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

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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 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
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, 2x2 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 β2 microglobulin clearance <10 ml/min vs high β2 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 35 l of estimated total body water; were unable to achieve an enPCR 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.

Measure 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 from 2-day diet diary-assisted recalls. 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 assessed.

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.

Case-mix variables and comorbidity 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 patients.
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 $\chi^2$ 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, $\chi^2$ and Cochran–Mantel–Haenszel $\chi^2$ 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 $0.017$/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
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%), respectively.
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
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
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 for 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.
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.

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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.

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