetite was associated with lower dietary protein and energy intakes reported on diet records, and also lower enPCR measured by urea kinetics, validating the appetite question as a proxy

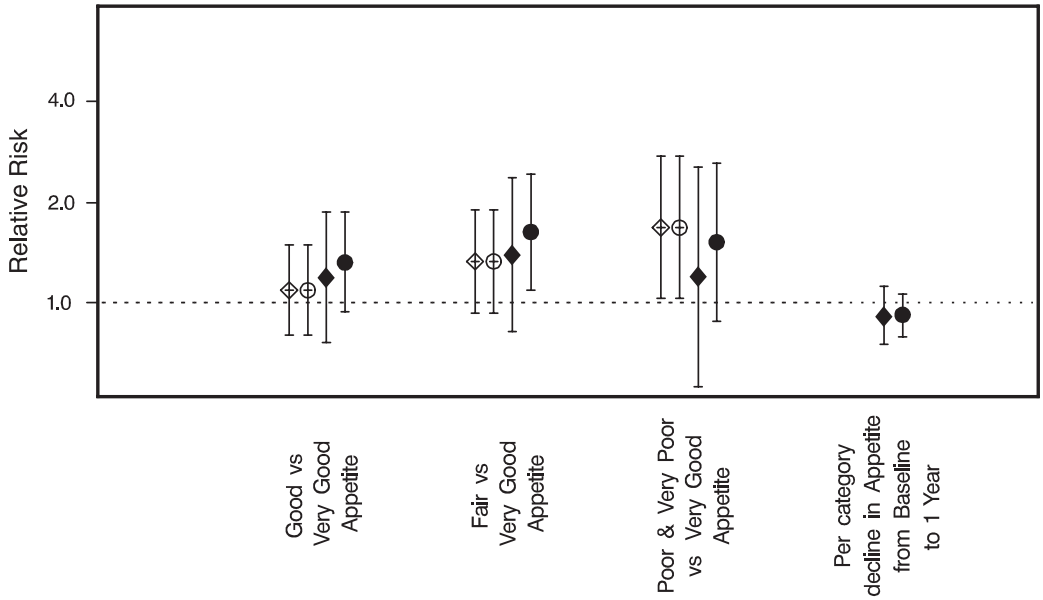


Fig. 2. Relative risks for additional non-access related hospitalizations per year (and 95% CI) for comparing self-reported appetite categories by model and follow-up period (adjusting for co-morbidity). Relative risks shown for the baseline model with <1 year of follow-up (diamond) and ≥1 year of follow-up (circle); for the year-1-with-change model, 1–2 years of follow-up (solid diamond) and >2 years of follow-up (solid circle).

for dietary protein and energy intakes. Dietary protein and energy intakes are often reduced in maintenance haemodialysis patients [19,20]. In this study, we found that dietary protein intake was below levels recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Nutrition Guidelines (1.2 g/kg/day), even for persons who reported very good appetite. Energy intake fell even further below K/DOQI targets (>30% below K/DOQI recommendations of 30–35 kcal/kg/day), particularly among those with poorer appetite. Therefore, more detailed nutritional assessments are needed to help detect PEM.

Diminished appetite at baseline was also associated with decreased concentrations of biochemical markers of nutritional status such as serum albumin and serum creatinine, and with anthropometric markers such as post-dialysis body weight and upper arm and calf circumferences. Declines in appetite were also associated with lower mental scores for quality of life (which captures mental health, role functioning and pain) and physical summary scores, as well as, seven of the eight co-morbid conditions common to maintenance haemodialysis patients (i.e. congestive heart failure, arrhythmias and conduction problems, ischaemic and other heart disease, cerebral and peripheral vascular disease, respiratory disease, non-vascular nervous system disease, gastrointestinal and hepatobiliary disease, and malignancy). Our results confirm and extend previously published work [3,9]. The associations of appetite ratings with anthropometric and co-morbidity markers, however, are new and would seem to suggest that anorexia gave rise to PEM.

To our knowledge, very few studies have investigated independent associations between appetite and clinical outcomes. The results of the study by Kalantar-Zadeh *et al.* found significant and much larger effects (greater than 2-fold) after testing for linear mortality effects across four appetite categories (i.e. very good, good, fair, and poor), and nearly a 5-fold effect after dichotomizing the categories into two groups [i.e. normal (very good and good) and anorexic (fair and poor)] [3]. However, those results were derived from survival analyses using 25 deaths, whereas our analyses incorporated 792 deaths. Part of this difference could also be attributed to the much healthier cohort studied by Kalantar-Zadeh *et al.* as evidenced by their higher quality of life and serum albumin values [3]. The previous study also assessed the severity of co-morbidity using the Charlson co-morbidity index, whereas our study availed itself of the eight individual IDS scores which had been pre-screened as independent baseline mortality predictors in the HEMO Study cohort (unpublished data).

The relation between poorer appetite and death was significant in unadjusted analyses, but became non-significant after adjusting for co-morbidity. This is not surprising given the different associations between appetite and various diseases that were causes of death. The association between self-reported appetite and hospitalization rate, however, was significant, even

with adjustment for co-morbidity, particularly among models that did not adjust for prior changes in appetite. With co-morbidity adjustment, risks for patients who reported fair and poor/very poor appetites were elevated by 20–42%, compared with those who rated their appetite as very good. Whether appetite is directly or indirectly related to mortality and hospitalization, identification of patients with poor/very poor appetites may help physicians and dietitians prioritize these individuals for interventions and follow-up.

The strengths of our study include the examination of the longitudinal changes in appetite, the large sample size ($N = 1846$), the length of follow-up (mean 2.8 years), and the accumulated number of deaths and non-vascular access related hospitalizations, which aided statistical power. However, four limitations to these analyses must be mentioned. The true effects of the impact of diminished appetite on the variables studied may be underestimated because of survival bias; patients with very poor appetites may have died early in follow-up and, therefore, not have been included in the 1 year longitudinal analyses. Also, patients with serum albumin concentration <26 g/l (as measured by nephelometry) were excluded from enrollment. This likely biased the appetite ratings upwards because patients with higher risk and poorer nutritional status (i.e., those with very poor appetite ratings) may have been underrepresented. Moreover, large patients who could not achieve the high dose of haemodialysis were excluded from the study; only 9 and 3.3% of subjects weighed more than 90 kg and 100 kg, respectively. Therefore, the results cannot be generalized to obese haemodialysis patients. Finally, the HEMO Study subjects were closely monitored by the study dietitians. Oral nutrition supplements were provided free when deemed necessary by the study dietitian, and all subjects received a daily renal multivitamin. This probably resulted in better nutrition than commonly occurs in clinical practice, and this could have attenuated the effects of worsening appetite.

In summary, among a large sample of subjects receiving maintenance haemodialysis, appetite self-report provided a valid surrogate for dietary protein and energy intake. Appetite was also associated with death and hospitalization rate after adjustment for demographic and clinical factors. The latter association remained significant even in the presence of co-morbidity. This study demonstrated that appetite assessment can be useful prognostically and, therefore, should be performed periodically as part of the routine nutritional assessment in maintenance dialysis patients. Patients who report poor and very poor appetite should be monitored closely and their dietary energy and protein intakes assessed. Whether more intensive nutritional counselling, oral supplementation, or nutrition support by enteral or parenteral routes might decrease the unacceptably high rates of mortality and morbidity associated with haemodialysis awaits additional study.

Acknowledgements. The HEMO Study was supported by grants from the National Institute of Diabetes, and Digestive and Kidney Disease of the National Institutes of Health. Some study dialyzers were provided by Baxter Healthcare Corporation (McGaw Park, IL) and Fresenius Medical Care, North America (Lexington, MA). Nutritional supplements were provided by Ross Products Division, Abbott Laboratories (Columbus, OH) and vitamins were provided by R&D Labs, Inc. (Marina del Ray, CA).

Conflict of interest statement. D.B.C. is employed by Ross Products Division, Abbott Laboratories, the company that provided the nutritional supplements to the subjects. J.W.K. is employed by the National Institute of Diabetes, Digestive and Kidney Disease of the National Institutes of Health, the sponsoring agency. The remaining authors declare no conflict of interest.

References

1. Aparicio M, Cano N, Chauveau P *et al*. Nutritional status of hemodialysis patients: a French national cooperative study. *Nephrol Dial Transplant* 1999; 14: 1679–1686
2. Herselman M, Moosa MR, Kotze TJ *et al*. Protein-energy malnutrition as a risk factor for increased morbidity in long-term hemodialysis patients. *J Ren Nutr* 2000; 10: 7–15
3. Kalantar-Zadeh K, Block G, McAllister CJ *et al*. Appetite and inflammation, nutrition, anemia and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 2004; 80: 299–307
4. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. *Am J Kidney Dis* 2001; 38: 1343–1350
5. Kalantar-Zadeh K, Kopple JD, Block G *et al*. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001; 38: 1251–1263
6. Bergstrom J. Regulation of appetite in chronic renal failure. *Miner Electrolyte Metab* 1999; 25: 291–297
7. Ginsberg N, Fishbane D, Lynn R. The effect of improved dialytic efficiencies on measures of appetite in peritoneal dialysis patients. *J Renal Nutr* 1996; 6: 217–221
8. Ohri-Vachaspati P, Sehgal AR. Correlates of poor appetite among hemodialysis patients. *J Renal Nutr* 1999; 9: 182–185
9. Burrowes JD, Larive B, Cockram DB *et al*. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross-sectional results from the HEMO Study. *J Renal Nutr* 2003; 13: 191–198
10. Eknoyan G, Beck GH, Cheung AK *et al*. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *New Engl J Med* 2002; 347: 2010–2019
11. Burrowes JD, Powers SN, Cockram DB *et al*. Use of an appetite and diet assessment tool in the pilot phase of a hemodialysis clinical trial: Mortality and morbidity in hemodialysis study. *J Renal Nutr* 1996; 6: 229–232
12. Rocco MV, Dwyer JT, Larive B *et al*. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: results of the HEMO Study. *Kidney Int* 2004; 65: 2321–2334
13. Chumlea WC, Guo SS, Steinbaugh ML. Prediction of stature from knee height for black and white adults and children with application to mobility-impaired or handicapped persons. *J Am Diet Assoc* 1994; 94: 1385–1391
14. Ware JE. *SF-36 Health Survey: Manual and Interpretation Guide*. The Health Institute, New England Medical Center, Boston, MA, 1993
15. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73: 13–22

16. Cox D. The analysis of exponentially distributed life-times with two types of failure. *J Royal Stat Soc* 1959; 59: 411–421
17. Cox D. Regression models and life-tables. *J Royal Stat Soc* 1972; 34: 187–220
18. McCullagh P, Nelder JA. *Monographs on Statistics and Applied Probability: Generalized Linear Models*. Chapman & Hall, Norwell, MA, 1989
19. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2000; 32: S1–S104
20. Lorenzo V, DeBonis E, Rufino M *et al*. Calorie rather than protein deficiency predominates in stable chronic hemodialysis patients. *Nephrol Dial Transplant* 1995; 10: 1885–1889

Received for publication: 16.02.04
Accepted in revised form: 12.8.05