Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite[1–3]

Juan Jesús Carrero, Abdul Rashid Qureshi, Jonas Axelsson, Carla María Avesani, Mohammed E Suliman, Sawako Kato, Peter Bárány, Sunna Snaedal-Jonsdottir, Anders Alvestrand, Olof Heimbürger, Bengt Lindholm, and Peter Stenvinkel

ABSTRACT

Background: Anorexia is common in chronic kidney disease and worsens as the disease progresses. Sex hormones and inflammatory cytokines may be related to feeding behavior.

Objective: We hypothesized that appetite would be related to inflammation and outcome in hemodialysis patients but that sex may account for differences in the symptoms associated with poor appetite.

Design: A cross-sectional study was conducted in patients undergoing prevalent hemodialysis ($n = 223$; 127 M; $\bar{x} \pm$ SD age: 66 $\pm$ 14 y). Anthropometric markers of body composition, handgrip strength, and nutritional and inflammatory status were measured, and 3 groups according to their self-reported appetite were established. Overall mortality was assessed after 19 mo (range: 2–29 mo) of follow-up.

Results: Poor appetite was associated with a longer vintage time, increased inflammation (higher serum concentrations of interleukin 6 and C-reactive protein), and a worse nutritional status (lower serum concentrations of insulin-like growth factor I, albumin, urea, and creatinine). However, across worsening appetite scale, handgrip strength was incrementally lower in men but not in women (multivariate analysis of variance). In a multivariate logistic regression analysis (pseudo $r^2 = 0.19$), appetite loss was associated with sex [odds ratio (OR): 0.41; 95% CI: 0.24, 0.72], insulin-like growth factor I (3.58; 2.10, 6.32), and C-reactive protein > 10 mg/L (2.39; 1.34, 4.11). Finally, appetite loss was associated with worse clinical outcome even after adjustment for age, sex, inflammation, dialysis vintage, and comorbidity (likelihood ratio $= 44.3$; $P < 0.0001$).

Conclusions: These results show a close association among appetite, malnutrition, inflammation, and outcome in patients undergoing prevalent hemodialysis. Moreover, our data suggest that uremic men may be more susceptible than are women to inflammation-induced anorexia. *Am J Clin Nutr* 2007;85:695–701.

KEY WORDS Hemodialysis, inflammation, malnutrition, appetite, anorexia, sex, outcome

INTRODUCTION

Chronic kidney disease (CKD) is characterized by an exceptionally high mortality rate, primarily due to cardiovascular disease (CVD). Chronic inflammation is common among patients with renal disease and probably contributes to CVD (1). Moreover, the prevalence of protein energy wasting (PEW) among patients with CKD is high and is associated with a proinflammatory state (2, 3). Malnutrition, inflammation, and atherosclerosis often coexist among patients with CKD, and each of these risk factors independently predicts outcome in these patients (4, 5).

Patients with CKD frequently experience loss of appetite (anorexia), which increases in severity during the progression of the disease and which may lead to metabolic disturbances, PEW cachexia, and high rates of morbidity and mortality (6, 7). Multiple mechanisms may be involved in the pathophysiology of anorexia in CKD, and it is unclear how and to what extent a reduced appetite is a cause or a consequence of inflammation, PEW, or both. However, evidence is now convincing that inflammatory cytokines play an important role in the control of appetite, food intake, and energy homeostasis by interacting in several central nervous system pathways and that these cytokines also have both direct and indirect effects on specific brain areas (7–9). Indeed, Kalantar-Zadeh et al (10) found that inflammation was strongly associated with appetite and outcome in a well-characterized group of patients undergoing prevalent hemodialysis.

Sex is physiologically associated with feeding behavior (11) and inflammatory status (12), and men undergoing dialysis who have inflammation seem to have a shorter survival than do women with the same conditions (13). A sex-specific regulation of feeding is unclear; however, higher anorectic signals and earlier satiety were reported in men with chronic illnesses (14, 15),

[1] From the Divisions of Renal Medicine and the Baxter Novum Clinical Research Laboratory, Department of Clinical Science, Intervention and Technology, Karolinska Institute, Karolinska University Hospital at Huddinge, Stockholm, Sweden (JJC, ARQ, JA, MES, SK, PB, SS-J, AA, OH, BL, and PS); the Division of Nephrology, Department of Medicine, Federal University of São Paulo, Brazil (CMA); and the Division of Nephrology, La Paz University Hospital, Madrid, Spain (JJC).

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[3] Address reprint requests to P Stenvinkel, Division of Renal Medicine, K56, Karolinska University Hospital at Huddinge, 141 86 Stockholm, Sweden. E-mail: peter.stenvinkel@ki.se.

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perhaps contributing to a different response pattern to anorexigenic diseases (eg, heart failure and cancer) among men and women (16).

Recently, the Hemodialysis (17) and the Nutritional and Inflammatory Evaluation of Dialysis (10) studies, with the use of a simple, standardized questionnaire to determine a patient's self-reported appetite intensity, showed some consistent and some contradictory results about the appetite evaluation in patients undergoing hemodialysis. Hence, the current study strives to elucidate some of these inconsistencies and hypothesizes that sex might account for differences in the regulation of appetite and its relation to inflammation and PEW. To test these hypotheses, we performed a cohort study in a well-characterized group of patients undergoing prevalent hemodialysis to investigate the conditions associated with loss of appetite and the predictive value of self-reported appetite in relation to sex.

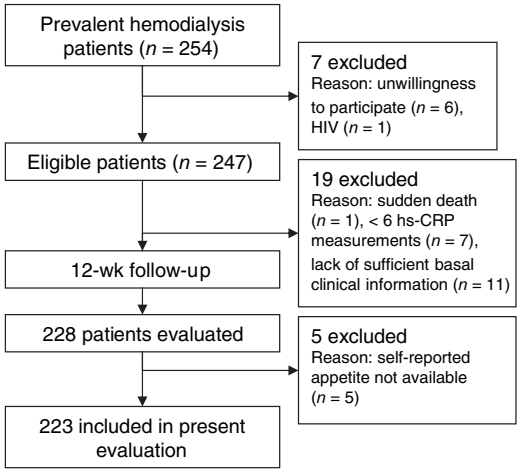

FIGURE 1. Flow of participants during the study. hs-CRP, high-sensitivity C-reactive protein.

SUBJECTS AND METHODS

Subjects

The current study was performed at the Karolinska University Hospital in Stockholm (including 4 satellite dialysis units), Danderyds Hospital, and Uppsala Academic Hospital. It was a post hoc analysis from a cross-sectional study with a follow-up that originally aimed at investigating the variability of inflammatory markers in patients undergoing prevalent hemodialysis ($n = 254$) over time. Recruitment of the patients occurred from October 2003 through March 2004. All patients who were currently receiving regular therapy at any of the units were invited to participate; 6 patients declined, and 1 patient with HIV infection was excluded. The 247 eligible patients were then followed for 12 wk, during which time the concentration of high-sensitivity C-reactive protein (hs-CRP) was measured weekly. Because the aim of the original study was to investigate the variability of inflammatory markers, patients were excluded from the study if available for fewer than 6 of these weekly hs-CRP measurements. Eleven patients were excluded because insufficient baseline clinical information was available, 7 were excluded because of insufficient hs-CRP measurements, and 1 patient died. The remaining 228 patients were further followed for assessment of overall and cardiovascular mortality in relation to biochemical markers. For the present study, 5 more patients were excluded because no self-report of appetite intensity was available, which left 223 patients for inclusion in the analysis. The current study is limited only to baseline values. A patient's flow chart is shown in **Figure 1**.

Survival was determined after a mean follow-up of 19 mo (range: 2-29 mo). Each patient's medical chart was thoroughly reviewed by a nephrologist (SS-J), who extracted data pertaining to underlying kidney disease, history of CVD, and other comorbid conditions. The Davies comorbidity index was used to assess the severity of comorbid conditions (18).

Written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Karolinska Institute at Huddinge University Hospital (Stockholm, Sweden).

Nutritional status and appetite assessment

Self-reported appetite is a part of the subjective global assessment (SGA) questionnaire (2, 19). The SGA questionnaire includes 6 different components: 3 subjective assessments that are performed by the patients and that concern the patient's history of weight loss, incidence of anorexia, and incidence of vomiting and 3 assessments that are performed by the evaluators and that are based on the subjective grading of muscle wasting, the presence of edema, and the loss of subcutaneous fat. On the basis of these assessments, each patient received a nutritional status score: *1*) normal nutritional status, *2*) mild malnutrition, *3*) moderate malnutrition, and *4*) severe malnutrition. For the purposes of the current study, malnutrition was defined as an SGA score >1. With respect to the self-reported appetite assessment, all patients were asked to grade their appetite according to the following scale: *1*) good, *2*) sometimes bad, *3*) often bad, and *4*) always bad.

Anthropometric evaluation

Body weight, body mass index (BMI; in kg/m^2), and anthropometric and dynamometric measurements were taken on a dialysis day. Height was obtained from the patient's chart. Fat mass and lean body mass were assessed according to Durnin et al (20), and body composition was assessed by using the 4 skinfold thicknesses (biceps, triceps, subscapular, and suprailiac), measured with a conventional skinfold caliper (Cambridge Scientific Instruments, Cambridge, MD). Fat BMI (FBMI) and lean BMI were calculated (21). Midarm circumference was measured with a plastic tape measurer and was normalized with measurements from healthy subjects; midarm muscle circumference was calculated by using the following formula: midarm circumference $-\ \pi\times$ triceps skinfold thickness (20). Handgrip strength was measured in both the dominant and nondominant hands by using a Harpenden Handgrip Dynamometer (Yamar, Jackson, MI). Each measurement was repeated 3 times for each arm, and the highest value for each arm was noted. For our analysis, we used the right arm handgrip strength, because fistulas were usually placed in the left arm.

Laboratory analysis

Blood samples were collected before the dialysis session. The plasma was separated within 30 min, and samples were kept frozen at −70 °C if not analyzed immediately. Concentrations of hs-CRP (nephelometry), serum urea, hemoglobin, hypochromic

red blood cells, serum creatinine, and serum albumin (bromcresol purple) were measured by routine methods at the Department of Laboratory Medicine, Karolinska University Hospital, Huddinge.

Plasma concentrations of insulin-like growth factor I (IGF-I) and interleukin 6 were measured in an Immulite Automatic Analyzer (Diagnostic Products Corporation, Los Angeles, CA). We used assays manufactured for this analyzer and followed the manufacturer's instructions.

Statistical analysis

Normally distributed variables were expressed as means ± SDs (unless otherwise noted), and nonnormally distributed variables were expressed as medians and ranges. Statistical significance was set at $P < 0.05$. All statistical analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC). A 2-factor multivariate analysis of variance with Wilks λ was used to measure the degree of correlation among the variables. The model included a test for the effect of order. The general linear model procedure with least-squares means was used to identify significant interactions among factors. When a significant interaction was found between factors (A × B), those factors were identified with simple main-effects tests. Differences among the appetite groups were analyzed with the Kruskal-Wallis analysis of variance, followed by the post hoc Dunn test for nonparametric comparisons. A chi-square test was used for categorical variables. A multinomial logistic regression model was used to assess the predictors for self-reported appetite; this model included all variables significantly associated with self-reported appetite in univariate analysis. Survival analyses used the Kaplan-Meier survival curve and the Cox proportional hazards model. The Cox proportional hazards model was used to examine survival differences after the analysis had been adjusted for potential confounding factors.

RESULTS

The study population consisted of 223 patients undergoing hemodialysis (127 men; 57%) with a median age of 66 y (range: 23–87 y). The patients had undergone hemodialysis for a median of 30 mo (range: 1-378 mo) and had an average BMI of 24.5 ± 5.2. Of these patients, 57 (25%) had diabetes, 43 (19%) had CVD, 84 (38%) had inflammation (hs-CRP > 10 mg/L), and 96 (43%) were malnourished (SGA score > 1).

Self-reported appetite score was analyzed. Of the 223 patients, 124 (56%) reported a good appetite, 65 (29%) described their appetite as sometimes bad, 20 (9%) described it as often bad, and 14 (6%) described it as always bad. Because of the small sample size for the groups with poor appetite, the score was rearranged into 3 main groupings for further comparisons; according to these new categories, 124 patients (56%) reported a good appetite, 65 (29%) reported sometimes bad appetite, and 34 (15%) reported a poor appetite (combining often-bad and always-bad appetites).

Clinical data, anthropometric measurements, biochemical markers, and self-reported ratings of appetite for all 223 patients are shown in **Table 1**, along with the multivariate analysis of variance interactions. The proportions of men became progressively and significantly lower as the appetite scale worsened (64% men in the category good appetite; 54% men in the category sometimes bad appetite; 35% men in the category poor appetite; $P = 0.0008$). No significant differences were observed in the Davies comorbidity scores between patients in the 3 appetite categories.

A poor appetite was associated with a worse nutritional status, because serum concentrations of serum albumin, creatinine, and urea and IGF-I were lower among appetite categories. Furthermore, a poor appetite was also associated with worse anthropometrics, measured as BMI and FBMI, and with a higher inflammatory status, measured as serum concentrations of hs-CRP and interleukin 6 (**Figure 2**). Across the worsening appetite scale, handgrip strength was incrementally lower in men ($P = 0.0002$; **Figure 3**) but not in women.

To determine which variables were significantly associated with appetite, we created a multinomial logistic regression model (pseudo $r^2 = 0.19$; $P < 0.0001$) in which IGF-I [>159 ng/mL compared with <159 ng/mL; odds ratio (OR): 3.58; 95% CI: 2.10, 6.32], presence of inflammation (hs-CRP <10 mg/L compared with >10 mg/L; OR: 2.39; 95% CI: 1.34, 4.11), and sex (women compared with men; OR: 0.41; 95% CI: 0.24, 0.72) were significant predictors of appetite (**Table 2**).

Kaplan-Meier curves illustrating the cumulative proportion of surviving patients in different appetite groups are presented in **Figure 4**. As expected, the survival rate was worse for patients reporting a poor appetite than for patients reporting a good appetite [Figure 4A; log rank (chi-square test): 6.85; $P < 0.05$]. Significant differences in survival among the 3 groups persisted after the analysis was adjusted for potential confounding factors [ie, age, sex, inflammation (CRP > 10 mg/L), dialysis vintage, and Davies comorbidity index] by using a Cox proportional hazards model [Figure 4B; likelihood ratio (chi-square test): 44.3; $P < 0.0001$]. Self-reported poor appetite was significantly associated with higher mortality [hazard ratio (HR): 2.72; 95% CI: 1.29, 5.72; $P = 0.008$). Although the patients reporting sometimes bad appetite also tended to be associated with higher mortality, this association was not significant (HR: 1.26; 95% CI: 0.63, 2.53).

DISCUSSION

This study shows a close relation among self-reported appetite, PEW, inflammation, and outcome for patients undergoing hemodialysis (10, 17). Moreover, this study suggests that sex may determine the severity of symptoms, such as handgrip strength, among patients who report a poor appetite. This observation supports the hypothesis that uremic men may be more susceptible than are women to inflammation-induced anorexia.

A reduced appetite is an early and common sign of uremia and becomes increasingly more prominent as the glomerular filtration rate declines (22–24). In this study, we confirm previous findings (10, 17) about the predictive value of self-reported appetite on the outcome of hemodialysis patients, both men and women. This predictive value is mainly due to the expected correlation with PEW but also to a strong association with inflammation. In contrast to the findings by Kalantar-Zadeh et al (10), but in agreement with the findings of Burrowes et al (17), our findings indicate that loss of appetite is accompanied by poorer anthropometric values. In addition, we found a strong inverse association between appetite and plasma concentrations of IGF-I; these concentrations were suggested to be a good nutritional marker relating to lean body mass for patients undergoing dialysis (25). Because IGF-I is part of the major anabolic

TABLE 1
Clinical characteristics, anthropometric measurements, and biochemical markers of nutritional and inflammatory status in 223 prevalent hemodialysis patients, divided according to sex and self-reported appetite[1]

	Self-reported appetite scale						
	Men (n = 127)			Women (n = 96)			
	Good (n = 80)	Sometimes bad (n = 35)	Poor (n = 12)	Good (n = 44)	Sometimes bad (n = 30)	Poor (n = 22)	MANOVA[2]
Clinical characteristics							
Age (y)	64 (29–86)[3]	62 (37–85)	65 (51–84)	70 (38–84)	63 (23–87)	71 (30–81)	NS[4]
Dialysis vintage (mo)	24 (1–253)	29 (2–225)	83 (15–378)	29 (1–287)	48 (11–269)	39 (1–242)	S, S × A
Diabetes mellitus (%)	26	32	25	21	27	23	NS[5]
CVD (%)	18	20	8	21	20	27	NS[6]
Davies comorbidity score							
Low	20	14	25	23	17	14	NS[7]
Medium	51	60	58	52	70	59	
High (%)	29	26	17	25	13	27	
Biochemical markers of nutritional and inflammatory status							
Hemoglobin (g/L)	123 ± 12[8]	116 ± 12	119 ± 12	114 ± 13	120 ± 12	113 ± 3	S × A
Hypochromic RBCs (%)	1.8 ± 2.7	4.1 ± 3.9	5.3 ± 5.9	2.9 ± 3.2	2.2 ± 1.5	2.8 ± 2.4	S, A, S × A
Serum albumin (*g/L*)	35.4 ± 3.6	34.2 ± 5.1	31.1 ± 4.6	34.7 ± 4.2	35.5 ± 4.0	31.4 ± 5.3	A
Creatinine (μmol/L)	885 ± 211	738 ± 208	732 ± 165	689 ± 157	762 ± 174	584 ± 138	S, A, S × A
Serum urea (mmol/L)	25.6 ± 5.9	22.2 ± 5.8	22.5 ± 3.8	23.9 ± 5.1	21.7 ± 5.8	18.7 ± 6.2	S, A
IGF-I (ng/mL)	191 (60–563)	137 (25–282)	90 (52–276)	177 (43–673)	145 (30–504)	109 (63–430)	A
hs-CRP (mg/L)	5.4 (0.4–151.0)	11.0 (0.6–98.0)	26.6 (3.6–123.0)	5.8 (0.2–67.0)	6.2 (0.3–83.0)	10.0 (0.9–101.0)	S, A
IL-6 (pg/mL)	7.1 (1.7–83)	9.1 (1.6–91)	15.8 (4.6–65)	6.9 (0.94–72.8)	9.3 (1.8–79.4)	10.1 (2.2–102)	A
Anthropometric measurements							
BMI (kg/m^2)	25.1 ± 4.1	22.7 ± 4.2	21.6 ± 3.8	25.9 ± 7.2	24.5 ± 5.3	23.7 ± 4.7	A
LBMI (kg/m^2)	17.5 ± 2.3	16.4 ± 2.2	16.4 ± 2.5	15.9 ± 3.3	15.2 ± 2.4	15.1 ± 2.1	S, A
FBMI (kg/m^2)	7.4 ± 2.3	6.1 ± 2.6	5.1 ± 1.7	9.9 ± 4.1	8.9 ± 3.0	8.6 ± 3.0	S, A
MAMC (cm)	26.0 ± 3.4	23.2 ± 3.3	23.6 ± 3.1	23.6 ± 3.8	22.6 ± 3.4	22.3 ± 2.6	S, A
Handgrip strength (kg)	32 ± 12	24 ± 9	23 ± 7	17 ± 7	17 ± 6	16 ± 4	S, A, S × A

[1] CVD, cardiovascular disease; LBMI, lean BMI; FBMI, fat BMI; MAMC, midarm muscle circumference; RBCs, red blood cells; IGF-I, insulin-like growth factor I; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.
[2] Two-factor multivariate ANOVA (MANOVA). Significant ($P < 0.05$) effects are given for sex (S), appetite (A), and the sex × appetite (S × A) interaction.
[3] Median; range in parentheses (all such values).
[4] No MANOVA interaction was found.
[5] No difference was found by chi-square test: 1.4; $P = 0.95$.
[6] No difference was found by chi-square test: 2.1; $P = 0.84$.
[7] No difference was found by chi-square test: 5.5; $P = 0.85$.
[8] Mean ± SD (all such values).

pathway that mediates growth hormone actions in skeletal muscle, it is not surprising that a state of PEW also relates to low plasma concentrations of IGF-I, as a reflection of a catabolic state.

A novel finding of this study is the sex differences in the relation between handgrip strength among patients with poor appetite. Indeed, handgrip strength was recently proposed not only as a marker of body lean muscle mass but also as a prognostic factor and a nutrition-monitoring tool in patients undergoing dialysis (26). Although sociological sex differences and different cultural backgrounds may be present and may explain why a larger proportion of women in the current study than in the study by Burrows et al (17) reported poor appetite, the finding that both men and women exhibit decreasing serum concentrations of albumin, creatinine, urea, and IGF-I across appetite categories indicates that both groups are indeed malnourished. This observation is corroborated by the finding that adjustment of the analysis for sex did not affect the predictive value of appetite on the survival of patients on hemodialysis. However, our results indicate that the loss of handgrip strength is more pronounced among men with poor appetite than among women and that the patient's sex is a contributing factor to the degree of appetite reported among these patients.

Several studies have found sex differences in the regulation of appetite (16). Feeding behavior corresponding to the ovarian hormone cycle (27, 28) and a decrease in food intake are associated with elevated estradiol concentrations (27, 29). These sex differences apparently include both hormonal effects, which depend on gonadal function and estrogen concentrations, and lifelong effects, which arise directly from genetic differences or from the effects of gonadal hormones early in life (16). The existence of sex-specific orexigenic and anorexigenic mechanisms in response to inflammation was recently suggested in rats (30) and may imply differences in the up-regulation of leptin and ghrelin, which

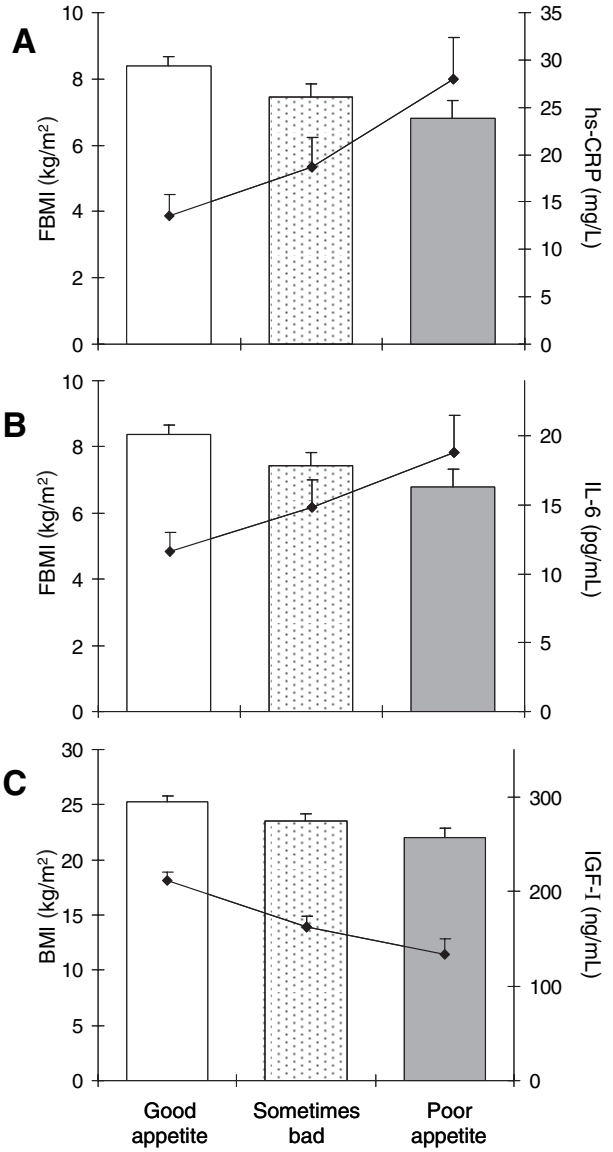

FIGURE 2. Mean (±SEM) concentrations of high-sensitivity C-reactive protein (◆; hs-CRP; A), interleukin 6 (◆; IL-6; B) in relation to fat body mass index (FBMI), and insulin-like growth factor I (◆; IGF-I; C) in relation to BMI among self-reported appetite categories in 223 patients undergoing prevalent hemodialysis. Differences across appetite categories were assessed by ANOVA or by Kruskal-Wallis test for the nonparametric variables: $P = 0.007$ for hs-CRP; $P = 0.04$ for FBMI; $P = 0.002$ for IL-6; $P < 0.0001$ for IGF-I; and $P = 0.005$ for BMI. This analysis comprised 124 patients reporting good appetite, 65 patients reporting sometimes bad appetite, and 34 patients reporting poor appetite.

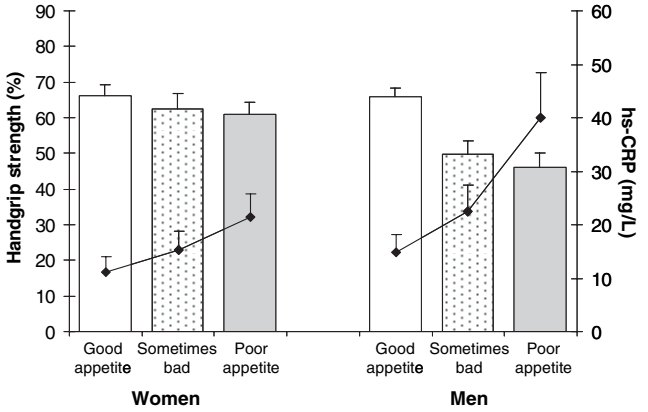

FIGURE 3. Mean (±SEM) concentrations of high-sensitivity C-reactive protein (◆; hs-CRP) in relation to handgrip strength among self-reported appetite categories in male and female patients undergoing prevalent hemodialysis. Multivariate ANOVA showed a significant appetite × sex interaction for handgrip strength values. Differences in handgrip strength across appetite categories were assessed by ANOVA: $P = 0.0006$ for men and $P = 0.6$ for women. The men reported good ($n = 80$), sometimes bad ($n = 35$), and poor ($n = 12$) appetites, and the women reported good ($n = 44$), sometimes bad ($n = 30$), and poor ($n = 22$) appetites.

contributes to a weaker anorexic response (lower plasma leptin) and a weaker orexic response (poorer feeding and lower plasma ghrelin) in male rats. The cause of anorexia among patients with CKD is probably multifactorial. However, it is plausible that proinflammatory cytokines may play an important role by acting on the central nervous system to alter the release or function (or both) of several key neurotransmitters, thereby altering both appetite and metabolic rate (8, 9). Indeed, anorexic patients undergoing peritoneal dialysis have higher concentrations of tumor necrosis factor α than do nonanorexic patients (31). Furthermore, recent data have shown that the inflammation present in uremia stimulates leptin expression (32, 33) by signaling through the central melanocortin system (34), although it also affects ghrelin concentrations (35, 36). Because men on dialysis who have inflammation seem to have a worse survival than do women with the same condition (13), it is plausible to hypothesize that the differences in the inflammatory burden between men and women (37) may differently influence the feeding behavior.

Sex hormones may also contribute to the different severity of symptoms associated with poor appetite in men and women. In fact, inflammation-induced anorexia was reported to be more severe among male rats (38), and previous reports suggest that estradiol and progesterone have inhibitory effects under both basal (39, 40) and inflammatory (41) conditions, whereas progesterone injections decreased the severity of anorexia among female rats (38). It is interesting that nephrectomized male rats developed anemia and malnutrition, whereas matched females rats were free from these symptoms, which shows sex divergences in expression and alteration of several sex hormone receptors in the kidney tissue (42). Moreover, the use of low doses of progestagen megestrol acetate was shown to improve the nutritional and inflammatory status, as well as anorexia, in maintenance dialysis patients (43, 44). We did not assess estrogen concentrations in the current study; however, whereas most of the women investigated were postmenopausal, it may be that continuous estrogen protection during menstruating years and other genetic differences yielded a physiology that is better protected against the inflammatory burden of CKD (13).

The Women's Health Initiative showed that the administration of estrogen and progestin during 3 y in 400 postmenopausal women resulted in less loss of lean soft tissue mass and a lower ratio of trunk to leg fat mass than were seen in postmenopausal control subjects (45). This observation is of interest for CKD patients, because a gain in fat mass in this population is associated with improved survival (46). In agreement with this finding, markers of muscle mass are poor predictors of survival in CKD women but not in men (47). Because sex differences involve not only metabolic and neural pathways that are responsible for

TABLE 2
Significant predictors of self-reported appetite in a multinomial logistic regression including 223 prevalent hemodialysis patients[1]

		95% CIs		
	Odds ratio	Lower	Upper	*P*
Intercept of poor appetite				<0.0001
Intercept of sometimes bad appetite				0.01
IGF-I (> compared with < 159 ng/mL)	3.59	2.05	6.27	<0.0001
Inflammation (hs-CRP < compared with > 10 mg/L)	2.39	1.38	4.15	0.002
Sex (women compared with men)	0.41	0.24	0.72	0.002
Age (< compared with 66 y)	0.85	0.49	1.46	0.55

[1] The model included self-reported appetite as the dependent variable and all factors significantly associated with the dependent variable in univariate analysis. IGF-I, insulin-like growth factor I; hs-CRP, high-sensitivity C-reactive protein. Pseudo $r^2 = 0.19$; $P < 0.0001$.

controlling the systemic inflammatory response but also differences in the immune systemic response, we hypothesize that sex hormone protection in women may contribute to a lower susceptibility to the inflammation-induced anorexia associated with CKD.

Some limitations of the present study should be considered. First, the results may have been influenced because the self-reported appetite intensity and anthropometric measurements were assessed on the day of hemodialysis. Second, patients with poor appetite had longer dialysis vintage time than did the other patients, which indicates that long-term dialysis itself may be another cause of loss of appetite. However, adjustment for dialysis vintage did not affect survival. Third, the relatively low number of patients may have masked other interactions in inflammatory and nutritional markers that would have strengthened our hypothesis, which should be assessed in bigger cohorts. Finally, that fact that this was a cross-sectional analysis may limit the value of the study. Thus, the present study does not provide a mechanistic explanation for the effect of sex differences on the regulation of the severity of symptoms during anorexia. Studies that provide such an explanation will add substantially to the strength of our findings.

In conclusion, our findings confirm the usefulness of self-reports of appetite level as a predictor of outcome for patients undergoing hemodialysis. Because sex may determine the severity of symptoms, such as handgrip strength, among patients who report a poor appetite, this study also supports the hypothesis that uremic men may be more susceptible than women to inflammation-induced anorexia. Altogether, we speculate that the mechanisms behind anorexia in women differ from those in men, perhaps involving the cardioprotective effects of sex hormones.

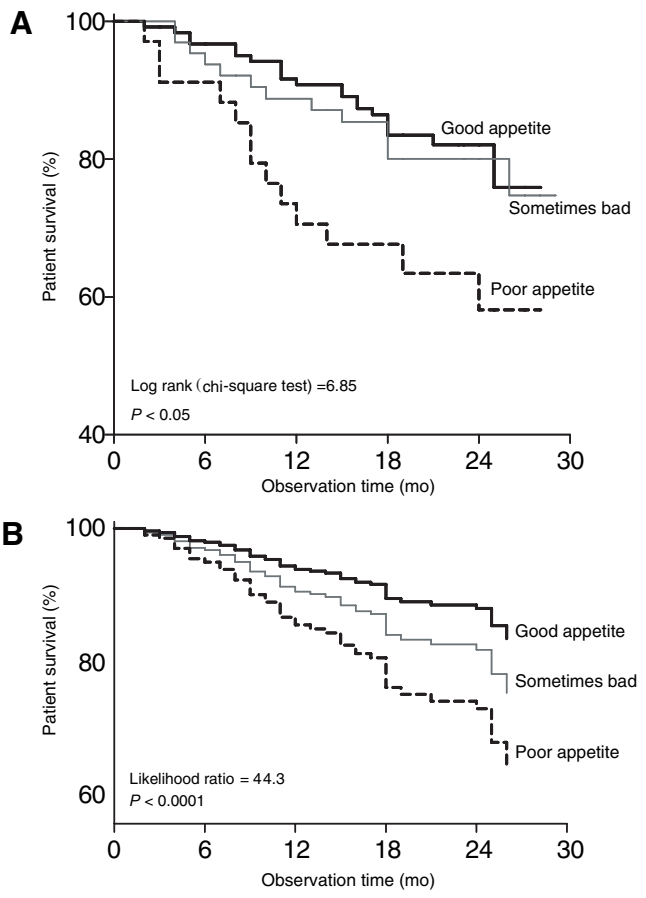

FIGURE 4. Unadjusted (A) and adjusted (B) survival of patients in each of the 3 appetite categories. Adjustment for potential confounding factors [age, sex, inflammation [C-reactive protein (CRP) > 10 mg/L], dialysis vintage, and Davies comorbidity index] was conducted with the Cox proportional hazards model. This analysis comprised 124 patients reporting good appetite, 65 patients reporting sometimes bad appetite, and 34 patients reporting poor appetite followed for ≤30 mo.

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JJC, ARQ, JA, and PS were responsible for the study concept and design. SS-J, PB, and OH were involved in patient recruitment and data collection. CMA, MES, and SK contributed to the laboratory procedures. JJC, ARQ, CMA, and MES were involved in analysis and data interpretation. ARQ and JJC were responsible for the statistical analyses. JJC, ARQ, JA, and SK wrote the first draft of the manuscript, which was reviewed by all coauthors. BL and AA participated administratively, technically, and materially in the study and acted as study supervisors BL is affiliated with Baxter Healthcare Inc. None of the other authors had any personal or financial conflict of interest.

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