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A J-shaped association between high-sensitivity C-reactive protein and mortality in kidney transplant recipients

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Abstract

In kidney transplant recipients (KTR), C-reactive protein (CRP) has been shown to be associated with increased mortality, but data on this association within the high-sensitivity (hs) range of CRP (<5 mg/l) are lacking. We prospectively studied 710 prevalent and stable KTR over >6 years. We thawed frozen plasma and measured baseline hs-CRP using an ultrasensitive assay. Detailed clinical and demographic baseline characteristics were available for study. We stratified patients by quartile of hs-CRP within the hs range (<5 mg/l), and also included KTRs whose hs-CRP was above the hs range (>5–10 and >10 mg/l). We used multivariate proportional hazards models to test for independent associations. After careful multivariate adjustment, we found a J-shaped association between hs-CRP and mortality. Compared with KTR whose hs-CRP was in the second lowest quartile of hs-CRP (0.06–1.26 mg/l), patients in the lowest quartile (<0.06 mg/l) had more than twice their mortality risk (HR = 2.07; 95% CI: 1.05–4.07), as did patients whose hs-CRP was ≥2.44 mg/l (all HRs >2.27). No association was found between hs-CRP and death-censored allograft loss. In contrast to the general population, the association between hs-CRP and mortality in KTRs is not linear, but J-shaped, suggesting that KTRs with very low hs-CRP may also be at increased risk of death.

Introduction

C-reactive protein (CRP) is a hepatically synthesized acute phase reactant that has long been investigated in kidney transplantation. While first proposed for detection and monitoring of the course of acute rejection [1], CRP has more recently received attention as a potential risk factor for long-term outcomes such as mortality or cardiovascular events. The renewed interest has been triggered by several pivotal studies conducted by Ridker *et al.* [2,3], in which they demonstrated an association between CRP and the risk of cardiovascular outcomes such as myocardial infarction, stroke and peripheral vascular disease. These associations were direct and the risk gradient was even evident in patients with very low CRP concentrations [4], which can only be detected and measured by using new generation assays with high sensitivity (high-sensitivity, hs-CRP).

While the prognostic role of CRP in kidney transplant recipients (KTR) has been investigated in a few studies,

nearly all of these measured CRP using older assays of low sensitivity. Winkelmayer *et al.* [5,6] found that KTR who had a baseline concentration of CRP >5 mg/l experienced a 53% increased mortality compared with patients whose CRP was ≤5 mg/l (95% confidence interval (CI): 1–131%). However, 83% of their patients were in the latter group, but assays for measurement of CRP below 5 mg/l were not available at the time of that study. Hence, the question remained unanswered whether there was a risk gradient within this hs range of CRP.

This study was designed to fill this void. We specifically sought to test the hypothesis whether CRP concentrations within the high-sensitivity range (≤5 mg/l) predicted mortality or allograft loss in KTR.

Patients and methods

Study population and follow-up

This aspect of our study has been described in previous work [7]. All patients gave informed consent in accordance with the Declaration of Helsinki and the Austrian Law on Gene Technology, and an institutional review board gave study approval.

Between 1996 and 1998, we prospectively enrolled 733 stable KTR who received routine follow-up at the transplant clinic of the Vienna General Hospital into this study. We used the Austrian Dialysis and Transplant Registry (OeDTR) to prospectively follow these patients. The OeDTR collects longitudinal information on all dialysis patients and KTR residing in Austria. Follow-up in this database has been practically complete for many years, and reliable information on timing and occurrence of patient death and modality switches, such as re-initiation of maintenance dialysis after kidney graft failure, is available for study.

Patient characteristics and sample collection

During the baseline visit, citrated blood and blood without additive were drawn from each patient for laboratory analyses. Blood was allowed to clot at room temperature followed by centrifugation to obtain serum. Laboratory measures assessed immediately in serum of each patient included total cholesterol, triglyceride, creatinine, serum iron, hemoglobin, and total plasma homocysteine concentrations. We then used the Cockcroft-Gault formula to estimate creatinine clearance (C_{Cr}), which was then standardized to a body surface area of 1.73 m^2 [8]. For determination of hs-CRP concentrations, citrated blood was placed on ice and centrifuged at 4 °C within 60 min. Plasma aliquots were snap frozen and stored at −80 °C for 8–10 years before nephelometric analyses. These conditions were appropriate and allowed for accurate determination of hs-CRP concentrations even after long-term storage of the samples [9]. Body mass index (BMI) was calculated as the weight in kilograms divided by the squared height in meters. Immunosuppressive therapies at study baseline were also recorded.

From the OeDTR, we assessed each patient's age, gender, the underlying renal disease that likely caused the kidney failure, number of previous kidney transplants, time from first renal replacement therapy to transplantation, and time since the most recent kidney transplantation.

From the registry of the Eurotransplant Foundation, the joint organ procurement agency for Austria, Belgium, Germany, Luxemburg, The Netherlands, and Slovenia, we obtained information on the organ donor (donor age, gender, and living versus cadaveric donor) and on the specific circumstances of the transplantation procedure [cold ischemia time, number and type of human leukocyte antigen (HLA)-mismatch, and recipient panel reactive antibody-titer].

Main exposure

Frozen plasma was thawed and hs-CRP was measured using a particle-enhanced immunonephelometry assay (N High Sensitivity CRP, Dade Behring Austria GmbH, Vienna, Austria). We then stratified the patients into six groups dependent on their hs-CRP concentration. We decided to keep the following categories that had been used in previous studies: hs-CRP >5 to 10 mg/l and >10 mg/l. Within the high-sensitivity range of hs-CRP (≤5 mg/l), we stratified patients into quartiles.

Outcomes

The outcomes of this study were all-cause mortality and kidney allograft loss; the latter was defined as the composite end-point of patient death and re-initiation of maintenance dialysis. Additional analyses using graft failure as the main outcome, but using death as a censoring rather than an outcome event were also conducted. Median follow-up was 6.1 years.

Statistical analyses

Baseline characteristics were displayed for each CRP-stratum as count/percentage and mean/SD, respectively. Follow-up started on the date of study inclusion and lasted until a patient reached an end-point, or the date (s)he was last seen at the transplant clinic. Univariate and multivariate Cox proportional hazards models were then fit to test for potential risk factors of the study outcomes. The measure of association was the hazards ratio (HR) accompanied by the corresponding 95% CI. Associations

between continuous variables and the outcomes were examined for linearity and used in categories otherwise (i.e. coded as separate dummy variables). BMI was used in five categories as the associations between this variable and all outcomes of this study are known to be U-shaped [10]. For multivariate model building, we used an automated stepwise variable selection procedure that included all variables at $P < 0.20$ into the model. Recipient age, gender, C_{Cr}, and the categories of hs-CRP were forced into all models. From there, we introduced all other variables individually and then assessed whether they confounded the association between the main exposure variables and the outcome (defined as a change in the regression coefficient >10%), in which case the variable would be included regardless of the significance level. We used the SAS for Windows (Release 8.2, The SAS Corporation, Cary, NC, USA) software for all statistical analyses.

Results

Of the 733 patients enrolled into the cohort, seven received their follow-up care outside Austria and information on another 16 patients' donors was unavailable from the Eurotransplant Foundation registry. After exclusion of these 23 patients, 710 patients remained for study. Of these, 180 KTR (25.4%) had an hs-CRP above the hs range (>5 mg/l), a range that was also captured with older nonsensitive assays. The remaining 630 patients, stratified in quartiles of hs-CRP, had a measurement in the hs range and thus constituted the focus of this study. Table 1 shows baseline characteristics by stratum of hs-CRP. It appears that patients with higher hs-CRP were older, had fewer years between first dialysis and most recent transplantation, a higher BMI, and they were less likely to have been diagnosed with glomerulonephritis as the underlying disease and more likely to be on mycophenolate. It is also notable that serum iron concentrations decreased with higher hs-CRP; kidney function as determined by estimated C_{Cr} did not differ across hs-CRP strata. There was no evident systematic difference in other patient or transplantation-related characteristics (Tables 1 and 2).

From univariate Cox proportional hazards models, it became evident that the association between hs-CRP and all-cause mortality was not linear, but rather J-shaped. Hence, we selected the stratum with the lowest risk (quartile 2) as the reference group (Table 3). Compared with patients whose hs-CRP was between 0.06 and 1.26 mg/l, the relative risk of dying increased with greater concentration of hs-CRP and reached a nearly fourfold risk in those patients with an hs-CRP >10 mg/l (HR = 3.91; 95% CI: 2.08–7.36). It appeared that patients with the lowest hs-CRP, however, also had an increased risk of mortality (HR = 1.65; 95% CI: 0.86–3.14). After multivariate adjustment, this latter finding was even more pronounced. Compared with KTR whose hs-CRP was between 0.06 and 1.26 mg/l, patients with a lower hs-CRP experienced twice the mortality risk (HR = 2.07; 95% CI: 1.05–4.07). Similarly, patients whose hs-CRP exceeded the ones in the reference group continued to experience a greater mortality, with a doubling of risk above hs-CRP concentrations of 2.44 mg/l (Table 3).

Studies of the association between hs-CRP and kidney allograft loss from any cause did not reveal a difference in risk among patients within the hs range of CRP. Compared with patients whose hs-CRP was between 0.06 and 1.26 mg/l, patients whose hs-CRP was >10 mg/l had a 63% increased risk of kidney allograft loss (HR = 1.63; 95% CI: 1.04–2.54; Table 3). Multivariate adjustment did not change this finding (HR = 1.60; 95% CI: 1.01–2.54).

Last, we conducted analyses on the event of kidney allograft loss, but censored patients for death rather than including this as a cause of allograft loss (death-censored allograft loss). We found no associations between hs-CRP and this end-point, neither in univariate nor in multivariate analyses (Table 3).

We tested for violations of the proportionality assumption of Cox models using interactions with time, as well as for the presence of interaction among study variables. No evidence was found to support either.

Discussion

The present study fills an important gap in the evidence on the prognostic role of CRP in KTR. In previous work, we had demonstrated that patients whose CRP was >5 mg/l experienced twice the mortality of KTR whose CRP was below that threshold [5]. In that study, however, an older CRP assay was used which precluded us from studying the hs range of CRP. In the present study, we used frozen samples to assess the associations between hs-CRP and important health outcomes in KTR. We found a J-shaped association between hs-CRP and all-cause mortality in that both patients with very low hs-CRP concentrations and patients with higher hs-CRP concentrations had increased mortality; these risks were compared with those of patients whose hs-CRP was between 0.06 and 1.26 mg/l. These findings are novel and arose from carefully adjusted multivariate analyses.

The interpretation of these findings is challenging. The easiest option is to dismiss these results data as a result of random chance, which is a possibility, albeit small. These findings are in clear contrast to results obtained from the general population. Ridker and Cook [4] found a monotonous increase in cardiovascular risk with increasing hs-CRP in a large cohort of healthy women, and the linearity of risk was evident across the full spectrum of

Table 1. Characteristics of study patients by stratum of baseline high-sensitivity C-reactive protein concentration.

Variable	High-sensitivity C-reactive protein (mg/l)					
Number (%) or mean (±SD)	<0.06 (n = 135)	0.06–1.26 (n = 132)	1.27–2.43 (n = 132)	2.44–5.0 (n = 131)	5.01–10.0 (n = 104)	>10.0 (n = 76)
Recipient age (years)	48.5 (±13.3)	48.9 (±13.7)	52.2 (±13.4)	55.1 (±12.9)	54.2 (±12.4)	56.9 (±11.1)
Recipient gender (male)	85 (63.0%)	78 (59.1%)	82 (62.1%)	72 (55.0%)	64 (61.5%)	46 (60.5%)
Years from first renal replacement therapy to transplantation	3.7 (±4.0)	3.6 (±4.3)	2.5 (±2.5)	3.2 (±3.6)	3.2 (±3.6)	2.6 (±3.0)
Median (25th; 75th percentile)	1.8 (0.8; 5.0)	2.3 (1.0; 4.5)	1.6 (0.9; 3.4)	1.8 (1.0; 3.8)	2.1 (1.2; 3.7)	1.6 (0.9; 3.3)
Years since transplantation	5.2 (±4.9)	4.8 (±3.7)	4.7 (±3.5)	4.7 (±3.4)	5.0 (±4.1)	5.6 (±4.4)
Median (25th; 75th percentile)	3.7 (1.0; 8.0)	4.7 (1.6; 9.3)	4.0 (2.1; 6.6)	4.2 (1.9; 6.9)	3.8 (1.6; 7.3)	5.5 (1.4; 8.7)
Estimated creatinine clearance (ml/min/1.73 m^2)	55.0 (±19.0)	52.8 (±19.9)	57.7 (±18.6)	56.4 (±20.4)	58.5 (±21.0)	54.4 (±21.8)
Body mass index (BMI) (kg/m^2)	23.6 (±3.6)	24.0 (±3.6)	25.4 (±3.9)	26.9 (±4.4)	27.0 (±4.7)	26.2 (±4.4)
Total plasma homocysteine (μmol/l)	16.7 (±6.8)	17.3 (±7.7)	17.4 (±11.4)	16.9 (±7.6)	16.6 (±9.0)	18.2 (±10.6)
Total cholesterol (mg/dl)	228 (±52)	238 (±72)	237 (±45)	236 (±54)	238 (±53)	222 (±54)
Triglycerides (mg/dl)	175 (±138)	191 (±202)	202 (±127)	218 (±194)	192 (±100)	176 (±82)
Iron (mg/dl)	94 (±37)	82 (±40)	80 (±30)	77 (±30)	72 (±27)	58 (±26)
Hemoglobin (g/dl)	12.4 (±2.0)	12.6 (±2.0)	13.3 (±1.9)	13.0 (±2.0)	12.9 (±2.0)	12.5 (±1.8)
Underlying renal disease						
Diabetic nephropathy	5 (3.7%)	4 (3.0%)	10 (7.6%)	12 (9.2%)	11 (10.6%)	5 (6.6%)
Glomerulonephritis	58 (43.0%)	48 (36.4%)	48 (36.4%)	38 (29.0%)	30 (28.9%)	21 (27.6%)
Interstitial nephritis	15 (11.1%)	20 (15.2%)	22 (16.7%)	28 (21.4%)	18 (17.3%)	11 (14.5%)
Various other, specified	12 (8.9%)	10 (7.6%)	7 (5.3%)	14 (10.7%)	11 (10.6%)	5 (6.6%)
Polycystic kidney disease	19 (14.1%)	21 (15.9%)	17 (12.9%)	16 (12.2%)	13 (12.5%)	11 (14.5%)
Unspecified/unknown	26 (19.3%)	29 (22.0%)	28 (21.2%)	23 (17.6%)	21 (20.2%)	23 (30.3%)
Immunosuppressive regimen						
CsA + Corticosteroid + Azathioprine	49 (36.3%)	71 (53.8%)	66 (50.0%)	60 (45.8%)	46 (44.2%)	25 (32.9%)
CsA + Corticosteroid	29 (21.5%)	34 (25.8%)	33 (25.0%)	39 (29.8%)	23 (22.1%)	27 (35.5%)
CsA + Corticosteroid + mycophenolate (MMF)	35 (25.9%)	22 (16.7%)	20 (15.2%)	16 (12.2%)	20 (19.2%)	13 (17.1%)
Other	22 (16.3%)	5 (3.8%)	13 (9.9%)	16 (12.2%)	15 (14.4%)	11 (14.5%)

Table 2. Transplantation-specific characteristics of study population.

Variable	High-sensitivity C-reactive protein (mg/l)					
Number (%) or mean (±SD)	<0.06 (n = 135)	0.06–1.26 (n = 132)	1.27–2.43 (n = 132)	2.44–5.0 (n = 131)	5.01–10.0 (n = 104)	>10.0 (n = 76)
Number of previous kidney transplants						
0	102 (75.6%)	103 (78.0%)	113 (85.6%)	109 (83.2%)	83 (79.8%)	66 (86.8%)
1	26 (19.3%)	24 (18.2%)	16 (12.1%)	18 (13.7%)	20 (19.2%)	9 (11.8%)
2/3	7 (5.2%)	5 (3.8%)	3 (2.3%)	4 (3.1%)	1 (1.0%)	1 (1.3%)
Donor organ type (living versus cadaveric)	11 (8.2%)	4 (3.0%)	5 (3.8%)	7 (5.3%)	3 (2.9%)	3 (4.0%)
Donor age (years)	38.3 (±15.6)	39.8 (±15.0)	40.3 (±16.5)	37.5 (±15.4)	36.9 (±15.6)	36.7 (±15.5)
Donor gender (male)	84 (62.2%)	81 (61.4%)	88 (66.7%)	86 (65.7%)	61 (58.7%)	49 (64.5%)
Number of human leukocyte antigen-mismatches	2.2 (±1.2)	2.2 (±1.1)	2.3 (±1.2)	2.2 (±1.1)	2.1 (±1.2)	1.8 (±1.3)
Cold ischemia time (hours)	21.0 (±8.3)	20.9 (±7.6)	21.4 (±8.0)	19.6 (±7.5)	20.7 (±6.9)	21.6 (±7.2)
Panel reactive antibody titer (>50 vs. ≤50%)	8 (5.9%)	10 (7.6%)	8 (6.1%)	9 (6.9%)	7 (6.7%)	5 (6.6%)

hs-CRP. The comparability of their and our findings is uncertain, however, as an important difference between healthy women and KTR is the presence of chronic kidney disease and therapeutic immunosuppression in the latter. Indeed, the lowest decile of hs-CRP in Ridker and Cook's study was 0.36 mg/l, which is considerably higher than the cutoff value of the lowest stratum in our cohort. Studies in KTR with similar granularity of hs-CRP are not available. Ducloux *et al.* [11] followed 344 KTR for over 6 years for the occurrence of a composite cardiovas-

Table 3. Associations between categories of high-sensitivity C-reactive protein and study outcomes.

	High-sensitivity C-reactive protein (mg/l)					
Hazard ratio (95% CI)	<0.06 (n = 135)	0.06–1.26 (n = 132)	1.27–2.43 (n = 132)	2.44–5.0 (n = 131)	5.01–10.0 (n = 104)	>10.0 (n = 76)
All-cause mortality (univariate)	1.65 (0.86–3.14)	1.0 Referent	1.51 (0.79–2.92)	2.69 (1.47–4.91)	2.94 (1.58–5.46)	3.91 (2.08–7.36)
All-cause mortality (multivariate)*	2.07 (1.05–4.07)	1.0 Referent	1.44 (0.72–2.90)	2.29 (1.22–4.30)	2.27 (1.18–4.36)	2.94 (1.50–5.78)
Kidney allograft loss (univariate)	1.00 (0.66–1.53)	1.0 Referent	0.94 (0.61–1.43)	1.35 (0.91–2.01)	1.39 (0.91–2.11)	1.63 (1.04–2.54)
Kidney allograft loss (multivariate)†	1.12 (0.73–1.71)	1.0 Referent	1.04 (0.68–1.61)	1.40 (0.93–1.61)	1.36 (0.88–2.10)	1.60 (1.01–2.54)
Kidney allograft loss (death-censored; univariate)	0.93 (0.56–1.54)	1.0 Referent	0.85 (0.51–1.42)	1.07 (0.65–1.76)	1.04 (0.61–1.77)	1.00 (0.54–1.84)
Kidney allograft loss (death-censored; multivariate)‡	1.03 (0.62–1.71)	1.0 Referent	1.08 (0.64–1.84)	1.37 (0.82–2.29)	1.23 (0.71–2.15)	1.04 (0.55–2.00)

*Multivariate model adjusted for recipient age, gender, C_{cr}, body mass index (BMI) (first and second-order term), diabetic nephropathy, serum iron concentration, total plasma homocysteine, time from first renal replacement therapy (RRT) to transplantation.

†Multivariate model adjusted for recipient age, gender, C_{cr}, BMI (first and second-order term), diabetic nephropathy, total plasma homocysteine, time from first RRT to transplantation.

‡Multivariate model adjusted for recipient age, gender, C_{cr}, BMI (first and second-order term), donor gender, dual immunosuppression with cyclosporine and corticosteroid (versus all other), total plasma homocysteine, time from first RRT to transplantation.

cular end-point. After multivariate adjustment, these colleagues found a monotonous increase in cardiovascular risk; compared with those in the lowest quartile of hs-CRP (<2.1 mg/l), patients in the highest quartile (hs-CRP ≥5.2 mg/l) had a 2.7-fold cardiovascular risk. No further analyses were presented among patients in the lowest quartile of hs-CRP that would confirm or refute our findings. A small German study found an association between serologic evidence of *Chlamydia pneumoniae* infection and cardiovascular death, but no such association with CRP [12]. All other studies in KTR have used pretransplant measurements of CRP, and only few patients were evaluated [6,13]; both factors limit the interpretability of their findings in relation to the ones obtained from our study.

To the experienced transplant epidemiologist, the J-shaped association between hs-CRP and mortality in KTR follows a familiar pattern. One other risk factor exhibits a similarly complex association: KTR in the extremes of BMI are also at an increased risk of mortality compared with patients with normal BMI [5,10]. It is important to synthesize these observations in light of a recent paper that demonstrated that abdominal obesity was an important independent determinant of hs-CRP in KTR [14]. Table 1 shows that this may also be true in our cohort. Hence, it is important to carefully control for BMI in multivariate models to control for possible confounding by BMI. We did so in our analyses using both a continuous variable for BMI and for BMI-square and found independent and U-shaped associations with mortality for both hs-CRP and for BMI. Thus, one can only speculate about the possible mechanisms that might link very low hs-CRP with increased mortality: overly excessive immunosuppression, malnutrition or liver failure?

Although there is an increased risk of all cause mortality in patients with very low or very high CRP, there were some differences between these two groups indicating that the causes of mortality in these groups may be different. There was a higher percentage of living donors and a higher likelihood of being on myophenolate in the very low CRP group. A greater portion of the patients in the high CRP group were on dual immunosuppression compared with the other CRP groups. Cueto-Manzano *et al.* [15] studied a small number of patients before and after renal transplantation and found that post-transplant hs-CRP, unlike other markers of inflammation, dropped below pretransplant values, possibly indicating the effect of immunosuppression on CRP. Support for the idea that immunosuppression can lower CRP levels comes from another study of renal transplant patients [16]. In this study, patients with cyclosporine toxicity had a significantly lower median CRP value compared with patients with stable transplant function, who had a lower median

CRP compared with patients with biopsy proven acute rejection. These studies indicate that immunsuppression can lower CRP and it is therefore possible that cause of death in patients with very low CRPs is related to 'over-immunosuppression' (e.g. via infectious causes) rather than cardiovascular disease, a new hypothesis from this work. Unfortunately, we did not have any data on lymphocyte subtypes such as CD4 cell counts [17]. Further, information on cause of death is not available for our cohort; therefore, we have no data to support or refute these hypotheses, and further research is clearly needed.

To our knowledge, this study is also the first to show that hs-CRP is associated with future allograft loss. Compared with patients with low concentrations of hs-CRP, those whose hs-CRP exceeded 10 mg/l had a 60% greater chance of losing their graft, either through death or from another cause. Analyses that censored for death, however, did not show such an association, indicating that the former finding is solely attributable to patient death with functioning allograft.

We acknowledge the limitations of this study. Most importantly, no updated information was available on laboratory and other clinical parameters. Thus, this study puts one-time measurements of clinical data in a typical cohort of prevalent KTRs in relation to prospectively collected future events. While this design has certain strengths, we are unable to comment on any changes in these parameters over time and the outcomes associated with such changes. Information on one potentially important parameter is missing: smoking has been shown to be a predictor of both hs-CRP concentrations and of mortality in KTR [11,14]. Thus, the associations between high levels of hs-CRP and mortality may be overestimated. Absence of smoking status, however, would underestimate the true association between very low hs-CRP and greater mortality. Another parameter that is missing for study is albumin concentration. While albumin has been associated with hs-CRP, it was not a confounder of the association between hs-CRP and cardiovascular disease in the Modification of Diet in Renal Disease study [18]. Finally, our study is limited by absence of information on cause of death and on nonfatal cardiovascular events. While the latter would be desirable to increase power, the former is probably not of concern as the majority of KTR die from cardiovascular causes.

In conclusion, we report a complex association between hs-CRP and mortality in KTR. Both very low and elevated concentrations of this parameter are associated with increased mortality risk. Further studies are needed to confirm these findings, to elucidate the possible mechanisms underlying these phenomena, as well as to study the efficacy of potential therapeutic interventions.

Conflicts of interest

None of the authors has a conflict of interest to declare.

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