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Free *p*-cresol is associated with cardiovascular disease in hemodialysis patients

BKI Meijers[1,4], B Bammens[1,4], B De Moor[2], K Verbeke[3], Y Vanrenterghem[1] and P Evenepoel[1]

[1]*Division of Nephrology, Department of Medicine, University Hospital Leuven, Leuven, Belgium;* [2]*Division of Nephrology, Department of Medicine, Virga Jesse Hospital, Hasselt, Belgium and* [3]*Division of Gastroenterology, Laboratory of Digestion and Adsorption, University Hospital Leuven, Leuven, Belgium*

Cardiovascular disease (CVD) is highly prevalent in chronic kidney disease, suggesting that molecules retained in uremia might contribute to this increased risk. We explored the relationship between *p*-cresol, a protein-bound uremic retention solute, and CVD by comparing the strength of this relationship relative to traditional and novel cardiovascular risk factors. Univariate Cox proportional hazard analysis showed that the free serum *p*-cresol concentration was significantly associated with CVD when the primary end point was the time to the first cardiovascular event. In multivariate analysis, free *p*-cresol was significantly associated with CVD in non-diabetics. In diabetic patients, however, a significant relationship between *p*-cresol and cardiovascular events could not be demonstrated despite their having significantly higher *p*-cresol levels. Our study shows that free *p*-cresol is a novel cardiovascular risk factor in non-diabetic hemodialysis patients.

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Correspondence: *P Evenepoel, Dienst Nefrologie, Universitair Ziekenhuis Gasthuisberg, Herestraat 49, Leuven 3000, Belgium.*
E-mail: pieter.evenepoel@uz.kuleuven.ac.be

[4]These authors contributed equally to this work

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Mounting data point to the lethal synergy between chronic kidney disease (CKD) and cardiovascular disease (CVD).[1–5] Traditional cardiovascular risk factors are insufficient to predict true cardiovascular risk in patients with CKD.[6,7] Novel risk factors include the C-reactive protein (CRP) as a marker of inflammation, a disturbed mineral metabolism, albumin, and anemia.[8–12] Uremic retention solutes have been implicated in the pathogenesis of accelerated atherosclerosis as well.[13–17]

In recent years, the focus of the nephrology community is shifting toward protein-bound uremic retention solutes.[18] The HEMO and adequacy of dialysis Mexico studies[19,20] failed to show an improvement of patient outcome by increasing the removal of water soluble solutes above the current standards of care. The clinical importance of protein-bound uremic retention solutes is underscored by a recent observational study in hemodialysis patients in which we demonstrated that *p*-cresol, a prototypic uremic protein-bound retention solute, is independently associated with overall mortality.[21]

In vitro evidence suggests a deleterious effect of *p*-cresol on the endothelium.[22–24] The association between the protein-bound uremic retention solute *p*-cresol and CVD *in vivo* has not been investigated. The aims of this *post hoc* analysis of the *p*-cresol mortality study[21] were first to explore the relationship between *p*-cresol and CVD and second to compare the strength of this relationship relative to traditional and novel cardiovascular risk factors.

RESULTS

Study population

One hundred and seventy-five patients were included in the final analysis. Table 1 represents the demographic and baseline characteristics of the study population.

Relation between *p*-cresol and other parameters

The concentration of unbound *p*-cresol correlated significantly with age ($R=0.26$, $P=0.0004$), total calcium concentration ($R=0.21$, $P=0.004$), dialysis vintage ($R=0.23$, $P=0.002$), urea ($R=0.38$, $P<0.001$), single pool Kt/V (spKt/V) ($R=0.19$, $P=0.017$), and nPNA (normalized protein nitrogen appearance) ($R=0.41$, $P<0.001$) but not

Table 1 | Main demographic, clinical, and biochemical characteristics of study population

Age (years, median (range))	64.7 (26–89)
Sex (male/female (%))	108/67 (62/38)
Dialysis vintage (months, median (range))	29.8 (2.3–158.1)
sp*Kt/V*	1.64 (0.53)
r*Kt/V*	0.06 (0.13)
nPNA (g kg^{-1} day^{-1})	0.93 (0.26)
BMI (kg m^{-2})	23.9 (4.9)
Blood pressure (systolic/diastolic (mm Hg))	143 (19)/71 (11)
Diabetes (yes/no (%))	52/123 (29.7/70.3)
Current smoker (yes/no/unknown (%))	31/129/15 (18/74/8)
Cholesterol (mg per 100 ml)[a]	166.9 (32.0)
LDL (mg per 100 ml)[a]	92.8 (26.9)
Albumin (mg l^{-1})	36.4 (3.9)
PTH (ng l^{-1})	126.4 (177.5)
Calcium (mg per 100 ml)	9.5 (0.8)
Phosphate (mg per 100 ml)	4.8 (1.6)
Calcium × phosphate (mg^2 per 100 ml^{-2})	45.9 (15.7)
Urea (mg per 100 ml)	142.4 (39.7)
β_2-Microglobulin (mg l^{-1})	27.7 (10.6)
CRP (mg l^{-1})	21.8 (34.4)
Total *p*-cresol (mg l^{-1})	19.0 (11.9)
Free *p*-cresol (mg l^{-1})	2.59 (2.25)

BMI, body mass index; CRP, C-reactive protein; LDL, low-density lipoprotein; nPNA, normalized protein nitrogen appearance; PTH, parathyroid hormone; r*Kt/V*, residual *Kt/V*; sp*Kt/V*, single pool *Kt/V*.
Data are expressed as mean (s.d.), unless otherwise stated.
[a]One patient missing baseline data.

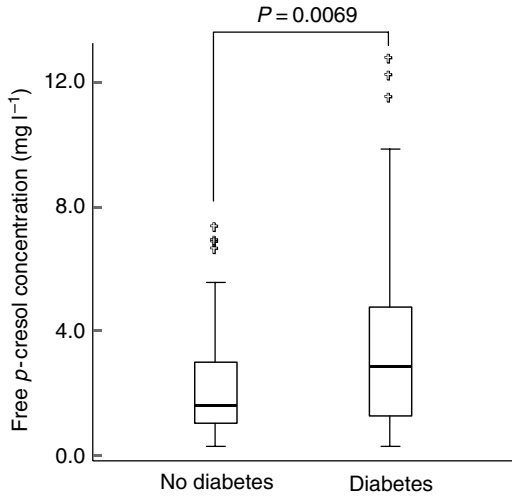

Figure 1 | Box plot of free *p*-cresol concentrations in patients with and without diabetes.

with smoking habit, body mass index, cholesterol concentration, CRP, albumin concentration, or the calcium phosphorus product. Patients with diabetes had significantly higher free *p*-cresol concentrations (analysis of variance (ANOVA), $P = 0.0069$) (Figure 1) as well as significantly higher total *p*-cresol concentrations (ANOVA, $P = 0.019$). Patients treated by hemodialysis had significantly higher free *p*-cresol concentrations (ANOVA, $P = 0.0008$) as well as significantly higher total *p*-cresol concentrations (ANOVA, $P = 0.023$) than those treated by hemodiafiltration.

Event analysis

After a mean follow-up of 56.2 months (s.d. 5.5, median 60.1, minimum–maximum 48.1–60.1 months), 78 patients reached the combined primary end point of a new cardiovascular event or death due to CVD. In univariate analysis, age, diabetes, CRP, albumin, systolic blood pressure, and free *p*-cresol were significantly ($P < 0.05$) associated with the primary end point (Table 2). Figure 2 shows the Kaplan–Meier curves of patients with free *p*-cresol concentrations above and below the median (1.97 mg l^{-1}). More patients had new fatal or non-fatal cardiovascular events in the group with high free *p*-cresol concentrations (log rank, $P = 0.022$).

A multivariate model was constructed to compare the observed association between *p*-cresol and CVD with a set of novel and traditional cardiovascular risk factors. All cardiovascular risk factors significant at the $P \leqslant 0.2$ level on univariate analysis (age, diabetes, treatment modality, systolic blood pressure, albumin, calcium, CRP, and free *p*-cresol) were included. In this model, age, diabetes, and CRP were found to be independently associated with CVD (Table 3).

As patients with diabetes have a significantly higher concentration of *p*-cresol, we performed grouped multivariate analyses of the patients with and without diabetes. In the group of non-diabetics, *p*-cresol as a continuous variable surpassed blood pressure, albumin, treatment modality, and calcium and was the last variable to be eliminated from the model. As a binary variable, besides age and CRP, *p*-cresol is the only other variable to remain in the model. Figure 2b shows the Kaplan–Meier estimate of patients without diabetes (log rank, $P = 0.019$).

Residual renal function (RRF) was not significantly associated with CVD in univariate analysis (Table 2). When RRF was forced into multivariate analysis, the observed relationship between *p*-cresol and CVD remained identical (data not shown).

DISCUSSION

The main finding of this study was that higher free *p*-cresol concentrations are associated with CVD in hemodialysis patients. This association persisted after adjustment for several covariates, including age and CRP, but was lost after adjustment for diabetes.

Cardiovascular mortality in CKD patients treated by hemodialysis is more than fivefold higher than in the general population, even after stratification for age, sex, race, and the presence of diabetes. Traditional cardiovascular risk factors are insufficient to accurately predict cardiovascular risk in patients with CKD.[7] Survival bias may disrupt the relationship between traditional risk factors and CVD.[25] Besides the traditional risk factors, an ever expanding list of novel cardiovascular risk factors has been proposed to contribute to the cardiovascular burden in CKD.[7–12] This is the first *in vivo* study to investigate the relationship between protein-bound uremic retention solutes, of which *p*-cresol is a prototypic representative, and CVD. In this study population, the strength of the association between *p*-cresol and CVD