C-reactive protein is associated with renal function abnormalities in a non-diabetic population


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Abstract

Background. C-reactive protein (CRP) has recently been introduced in cardiovascular medicine as a predictor of myocardial infarction, stroke and peripheral artery disease in different populations. We hypothesised that elevated CRP levels are associated with renal function abnormalities.

Methods and Results. To test this hypothesis we studied the relation between CRP levels and renal function loss measured as diminished creatinine clearance in a large non-diabetic population (7,317 subjects). In addition, the associations and confounding effects of established renal risk factors that could explain the association between CRP and diminished renal filtration were studied. Also, the association of CRP with early alterations in renal function, such as those evidenced by a relatively high glomerular filtration (‘hyperfiltration’), was examined. CRP levels were divided in quartiles. Subjects with CRP levels within the first quartile were defined as the reference group. Diminished renal filtration and hyperfiltration were defined as a creatinine clearance below or exceeding two times the prediction interval of the age and sex related reference group. Elevated CRP levels were positively associated with cardiovascular and renal risk factors: age, body mass index, blood pressure, serum cholesterol level, smoking, plasma glucose level and elevated urinary albumin excretion. Elevated CRP was positively associated with diminished filtration (OR 1.8 (1.2-2.6)). In multivariate analyses, CRP was independently associated with a diminished filtration (OR 1.9 (1.3-2.9)). Interestingly, CRP was also associated with hyperfiltration (highest quartile: OR 1.7 (95%CI: 1.2-2.5)). However, body mass index accounted for most of the relationship between CRP and hyperfiltration.

Conclusions. As in cardiovascular disease, CRP appears to be a risk marker for renal function loss. The mechanism of this relationship remains to be clarified. However, the association between CRP, body weight, and a relatively elevated creatinine clearance is a hypothesis-generating finding, suggesting that early inflammatory processes related to high body fat may predispose the kidney to glomerular hyperfiltration-related renal function loss.

Introduction

The risk of progressive atherosclerotic cardiovascular disease is determined by a set of classical risk factors such as diabetes, hypertension, hyperlipidemia, smoking, obesity\(^1\) and an elevated urinary albumin excretion.\(^2\) In addition, it has recently been shown that elevated serum levels of C-reactive protein (CRP) are present among subjects at risk for future atherothrombotic disease in the coronary,\(^3,4\) cerebral\(^5\) and peripheral circulation,\(^6\) independently of established cardiovascular risk factors.
risk factors. This led to the use of CRP as an additional marker of progressive cardiovascular disease.\textsuperscript{7}

For progressive renal disease the classical risk factors include diabetes,\textsuperscript{8} hypertension,\textsuperscript{9} hyperlipidemia,\textsuperscript{10} smoking,\textsuperscript{11,12} obesity,\textsuperscript{13} and an elevated urinary albumin excretion.\textsuperscript{8,14} However, the role of low-grade inflammation, as measured by a highly sensitive CRP method, is unknown in renal disease. We hypothesised that CRP could play a role in renal disease in relation to progressive renal function loss.
The mechanism of the relation between CRP and progressive cardiovascular disease is assumed to be based on CRP representing a low-grade inflammatory state either originating in the vasculature such as the endothelium, or a systemic effect on the vasculature due to inflammatory mediators released elsewhere in the body, for example, fat tissue, or due to external stimuli such as smoking. In either mechanism, interplay with such risk factors probably occurs. To our knowledge, no data or hypotheses on a comparable relation between CRP and risk factors are available in progressive renal function loss. CRP could provide a link between risk factors for renal disease and renal function loss, since these conditions are related to elevated CRP levels. On the other hand, CRP could be an independent correlate of renal function loss as in cardiovascular disease. If CRP plays an early role also in risk for progressive kidney disease, one may hypothesise that CRP is related to early indicators for progressive renal function loss. A higher than normal glomerular filtration rate (‘hyperfiltration’) is such an early indicator of susceptibility for renal function loss at least in diabetic subjects (non-insulin and insulin dependent diabetes mellitus) and hypertensive subjects.

To this end, we studied first the relationship between CRP with and diminished glomerular filtration (measured as creatinine clearance) in a large non-diabetic population, and whether this is influenced by other renal risk factors such as hypertension, hyperlipidemia, obesity, plasma glucose and smoking, as well as elevated urinary albumin excretion levels. Second, we investigated whether elevated CRP levels were associated with a relatively high glomerular filtration in this population, and whether this relationship was influenced by renal risk factors.

**Methods**

**Study Population and design**

This cross-sectional study is part of the ongoing PREVEND study (Prevention of Renal and Vascular End stage Disease), conducted in Groningen, the Netherlands. All inhabitants of the city of Groningen between the ages of 28 and 75 year (85,421 subjects) were asked to send in a morning urine sample and to fill out a short questionnaire. A total of 40,856 (47.8%) responded. From this group, 30,890 subjects had a urinary albumin concentration of <10 mg/L and 9,966 subjects had a urinary albumin concentration of ≥10 mg/L in their morning urine sample. After exclusion of subjects with insulin use and pregnant women, all subjects with a urinary albumin excretion ≥10 mg/L (n = 7,768) together with a randomly selected control group with a urinary albumin concentration of <10 mg/L (n = 3,395) were invited for further investigation in an outpatient clinic. Finally, the actual cohort of 8,592 subjects completed
two visits. Measurements performed were extensively described in previous reports. Briefly, both visits consisted of anthropometric measurements, supine blood pressure measurements for ten minutes (Dinamap XL Model 9300 series device), electrocardiograph recordings (Cardio Control, Rijswijk, the Netherlands), two 24 hours urine collections and fasting blood samples.

All participants completed a questionnaire on demographics and cardiovascular and renal history. All participants gave written informed consent. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki.

### Table 1. Associations of C-reactive protein categories with population variables tested for trend.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>1st (0.18-0.54)</th>
<th>2nd (0.54-1.20)</th>
<th>3rd (1.20-2.76)</th>
<th>4th (&gt;2.76)</th>
<th>Uncorrected</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (mg/L)*</td>
<td>0.3 (0.2-0.4)</td>
<td>0.8 (0.7-1.0)</td>
<td>1.9 (1.8-2.3)</td>
<td>7.25 (3.7-83.4)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.4</td>
<td>53.4</td>
<td>53.6</td>
<td>46.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (11)</td>
<td>48 (12)</td>
<td>51 (13)</td>
<td>52 (13)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.6 (3.0)</td>
<td>25.5 (3.4)</td>
<td>26.8 (3.9)</td>
<td>27.8 (4.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>3.0</td>
<td>9.3</td>
<td>19.1</td>
<td>27.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121 (16)</td>
<td>128 (19)</td>
<td>131 (21)</td>
<td>134 (21)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70 (9)</td>
<td>74 (10)</td>
<td>75 (10)</td>
<td>76 (10)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy (%)</td>
<td>3.8</td>
<td>8.4</td>
<td>13.8</td>
<td>17.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>13.7</td>
<td>26.9</td>
<td>36.9</td>
<td>41.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.3 (1.0)</td>
<td>5.6 (1.1)</td>
<td>5.8 (1.2)</td>
<td>5.8 (1.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>3.1</td>
<td>5.6</td>
<td>6.2</td>
<td>7.2</td>
<td>&lt;0.001</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>15.0</td>
<td>24.1</td>
<td>29.4</td>
<td>31.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.5 (0.6)</td>
<td>4.7 (0.6)</td>
<td>4.8 (0.7)</td>
<td>4.9 (0.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>38.4</td>
<td>40.0</td>
<td>47.6</td>
<td>51.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UAE (mg/24h)*</td>
<td>7.8 (5.9-12.0)</td>
<td>8.6 (6.0-14.8)</td>
<td>9.8 (6.4-18.4)</td>
<td>10.4 (6.6-24.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCR (ml/min/1.73 m²)</td>
<td>96 (19)</td>
<td>93 (20)</td>
<td>91 (21)</td>
<td>91 (23)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperfiltration (%)</td>
<td>2.7</td>
<td>3.3</td>
<td>2.6</td>
<td>4.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diminished filtration (%)</td>
<td>2.5</td>
<td>3.0</td>
<td>4.1</td>
<td>4.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP = blood pressure. VAE = UAE CCR = creatinine clearance A) Urinary albumin excretion and CRP are expressed as median with the 25th-75th percentiles, because of skewed distribution. B) Age and gender adjusted P value (for linear trend).
Calculations and definitions

C-reactive protein levels were divided in quartiles (detailed in the Results section). Systolic and diastolic blood pressures were calculated as the mean of the mean of the last two out of ten measurements of both visits. Hypertension was defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg or the use of antihypertensive medication. Body mass index (BMI) was calculated as the ratio between weight and the square of height (kg/m$^2$). Obesity was defined as a BMI $\geq$ 30 kg/m$^2$. Hypercholesterolemia was defined as a serum cholesterol level of $\geq$ 6.5 mmol/L or the use of lipid-lowering therapy. Smoking was defined as current smoking. Urinary albumin excretion rate (UAE) was calculated as the mean albuminuria of two 24 hours collections, and groups were defined as follows: normoalbuminuria (0-15 mg/24h), high-normal albuminuria (15-30 mg/24h), microalbuminuria (30-300 mg/24h) and macroalbuminuria (>300 mg/24h). Body surface area (BSA) was calculated according to DuBois and DuBois. Creatinine clearance was calculated by taking the mean of the two 24 hours urinary creatinine excretions divided by serum creatinine and corrected for BSA (ml/min/1.73 m$^2$). To identify the subjects with a relative low and high creatinine clearance, the following procedure was used: a reference group of subjects were defined with CRP levels within the first quartile of the whole sample. In these subjects, the regression of creatinine clearance by age was calculated separately for men and

Table 2. Odds ratios of diminished filtration according to concentration of C-reactive protein.

<table>
<thead>
<tr>
<th>Quartiles of C-reactive protein (mg/L)</th>
<th>1st (0.54)</th>
<th>2nd (0.54-1.20)</th>
<th>3rd (1.22-2.76)</th>
<th>4th (&gt;2.76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (RR)</td>
<td>1.0</td>
<td>1.3</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.9-1.9</td>
<td>1.1-2.4</td>
<td>1.2-2.6</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>1.2-2.6</td>
<td></td>
</tr>
<tr>
<td>Model 2 (RR)</td>
<td>1.0</td>
<td>1.4</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.9-2.1</td>
<td>1.3-2.8</td>
<td>1.4-3.2</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>NS</td>
<td>&lt;0.005</td>
<td>1.4-3.2</td>
<td></td>
</tr>
<tr>
<td>Model 3 (RR)</td>
<td>1.0</td>
<td>1.3</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8-2.0</td>
<td>1.1-2.5</td>
<td>1.3-2.9</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>1.3-2.9</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: Crude odds ratios. Model 2: Adjusted for age and gender. Model 3: Model 2 + BMI, glucose, systolic and diastolic blood pressure, antihypertensive use, cholesterol, lipid-lowering therapy, albuminuria groups and smoking.
women. Best fitting was reached by including the quadratic term of age into the model, that is, a non-linear decrease in creatinine clearance with increasing age (Figure 1). Renal function abnormalities, such as diminished filtration and hyperfiltration, were defined respectively as a creatinine clearance below (N=244) or exceeding (N=229) the 95% confidence interval (95%CI) of the individual mean (that is, prediction interval) of the age- and sex-related reference group.

Leukocyturia and/or erythrocyturia was defined as either erythrocytes >50/μL, or leukocytes >75/μL, or leukocytes=75/μL and erythrocytes >5/μL in the urine. Diabetes was defined as a fasting plasma glucose level >7.8 mmol/L or a non-fasting plasma glucose level >11.1 mmol/L or the use of antidiabetic medication. Present renal disease was defined as prior dialysis treatment and/or proteinuria as a consequence of renal disease reported by questionnaire.

Laboratory methods

Urinary albumin concentration was determined by nephelometry with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation of <2.2% and <2.6%, respectively. High sensitive CRP was also determined by nephelometry with a threshold of 0.175 mg/L and intra- and interassay

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Table 3. Joint effects of C-reactive protein and risk factors on relative risk of diminished filtration. Odds ratios (95%CI) adjusted for age and gender in models.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Limits</th>
<th>CRP &lt; 75th pct</th>
<th>CRP &gt; 75th pct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>No</td>
<td>1</td>
<td>1.51 (1.10-2.07)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.18 (0.72-1.95)</td>
<td>1.66 (1.03-2.67)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>1</td>
<td>1.56 (1.10-2.22)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.58 (1.09-2.27)</td>
<td>2.03 (1.32-3.14)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>No</td>
<td>1</td>
<td>1.55 (1.11-2.15)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.18 (0.81-1.72)</td>
<td>1.71 (1.08-2.71)</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>1</td>
<td>1.48 (0.97-2.26)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.33 (0.97-1.82)</td>
<td>1.94 (1.34-2.81)</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt; 5.1 mmol/L*</td>
<td>1</td>
<td>1.54 (1.11-2.13)</td>
</tr>
<tr>
<td></td>
<td>≥ 5.1 mmol/L</td>
<td>0.84 (0.56-1.25)</td>
<td>1.27 (0.80-2.03)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>0-15 mg/24h</td>
<td>1</td>
<td>1.72 (1.25-2.36)</td>
</tr>
<tr>
<td></td>
<td>15-30 mg/24h</td>
<td>0.40 (0.20-0.79)</td>
<td>0.39 (0.12-1.25)</td>
</tr>
<tr>
<td></td>
<td>30-300 mg/24h</td>
<td>1.30 (0.79-2.14)</td>
<td>1.36 (0.74-2.52)</td>
</tr>
</tbody>
</table>

* The cut-off point of glucose is based on the 75th percentile.
coefficients of <4.4% and <5.7%, respectively (BNII N, Dade Behring, Marburg, Germany). CRP levels below the detection level threshold were scored as 0.18 mg/L. Plasma glucose, serum cholesterol and serum and urinary creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY). Urinary leukocyte and erythrocyte measurements were done by Nephur-test+leuco sticks (Boehringer Mannheim, Germany).

Statistical analysis

All calculations were performed with SPSS version 10.0 software (SPSS, Chicago, IL). Continuous data are reported as mean ± SD; skewed distributions are presented as the median with the 25th and 75th percentiles. All P values are two-tailed. A P value of <0.05 was considered statistically significant. Differences among CRP quartiles with other variables were assessed by χ² analysis or analysis of variance (ANOVA).

To study the interaction of risk factors on the association between CRP and renal function abnormalities, CRP was dichotomised (low = three lowest quartiles of the distribution versus high = highest quartile) and compared with other risk factors, for instance, obesity (no/yes). When subjects with low CRP and low BMI are used as reference (OR=1), one can estimate the relative importance of high CRP and high BMI as risk factors for either hyperfiltration or diminished filtration by comparing the odds ratios (OR) in high-CRP-low-BMI and low-CRP-high-BMI categories.

Logistic regression analysis was used to test the association among the CRP quartiles with hyperfiltration and diminished filtration, respectively. After entering the four CRP categories into the model, we further adjusted for age and gender. Multivariate analyses included all variables significantly associated with elevated CRP levels according to table 1.

Because 24 hours urine collection might be inaccurate as a result of collection errors, we carried out a specific validation step. Therefore, we analysed our data after excluding subjects who had a difference between their 24 hours creatinine clearance of the first urine collection and of the second urine collection greater than 2x the standard deviation according to the Bland-Altman method.23

Our data were analysed also with the exclusion of subjects with a CRP level >10 mg/L (10 mg/L = 96th percentile), taking into account the possible effect of inflammatory disease on renal function. Secondly, the data were validated by analysing with creatinine clearance not corrected for BSA. Thirdly, subjects with macroalbuminuria were excluded to eliminate the potential for severe and inflammatory primary renal disease. These validation steps did not materially affect the results and, therefore, the results for the total sample population are shown.
Results

From the 8592 subjects studied, the exclusion criteria were subjects with either leukocyturia and/or erythrocyturia (N=451), diabetes mellitus (N=317) and renal disease (N=67). CRP levels could not be determined in 440 subjects due to missing samples. Thus, the final analysis included 7,317 non-diabetic subjects.

The characteristics of our study population according to the four quartiles of CRP are shown in Table 1. The following interquartile ranges were calculated: 1st quartile (0.18-0.54 mg/L), 2nd quartile (0.54-1.20 mg/L), 3rd quartile (1.20-2.76 mg/L) and 4th quartile (>2.76 mg/L). These interquartile ranges of CRP are in agreement with studies investigating its association with cardiovascular disease in apparently healthy men and women. Age, gender, BMI, systolic and diastolic blood pressures, use of antihypertensive medication, cholesterol, lipid-lowering therapy, plasma glucose concentration and smoking showed a significant linear trend in the subsequent quartile of CRP. These differences remained statistically significant after adjusting for age and gender for all variables, except lipid-lowering therapy. Concerning renal characteristics, median levels of urinary albumin excretion significantly increased with increasing CRP quartiles, also after adjusting for age and gender. Furthermore, the mean values of creatinine clearance followed a negative trend in the subsequent CRP quartiles.

The prevalence of diminished filtration as well as hyperfiltration increased with each CRP quartile. Thus, the mean creatinine clearance in the higher CRP quartiles is partly the result of subjects with either hyperfiltration or diminished filtration. Obviously, this mean value does not provide optimal information about the true relationship between CRP and creatinine clearance.

Diminished renal filtration

Univariate and multivariate models (Table 2) showed an elevated risk for diminished renal filtration in the third (crude odds ratio (OR) 1.6, range 1.1-2.4, \(P<0.01\)) and fourth quartiles (crude OR 1.8, range 1.2-2.6, \(P<0.005\)) of CRP, also after adjustment for age and gender. Further adjustment for potential confounders did not markedly attenuate this relationship with an odds ratio of 1.9 (1.3-2.9, \(P<0.005\)) in the highest quartile.

In the lowest three quartiles of CRP, only hypertension was significantly related to diminished filtration, whereas elevated UAE of 15-30 mg/24h was negatively associated (Table 3). As compared to subjects with low CRP, those with elevated CRP levels had an increased risk for diminished filtration, both in the absence and in the presence of other risk factors. This additive effect of elevated CRP was least in UAE groups 15-30 and 30-300 mg/24h with overlap
of confidence intervals. The point estimates of the data did not suggest synergistic effects of CRP and risk factors on the risk for diminished filtration. Thus, elevated CRP levels independently contributed to the risk of diminished renal filtration.

Hyperfiltration

Univariate and multivariate models showed that the highest CRP quartile was associated with an elevated risk for hyperfiltration compared with the reference group (crude OR 1.7, range 1.2-2.5, \( P < 0.002 \)), and also after adjustment for age and gender. However, BMI attributed in such a way to the relationship of CRP with hyperfiltration that the statistical significance was lost (OR 1.4, range 0.9-2.0). Adjustment for other potential confounders further attenuated this relationship to an OR of 1.2 (0.7-1.9).

No effect-modification was observed between risk factors and CRP on the risk of hyperfiltration, that is, no synergistic effects of CRP and risk factors on the risk of hyperfiltration were observed.

Discussion

The relationship between CRP and atherothrombotic cardiovascular disease has been established in a number of cross-sectional\(^{17,25} \) and prospective studies in apparently healthy subjects and in subjects with pre-existent cardiovascular disease.\(^ {4,24,26,27} \) To our knowledge, the current study is the first study to show that low-grade systemic inflammation, as measured by a highly sensitive method, is independently associated with diminished renal filtration in a large non-diabetic population. The fact that CRP was associated with higher than normal creatinine clearances, this relationship being confounded by body mass, suggests that low-grade inflammation may play a role in the susceptibility for, and possibly maintenance of, progressive renal disease.

Data concerning the role of low-grade inflammation on renal function abnormalities is scarce. In a small sample of type 2 diabetic subjects, Weiss \textit{et al} showed that elevated serum levels of neopterin, a monocyte activation marker, and free pentosidine, an advanced glycosylation end-product, predicted doubling of serum creatinine in four years.\(^ {28} \) Furthermore, in a small cross-sectional study of Myrup \textit{et al}, elevated levels of fibrinogen and interleukin-6 were observed in type 1 diabetic subjects with diabetic nephropathy compared to control subjects.\(^ {29} \) In both studies, no significant difference in CRP levels was observed between study groups. However, in both studies CRP levels tended to be higher in those subjects with clinical diabetic nephropathy. This result
is consistent with our finding of an association of high levels of CRP with diminished filtration. Reasons for our finding of significant associations could be the following. First, our population sample is larger, which yields increased statistical power. Second, we used a highly sensitive CRP assay in contrast with previous studies. These sensitive assays have high analytical precision and determine CRP levels well within the normal range. Therefore, the increased variance of the CRP data also yields more statistical power to detect small, but nonetheless important associations.

In line with our data is the study of Panichi et al., who showed that CRP and interleukin-6 levels were inversely related with creatinine clearance in chronic pre-dialysis patients. How should we interpret the observed associations between elevated CRP levels, and cardiovascular and renal risk factors that we found? Systemic inflammation at a low-grade level is held partly responsible for an excess of atherosclerotic vascular disease. CRP is a very sensitive marker of systemic inflammation. It is a major acute-phase protein, which production by the (normal) liver is tightly regulated. In the presence of tissue injury or trauma, CRP is quickly up-regulated, mainly in response to circulating interleukin-6. Important sources of cytokine production are adipose tissue and smoking. Increased fat mass is associated with an increased endogenous production of pro-inflammatory cytokines by adipocytes, including interleukin-6. The link between the acute-phase response and obesity is also observed at the epidemiological level. Obesity, a strong correlate of type 2 diabetes, is more and more believed to predict end-stage renal disease and the development of overt proteinuria. Smoking adversely affects progression of renal disease and the development of albuminuria in diabetic subjects and non-diabetic subjects. Elevated cytokine levels are also associated with the insulin resistance syndrome and associated features like hypertension and dyslipidemia. Hypertension and hyperlipidemia are equally important in renal disease progression. In our study, CRP was positively related to classical cardiovascular and renal risk factors. Interestingly, these possible confounders could not account for the observed link between inflammation and diminished filtration. Thus, CRP is independently associated with an impaired filtration as it is also independently associated with cardiovascular disease in general.

The relationship between elevated CRP levels and hyperfiltration, however, largely disappeared after adjustment for body mass index. There is a close relationship between obesity and renal hyperfiltration. Potential mechanisms underlying this association are numerous and include plasma volume expansion as a feature of the insulin resistance syndrome. The virtual disappearance of the association between CRP and renal hyperfiltration after adjustment for obesity is in accordance with the previously described link between obesity and the acute-phase response. However, this cross-sectional study cannot assess whether the observed relationship of CRP with hyperfiltration is an epiphenomenon of the obese state or whether other processes
related to obesity are responsible. For example, insulin resistance, as a common link, is tightly associated with obesity and renal hyperfiltration, as it is with a systemic low-grade inflammatory response.  

How should the data be interpreted on the association between CRP and diminished renal filtration? First, other factors could provide an alternative explanation. Atherosclerotic disease could be one of those factors, as elevated cytokine and CRP levels are associated with (subclinical) atherosclerotic disease and atherosclerotic disease activity. In fact, atherosclerosis is an inflammatory disease itself. It may be that arteriolosclerosis in the renal vasculature is responsible for the observed relationship. Other important mediators of vascular inflammation also may be responsible for the observed relationship between CRP and diminished filtration, like atherogenic infections, endothelial dysfunction and others. For example, Rassu et al have demonstrated the presence of Chlamydia pneumoniae in various atherosclerotic arteries including the renal artery. Unfortunately, the majority of available literature concerning inflammation and vascular disease has focused on the coronary circulation.

Second, it might be that CRP is a marker of local inflammatory response in the kidney. Because of the cross-sectional design of this study, one has to consider the possibility that renal function loss itself is an inflammatory condition. It is well known that gross albuminuria (>300 mg/24h) is an important mediator of interstitial inflammation. We showed that the presence of macroalbuminuria and minor rises in urinary albumin excretion did not attenuate or modify the association of CRP with diminished filtration. Thus, our data do not support that CRP is a marker of albuminuria-induced renal injury. Other studies support that CRP, as a causative agent, could be involved in local renal inflammatory pathways. Jabs et al showed that CRP is expressed by renal tubular cells after stimulation with tumour necrosis factor-α or interleukin-1α in vivo, and in acutely rejected kidney allografts (abstract A-3293; J Am Soc Nephrol, Volume 12, September 2001). They proposed that the acute-phase response not merely represents a systemic inflammatory reaction, but probably is part of and acts as a local inflammatory pathway in the kidney. Also, it has been reported that CRP localises in the kidney in various glomerular diseases in children.

A third explanation for the association between CRP and diminished filtration could be the result of a decreased renal clearance of CRP. However, the major determinant of serum CRP concentration is its rate of synthesis by the (normal) liver, and not excretion through the kidney. In patients with severe renal disease and in healthy subjects, CRP is excreted in negligible amounts in the urine. CRP can be filtrated, but like other proteins it is reabsorbed by the tubulus. Thus, it is very unlikely, though not excluded on these grounds, that the relationship between CRP and diminished filtration is explained just by a decrease in plasma clearance of CRP.
A fourth – and in our opinion the most likely – explanation of the association between CRP and diminished filtration is given by our finding of a relationship between CRP and hyperfiltration and body weight. Early inflammatory processes induced by overweight and/or smoking could damage the systemic and renal vasculature, in the absence of any renal function abnormality. In time, this could render the kidney more sensitive to other damaging insults occurring in life. The result of this could be the observed cross-sectional finding of CRP being related to both diminished and high filtration.

Another marker of cardiovascular and renal disease, namely elevated urinary albumin levels, was associated with CRP as shown previously in diabetic and non-diabetic subjects. Both markers are associated with almost all previously mentioned risk factors, so they may represent the same disease process. On the other hand, both CRP and microalbuminuria (UAE 30-300 mg/24h) have been proposed as independent predictors of cardiovascular disease. Our study suggests that CRP and elevated urinary albumin excretion are also independent and different correlates of renal function abnormalities as well.

C-reactive protein is not only important because it has provided insight into the pathophysiology of cardiovascular disease, it may serve as an early risk marker. Investigators have begun seeking therapies that may lower CRP concentrations and, presumably, cardiovascular disease risk. Several agents, equally important in renal disease, have the potential to diminish cardiovascular disease risk by modification of the (acute-phase) inflammatory response. The use of these agents could also be beneficial for renoprotection, which has not yet been studied.

Our study has several shortcomings. It is cross-sectional in design and, therefore, a hypothesis generating study. Furthermore, the definitions of diminished renal filtration and renal hyperfiltration were arbitrarily chosen, and calculated on a statistical basis rather than being measured in a more experimental design. In this epidemiological setting, however, we believe that these definitions are the best approximate measure of diminished filtration and hyperfiltration available. A similar critique could be made on the choice of CRP classes. However, changing the boundaries of our definitions on normal renal function or CRP did not alter the basic findings of our study. We defined albuminuria levels as the mean albumin excretion of two 24 hours urine collections, whereas the presence of microalbuminuria in at least two out of three (morning) samples is usually recommended in subjects with type 1 and 2 diabetes. Others propose the performance of a second urine sample when the first sample is positive for microalbuminuria in diabetic as well as non-diabetic individuals. The lower cut-off level of albuminuria is still under debate, since even smaller amounts of albumin in the urine are associated with cardiovascular risk and risk factors in non-diabetic subjects. We have only
misclassified 8% of all subjects having microalbuminuria according to our calculation compared to subjects having microalbuminuria according to the definitions mentioned above (data not shown).

In conclusion, as in cardiovascular disease, CRP appears to be a risk marker for renal function loss. The mechanism of this relationship remains to be clarified. However, the association between CRP, body weight, and a relatively elevated creatinine clearance is a hypothesis-generating finding. Early inflammatory processes related to high body fat may predispose the kidney to glomerular hyperfiltration-related renal function loss.
References


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