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Inflammation and outcome in end-stage renal failure: Does female gender constitute a survival advantage?

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Background. Elevated C-reactive protein (CRP) is a strong predictor of cardiovascular events and all-cause mortality in end-stage renal disease (ESRD) patients. However, although sex hormones may influence serum levels of inflammatory proteins, gender has not been taken into consideration in previous studies of inflammation and outcome in ESRD patients.

Methods. We included 663 (374 males) ESRD patients (59 ± 1 year) from three European renal centers (Sweden, Germany and Italy) in which CRP levels and outcome data (follow-up 33 ± 1 months) were available. The relation between outcome and serum levels of the soluble intercellular adhesion molecule (sICAM-1) was evaluated in 312 of the patients.

Results. The present study shows that elevated CRP is a strong predictor of outcome, but whereas no difference in all-cause mortality was observed between non-inflamed (CRP ≤3.4 mg/L) males and females, inflamed males had a significantly (log rank 6.1; $P = 0.01$) higher mortality rate than inflamed females. A strong positive correlation between CRP and sICAM-1 was found in the combined patient material ($\rho = 0.37$; $P < 0.0001$) as well as in the male ($\rho = 0.25$; $P < 0.01$) and female ($\rho = 0.52$; $P < 0.0001$) subgroups. The Cox proportional hazard model showed that whereas both elevated sICAM-1 and log CRP predicted outcome in males, neither predicted outcome significantly in females.

Conclusions. As inflamed female patients have a better outcome that inflamed males the present observation suggests that sex hormones may have important cardioprotective effects that limit the effect of inflammation on vascular injury in female ESRD patients.

Atherosclerotic cardiovascular disease (CVD), which recently has been regarded as an inflammatory disorder [1], remains the main cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The annual mortality rate due to CVD is approximately 10- to 20-fold higher than the general population, even when adjusted for age, gender, race and diabetes mellitus [2]. Several recent studies have reported that chronic inflammation, as defined by elevated C-reactive protein (CRP) levels, is a strong independent predictor of all-cause and cardiovascular mortality in ESRD patients [3–6]. Available data suggest that the association between inflammation and atherosclerosis is particularly strong in ESRD patients and CRP has been shown to be an independent predictor of intima media thickness and the number of atherosclerotic plaques in carotid arteries of dialysis patients [7]. Furthermore, a strong relationship between elevated CRP levels and the intima media area has been documented in predialysis patients [8].

Although inflammation has been shown to predict future cardiovascular events in both apparently healthy women [9] and men [10], comparative studies are scarce and the impact of gender on outcome has not been studied systematically in inflamed ESRD patients. In this respect it is of interest that recent studies in non-renal patients have shown that postmenopausal hormone replacement therapy, such as with estrogen, may modulate the concentrations of CRP and vascular adhesion molecules [11]. Vascular adhesion molecules, which are up-regulated by a chronic inflammatory response [12], may serve as indirect markers for endothelial dysfunction, which are considered to be an early event in the atherosclerotic process. Thus, by combining data from three large European renal centers (Sweden, Germany and Italy), we sought to determine if inflammation is an equally strong predictor of all-cause mortality in male and female ESRD patients, respectively.

METHODS

Six hundred sixty-three ESRD patients from Sweden ($N = 160$), Germany ($N = 278$) and Italy ($N = 225$)

Key words: gender and renal disease, cardioprotection, vascular injury, atherosclerotic cardiovascular disease, C-reactive protein, sICAM-1, mortality in kidney disease.

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were evaluated close to the start of, or during, dialysis treatment. They were all part of ongoing prospective studies and detailed clinical information about the patients included has been reported recently [3, 8, 13]. The Ethical Committees of the three University Hospitals approved the study protocols and informed consent was obtained from all patients. In summary, the Swedish patient material included patients with advanced ESRD (GFR 7 ± 1 mL/min) studied at a time-point close (34 ± 6 days) to start of dialysis treatment. Fifty-six patients in whom high sensitivity CRP levels were not available were not included in the analysis. Seventy-two hemodialysis (HD) patients were treated by conventional bicarbonate buffered dialysate using either polyamide, cellulose-acetate or hemophane filters, whereas 88 peritoneal dialysis (PD) patients were on a 4 to 5 exchanges per day schedule with standard dialysis bags. Both the German and Italian cohorts comprised patients on HD treatment using conventional bicarbonate-buffered dialysate. The Italian patients represented about 70% of the whole dialysis population being treated in dialysis centers linked to a Clinical Research center and to the Academic Unit. The remaining 30% of the patients were excluded because of the presence of circulatory congestion or major infections (20%), because they were hospitalized for inter-current illnesses, or for logistic reasons/unwillingness to participate in the study (10%). In the German cohort 23 patients with active illness were excluded from evaluation. The type of dialysis membranes used in the Italian [13] and German centers [3] have previously been described. In all centers dialysis prescriptions were individualized to achieve the recommended current adequacy targets. In the combined patient group 258 patients died during the observation period. Survival was determined after a mean follow-up of 33 ± 1 months (range 0.2 to 76.2 months) and measured from the day of examination until death or censoring, which was made at the end of the follow-up (December 2001 to January 2002) or at renal transplantation. We also performed a subanalysis of the 225 Italian and 87 of the Swedish patients, in whom data on soluble intercellular adhesion molecule (sICAM-1) was available. Data on sICAM-1 was not available in the German patients.

Determinations of CRP were carried out using a nephelometric immunoassay (NA Latex CRP Reagent; Behring Institute, Marburg, Germany) in Sweden and Germany and a commercially available kit (Behring, Scoppito, L'Aquila, Italy) in Italy. As the detection limit of CRP was 3.4 mg/L at the Italian renal center this value was chosen as the cut-off point in the Swedish and German cohorts also. The levels of sICAM-1 were determined by a commercially available enzyme-linked immunosorbent assay (ELISA) kit and standard (R&D Systems Europe Ltd., Abingdon, UK) in both the Swedish and Italian renal centers. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Overweight was defined as a BMI >27.5 kg/m^2 [14], whereas a BMI less than 20 kg/m^2 was defined as being underweight and 20 to 27.5 kg/m^2 was considered to be normal weight.

Statistical methods

Values are presented as mean ± SEM or medians with $P < 0.05$ taken to indicate significance. For comparisons of continuous data between the three renal centers the Kruskal-Wallis analysis and the Mann-Whitney U-test were used. For comparisons of nominal data between the three renal centers the Chi-square test was used. Correlations were determined with regression (r) or Spearman rank (ρ) analysis, as appropriate. Survival analyses were made with the Kaplan-Meier or the Cox proportional hazards model and the relative risk of death was calculated.

RESULTS

CRP and its relationship to outcome in males and females

The basal clinical characteristics of the ESRD patients from the three different European renal centers are given in Table 1. It is noteworthy that the median CRP levels did not differ significantly between the centers. It is likely that different criteria for patient selection may account for the differences observed in mean age, BMI and prevalence of diabetes mellitus (DM) between the three centers. Although no significant differences in age (59 ± 1 vs. 61 ± 1 years) or prevalence of DM (26 vs. 25%) were observed between 374 males and 289 females in the combined patient material, the median CRP level (9.2 vs. 5.2 mg/L) was significantly ($P < 0.001$) higher in males. Moreover, the prevalence of patients with elevated CRP (>3.4 mg/L) was significantly higher in males than females (76 vs. 62%; $P < 0.0001$).

Significant positive correlations were observed between age and log CRP in all patients ($r = 0.25$; $P < 0.0001$) as well as in the male ($r = 0.26$, $P < 0.00001$) and female ($r = 0.27$; $P < 0.0001$) subgroups, as shown in Figure 1. No difference in mortality rate was observed between the three centers as shown in Figure 2. A significantly higher total mortality rate was observed in males (log-rank 12.8; $P < 0.001$) compared to females. When the patient material was divided into quartiles according to CRP levels, a highly significant (log-rank 60.1; $P < 0.00001$) difference in mortality rate was observed (Fig. 2). The patient material also was divided according to the chosen cut-off point for CRP (3.4 mg/L) and gender. As expected, 284 inflamed males had a significantly (log-rank 21.9; $P < 0.00001$) higher mortality rate than 90 non-inflamed males. Similarly, 179 inflamed females had a significantly (log-rank 16.6; $P < 0.00001$) higher mortality rate than 110 non-inflamed females.

Table 1. Basal clinical data from three European renal centers

	Italy	Germany	Sweden	Kruskal-Wallis	Chi-square
Number	225	278	160	—	—
Age *years*	60 ± 1	62 ± 1	54 ± 1[a]	$P < 0.0001$	—
Body mass index kg/m^2	24.6 ± 0.3	23.3 ± 0.3[b]	24.8 ± 0.4	$P < 0.0001$	—
Mortality rate/year	13%	15%	13%	—	NS
Prevalence males	56%	54%	62%	—	NS
Prevalence diabetes mellitus	16%	29%[c]	28%[d]	—	$P = 0.001$
Median CRP *mg/L*	7.5 (<3.4–197.0)	7.6 (0.2–151.0)	8.0 (0.2–163.0)	NS	—
Prevalence CRP >3.4 *mg/L*	66%	74%	67%	—	NS

NS is not significant.
[a] $P < 0.0001$ vs. Italy and Germany
[b] $P < 0.01$ vs. Italy and Sweden
[c] $P < 0.001$ vs. Italy
[d] $P < 0.05$ vs. Italy

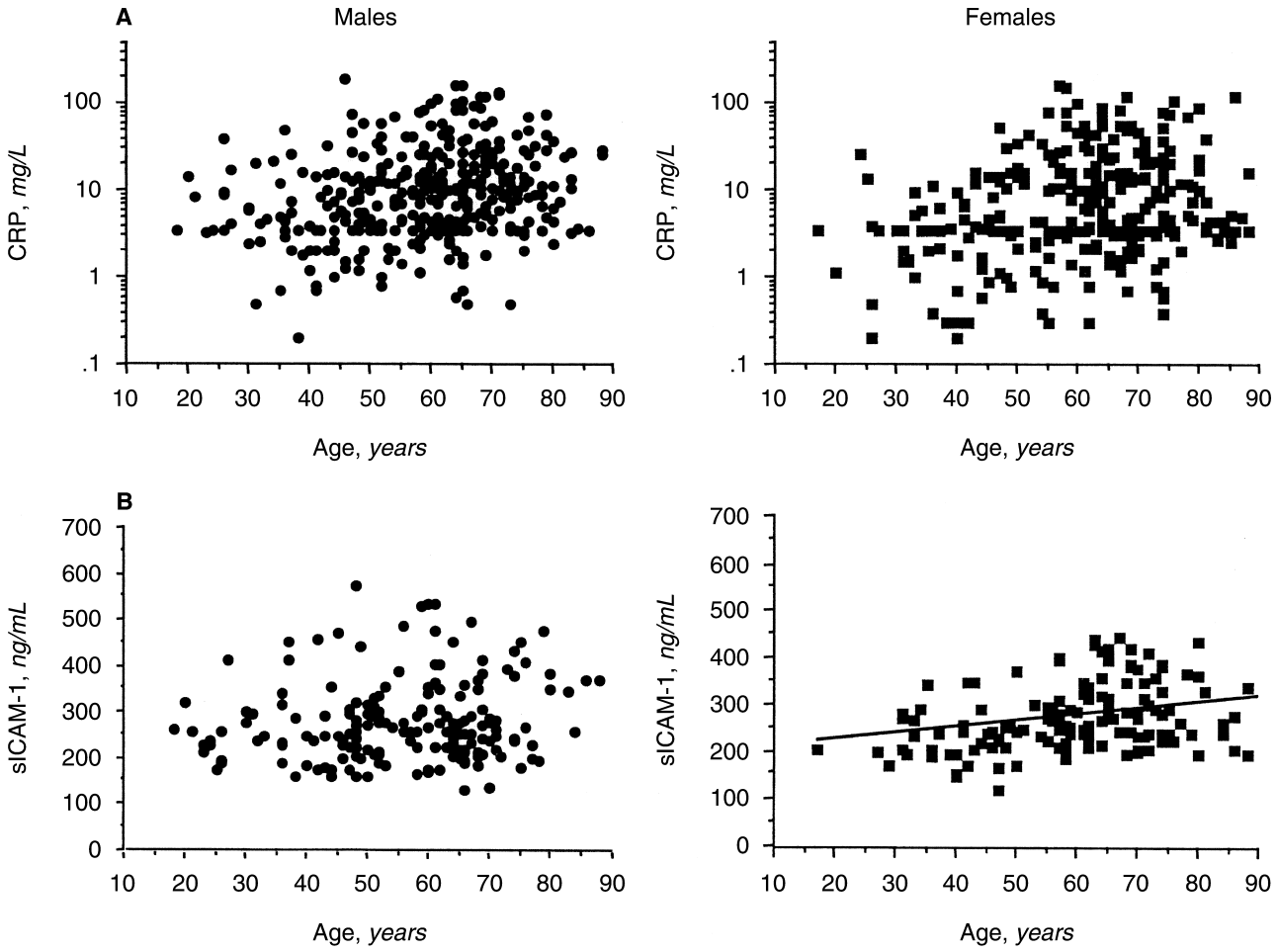

Fig. 1. Correlations between age and soluble intercellular adhesion molecule (sICAM-1; *B*) and log C-reactive protein (CRP; *A*) in male and female end-stage renal disease (ESRD) patients. In A, males, $N = 374$; $r = 0.26$; $P = 0.0001$; females, $N = 289$; $r = 0.27$; $P = 0.0001$. In B, males, $N = 181$; $r = 0.11$; NS; females, $N = 131$; $r = 0.32$; $P = 0.0002$.

However, the results also showed that, whereas no difference (log-rank 0.5; NS) in outcome was found between non-inflamed (CRP ≤3.4 mg/L) males and females, respectively, a significantly higher total mortality rate (log-rank 6.1; $P = 0.01$) was observed in inflamed males compared to inflamed females (Fig. 2). The median CRP level did not differ between inflamed males (12.4 mg/L; range 3.5 to 197.0 mg/L) and females (13.5 mg/L; range 3.5 to 166.0 mg/L). The Cox proportional hazard model was used to analyze unadjusted and adjusted relative

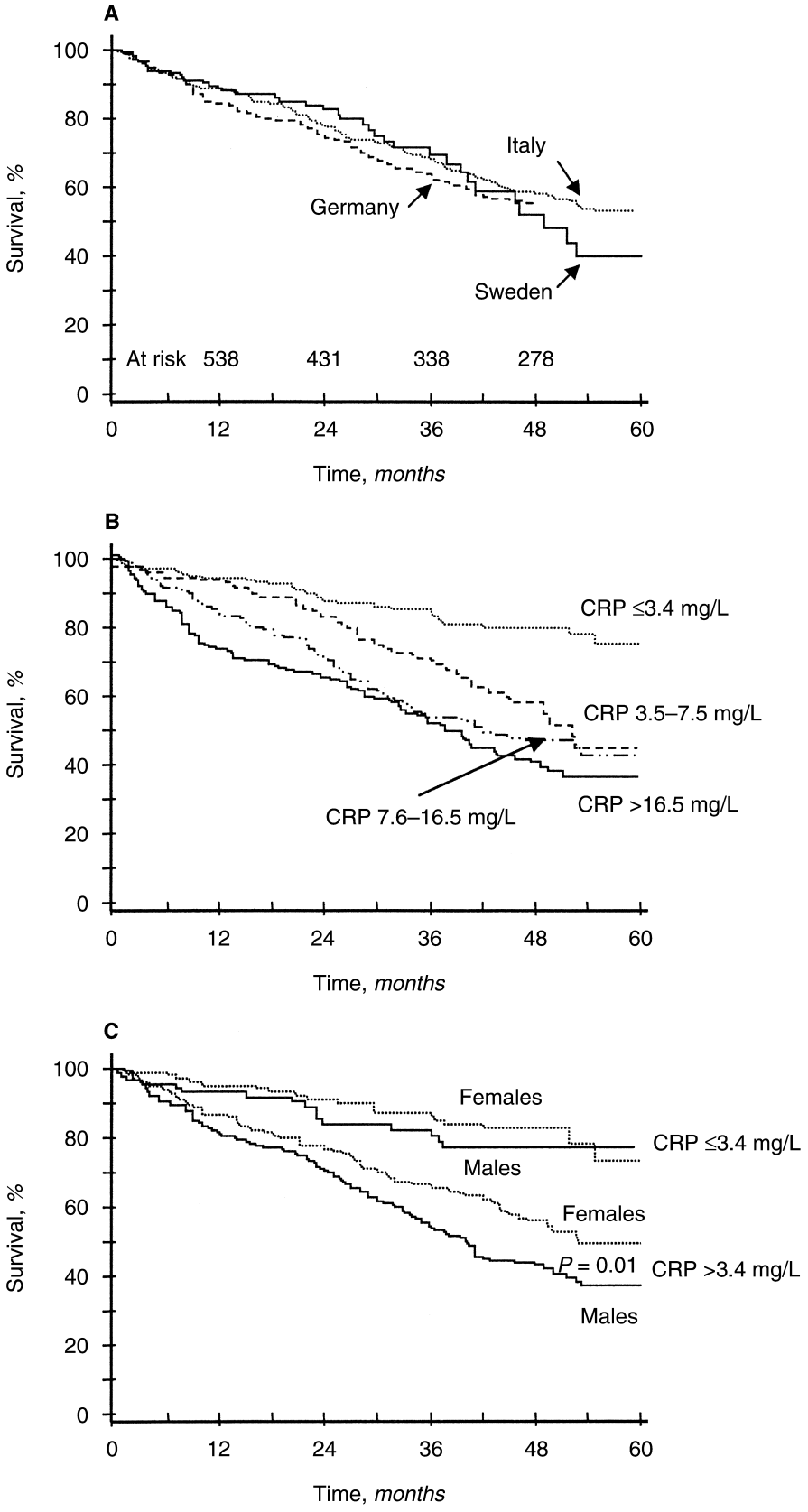

Fig. 2. (*A*) Survival (log-rank 0.8; not significant) by Kaplan-Meier in the three renal centers. (*B*) Survival (log-rank 60.1; $P < 0.0001$) by Kaplan-Meier in 663 ESRD patients divided into CRP-quartiles. (*C*) Survival by Kaplan-Meier according to gender and the presence of inflammation (CRP >3.4 mg/L) at the start of follow-up. Whereas no significant difference (log-rank 0.5) in outcome was observed between non-inflamed males and female, a significantly higher (log-rank 6.1; $P = 0.01$) mortality rate was observed in inflamed males compared to females.

Table 2. Unadjusted and adjusted relative risk for all-cause mortality in 663 end-stage renal disease patients

Variable	Unadjusted relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)[a]	*P* value
Age (*per year*) increase	1.05 (1.04–1.06)	<0.0001	—	—
Male gender	1.26 (1.11–1.43)	<0.001	—	—
BMI (*per kg/m²*) increase	0.99 (0.97–1.03)	NS	—	—
CRP *mg/L*				
≤3.4	1		1	
3.5–7.6	1.49 (1.20–1.85)	<0.001	1.37 (1.10–1.71)	<0.01
7.7–16.5	1.82 (1.49–2.22)	<0.0001	1.67 (1.36–2.06)	<0.0001
>16.5	2.00 (1.07–2.05)	<0.0001	1.72 (1.40–2.13)	<0.0001

[a] Adjusted for age, body mass index (BMI), renal center and gender

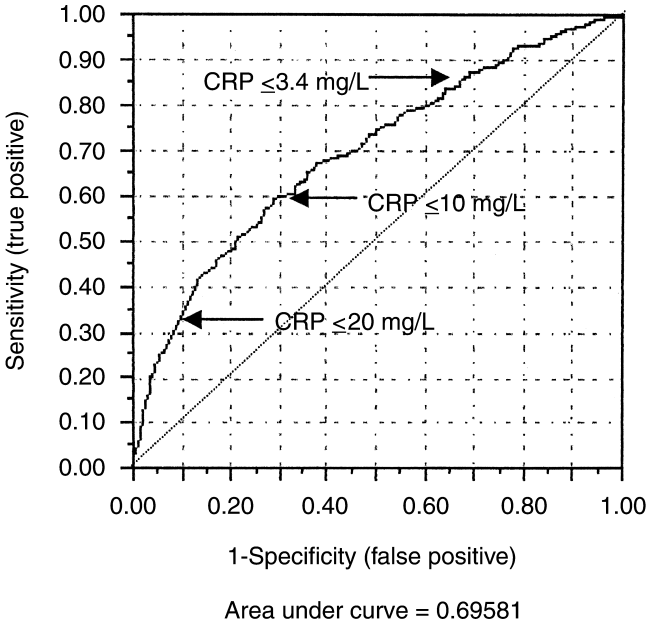

Fig. 3. Receiver operating characteristics (ROC) curve for C-reactive protein as a predictor of death. Data for CRP values <3.4 mg/L were based on 438 patients (Swedish and German cohorts) whereas data on the other cut-off points for were based on 663 patients.

risk of mortality according to CRP-quartiles, following correction for the impact of age, BMI, renal center and gender (Table 2). The results showed a stepwise increase in both unadjusted and adjusted relative risk for mortality with increasing CRP levels. Moreover, in another Cox proportional hazard model analyzing CRP as a continuous variable (log CRP) a strong independent association between log CRP (OR 2.40; 95% CI 1.88 to 3.07; $P < 0.00001$) and outcome was found independently of age, BMI and renal center. The receiver operating characteristics (ROC) curve for CRP as a predictor of death is shown in Figure 3. The area under the ROC curve was 0.696, standard error 0.020, 95% confidence interval 0.656 to 0.736. The cut-off point at which sensitivity and specificity were equal (65%) was at a CRP level of 9 mg/L.

No influence of BMI on mortality

The mean BMI for the whole patient group was 24.1 ± 0.2 kg/m². No difference in BMI was observed between males (24.2 ± 0.2 kg/m²) and females (24.1 ± 0.3 kg/m²). The prevalence of underweight (BMI <20 kg/m²) was 16.6% whereas 19.8% of the patients were considered overweight (BMI >27 kg/m²). Two hundred fifty-eight non-survivors had a similar BMI at start of follow-up (24.1 ± 0.3 kg/m²) compared to 405 survivors (24.1 ± 0.2 kg/m²). Similarly, a Kaplan-Meier survival analysis showed no difference in survival (log-rank 0.3) comparing normal weight, underweight and overweight ESRD patients. No significant correlation was observed between BMI and CRP ($\rho = 0.07$) in the whole patient group.

sICAM-1 and its relation to age and outcome

No significant difference (log-rank 1.2) in outcome was observed comparing 312 patients in which sICAM-1 was available to 351 patients in which it was not. Moreover, no significant difference in sICAM-1 level was found between males (284 ± 7 ng/mL; $N = 181$) and females (274 ± 6 ng/mL; $N = 131$). A significant ($P < 0.01$) difference in sICAM-1 levels was observed between Swedish (254 ± 9 ng/mL) and Italian (290 ± 6 ng/mL) patients. A strong positive correlation between CRP and sICAM-1 was found in the combined patient material ($\rho = 0.37$; $P < 0.0001$) as well as in males ($\rho = 0.25$; $P < 0.01$) and females ($\rho = 0.52$; $P < 0.0001$). Significant correlations were found between age and sICAM-1 levels in all patients ($r = 0.17$; $P < 0.01$) and in females ($r = 0.32$; $P < 0.001$), whereas no correlation was found between age and sICAM-1 levels in males ($r = 0.11$), as shown in Figure 1. Also, whereas significant positive correlations were observed between age and sICAM-1 in both Swedish ($r = 0.46$; $P < 0.01$) and Italian ($r = 0.27$; $P < 0.01$) females no significant correlations were observed between age and sICAM-1 in either Swedish ($R = 0.001$) or Italian ($R = 0.08$) men. In a stepwise multiple regression model including age, log CRP and gender, only log CRP ($P < 0.00001$) was significantly

associated to sICAM-1 levels. No significant difference in sICAM-1 levels (276 ± 14 vs. 289 ± 8 ng/mL) were observed between 65 males aged ≤50 and 116 males >50 years of age, respectively. On the other hand, 39 females ≤50 years of age had significantly lower serum levels of sICAM-1 (237 ± 10 vs. 289 ± 7 ng/mL; $P < 0.0001$) than 92 women aged >50 years.

The Cox proportional hazard model was used to adjust survival for age, diabetes mellitus, log CRP, gender, and sICAM-1 in the whole patient group as well as in the male ($N = 181$) and female ($N = 131$) subgroups. The results showed that besides age (OR 1.05; 95% CI 1.03 to 1.07; $P < 0.0001$), male gender (OR 1.38; 95% CI 1.13 to 1.69; $P < 0.01$) and diabetes mellitus (OR 1.33; 95% CI 1.06 to 1.63; $P < 0.05$) both elevated sICAM-1 (OR 1.003; 95% CI 1.001 to 1.005; $P < 0.01$) and log CRP (OR 1.87; 95% CI 1.24 to 2.84; $P < 0.01$) levels predicted poor outcome in the whole patient group. Subsequent subgroup analysis with regard to gender showed that besides age (OR 1.04; 95% CI 1.03 to 1.07; $P < 0.0001$), both elevated sICAM-1 (OR 1.003; 95% CI 1.001 to 1.005; $P < 0.05$) and log CRP (OR 2.17; 95% CI 1.30 to 3.54; $P < 0.001$) levels predicted poor outcome in males, whereas diabetes mellitus did not (OR 1.25; 95% CI 0.93 to 1.64). In females, on the other hand, only age (OR 1.06; 95% CI 1.03 to 1.10; $P < 0.0001$) predicted poor outcome significantly whereas log CRP (OR 1.26; 95% CI 0.56 to 2.72), sICAM (OR 1.005; 95% CI 1.000 to 1.010; $P = 0.08$) and diabetes mellitus (OR 1.39; 95% CI 0.97 to 1.96) did not.

DISCUSSION

Inflammation is a common feature and predicts outcome in ESRD

In the present study, 70% of all patients had CRP levels >3.4 mg/L whereas 45% of all patients had CRP levels >10 mg/L, which confirms that ESRD may be considered a chronic inflammatory state [15]. Also, in agreement with a previous observation by Yeun et al [4], our combined analysis shows that elevated CRP is strongly associated with poor outcome in ESRD patients independently of both age and gender (Fig. 2). Predicting survival in ESRD patients is important. In previous studies different cut-off points for CRP (8 to 15 mg/L) were chosen to show that elevated CRP predicts outcome [3, 5, 6]. The results from the present study, using receiver operating characteristics (ROC), shows that by using a cut-off point of 10 mg/L a sensitivity of about 60% (true positive values) is achieved whereas 30% are false positive (1-specificity; Fig. 3). It is of interest that the median CRP level did not differ between the three dialysis centers, indicating that yet undialyzed ESRD patients have CRP levels similar to ESRD patients on HD. This support the hypothesis that factors associated with ESRD, rather than the dialysis procedure per se, are the main cause of chronic inflammation in ESRD patients [16]. Indeed, Schindler et al have demonstrated that whereas optimized HD therapy using ultrapure dialysate and biocompatible dialyzer membranes was able to reduce elevated CRP levels in HD patients it did not normalize it [17].

Estrogen may modulate the effects of inflammation on vascular injury

An important and novel finding of the present study is that whereas survival does not differ between non-inflamed male and female ESRD patients, the influence of inflammation on survival was more pronounced in males than females. Thus, it could be speculated that female sex hormones, such as estrogen, may influence the inflammation-induced vascular injury. Several potential mechanisms by which estrogen may be able to modulate the atherosclerotic process have been suggested in the literature. As inflammation has been shown to increase oxidative stress [18], it is of interest that unlike most steroid hormones, estrogen has been shown to possess significant antioxidant properties [19]. Although the mechanism(s) by which an inflammatory reaction may cause accelerated atherosclerosis are not well understood, one key in the development of atherosclerosis is the adhesion of leukocytes to the vascular endothelium, a process mediated by vascular adhesion molecules, such as sICAM-1 [20]. Elevated levels of pro-inflammatory cytokines, which is a common phenomenon in ESRD patients [21], can up-regulate the expression of adhesion molecules from endothelial cells [12]. Thus, it has been suggested that an inflammatory response may be a major cause of endothelial dysfunction in ESRD patients [22]. In this respect it is of interest that endothelial function is abnormal in postmenopausal women [23] and that estrogen replacement therapy reverses endothelial dysfunction in postmenopausal women, especially if they are hypertensive [24]. In the present study we demonstrated a significant positive correlation between age and sICAM-1 in female ESRD patients only (Fig. 1). Thus, as lower levels of sICAM-1 were found in younger premenopausal women it could be suggested that estrogen exerts its cardioprotective effects is by limiting the inflammatory response to injury by modulating the expression of cellular adhesion molecules from the endothelium [25]. However, it should be pointed out that the direction and strength of the association with hormone replacement therapy use with inflammation markers seems to differ depending on the protein analyzed. Thus, whereas postmenopausal hormone therapy significantly increases CRP levels, they also might be considered anti-inflammatory as they reduce the concentration of adhesion molecules, such as sICAM-1 [26] and E-selectin [11]. Taken together, further studies are needed to investigate

whether postmenopausal hormone replacement therapy confers cardiovascular risk reduction through an inflammation-sensitive mechanism.

Does overweight constitute a survival advantage in European ESRD patients?

In the present study of European patients no difference in survival was observed when comparing overweight (BMI >27.5 kg/m^2), normal weight and underweight (BMI <20 kg/m^2) ESRD patients. Our findings differ from those recently presented by Fleishmann et al, who demonstrated that excess body weight was associated with a survival advantage in a predominantly black American HD patient population [27]. There may be several reasons for the discrepant findings reported. First, whereas the majority of our patients were of Caucasian origin, 89% of the patients in the study by Fleishmann et al were of African American race [27]. Second, whereas only about 20% of our patients were considered overweight almost 40% of all patients in the American study had a BMI >27.5 kg/m^2. Finally, it must be appreciated that the present study may not have included a sufficient number of patients to disclose significant differences and that different inclusion criteria and follow-up periods may have affected the results.

Limitations of the study

Several limitations of our data should be considered. At first, we relied on a single baseline determination and thus cannot take into consideration any variation of CRP that may have occurred over time. Second, as a combined analysis of data from three different renal centers in Europe was performed, we cannot rule out that different patient population, inclusion criteria and analysis methods may have influenced the results. However, although the prevalence of diabetic patients and mean age differed somewhat, the median and mean CRP levels were remarkably similar in the three centers. It also should be emphasized that whereas the Swedish cohort consisted of ESRD patients starting dialysis treatment, both the Italian and German cohorts constituted of prevalent HD patients. Thus, it could be speculated that lead-time bias may have affected the results. However, as survival was identical the first six months of observation (Fig. 2) we find it unlikely that lead-time bias may have affected the results. Third, in the present study all-cause mortality and not cardiovascular mortality was used as the final endpoint, and although the majority of the patients died of cardiovascular disease this needs to be considered. Fourth, although 90 non-inflamed males and 110 non-inflamed females were included in the present evaluation (which had a 80% power to detect a 1.8 higher likelihood of poor outcome in inflamed males), we cannot exclude that the observed non-different survival of non-inflamed males and females, respectively, may be related to an insufficient number of included patients. Finally, it must be emphasized that the majority of women in the present study were post-menopausal and serum levels of sex hormones were not assessed. Thus, further prospective studies are needed to investigate the possible impact of postmenopausal hormones, such as estrogen, on endothelial function during chronic inflammation in postmenopausal females with ESRD.

Conclusion

The present study, combining three large cohorts of patients from different parts of Europe, indicates a significantly better outcome for inflamed female than male ESRD patients. Indirectly, our results could suggest that sex hormones might have important cardioprotective effects that limit the effect inflammation might have on progressive vascular injury in ESRD patients. As research on the impact of gender on the prevalence of malnutrition, inflammation and atherosclerosis, until recently [28], has been a neglected area in nephrology, we propose that gender is an important factor that needs to be taken into consideration in future outcome studies.

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