



Article scientifique

Article

2012

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Not All Inflammatory Markers Are Linked to Kidney Function: Results from a Population-Based Study

Pruijm^a, Menno; Ponte, Belen; Vollenweider, Peter; Mooser, Vincent; Paccaud, Fred; Waeber, Gérard; Marques-Vidal, Pedro; Burnier, Michel; Bochud, Murielle

How to cite

PRUIJM^a, Menno et al. Not All Inflammatory Markers Are Linked to Kidney Function: Results from a Population-Based Study. In: American journal of nephrology, 2012, vol. 35, n° 3, p. 288–294. doi: 10.1159/000335934

This publication URL: <https://archive-ouverte.unige.ch/unige:90696>

Publication DOI: [10.1159/000335934](https://doi.org/10.1159/000335934)

Not All Inflammatory Markers Are Linked to Kidney Function: Results from a Population-Based Study

Menno Pruijm^a Belén Ponte^e Peter Vollenweider^b Vincent Mooser^c
Fred Paccaud^d Gérard Waeber^b Pedro Marques-Vidal^d Michel Burniera^a
Murielle Bochud^d

Departments of ^aNephrology, ^bInternal Medicine, ^cLaboratory Medicine, and ^dInstitute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne (CHUV), Lausanne, and ^eDepartment of Nephrology, University Hospital of Geneva (HUGE), Geneva, Switzerland

Key Words

Interleukin-1 β • Interleukin-6 • Tumor necrosis factor- α • C-reactive protein • Chronic kidney disease • Biomarkers • Microalbuminuria

Abstract

Background: Several studies have reported increased levels of inflammatory biomarkers in chronic kidney disease (CKD), but data from the general population are sparse. In this study, we assessed levels of the inflammatory markers C-reactive protein (hsCRP), tumor necrosis factor α (TNF- α), interleukin (IL)-1 β and IL-6 across all ranges of renal function. **Methods:** We conducted a cross-sectional study in a random sample of 6,184 Caucasian subjects aged 35–75 years in Lausanne, Switzerland. Serum levels of hsCRP, TNF- α , IL-6, and IL-1 β were measured in 6,067 participants (98.1%); serum creatinine-based estimated glomerular filtration rate (eGFR_{creat}, CKD-EPI formula) was used to assess renal function, and albumin/creatinine ratio on spot morning urine to assess microalbuminuria (MAU). **Results:** Higher serum levels of IL-6, TNF- α and hsCRP and lower levels of IL-1 β were associated with a lower renal function, CKD (eGFR_{creat} <60 ml/min/1.73 m²; n = 283), and MAU (n = 583). In multivariate lin-

ear regression analysis adjusted for age, sex, hypertension, smoking, diabetes, body mass index, lipids, antihypertensive and hypolipemic therapy, only log-transformed TNF- α remained independently associated with lower renal function (β -0.54 \pm 0.19). In multivariate logistic regression analysis, higher TNF- α levels were associated with CKD (OR 1.17; 95% CI 1.01–1.35), whereas higher levels of IL-6 (OR 1.09; 95% CI 1.02–1.16) and hsCRP (OR 1.21; 95% CI 1.10–1.32) were associated with MAU. **Conclusion:** We did not confirm a significant association between renal function and IL-6, IL-1 β and hsCRP in the general population. However, our results demonstrate a significant association between TNF- α and renal function, suggesting a potential link between inflammation and the development of CKD. These data also confirm the association between MAU and inflammation.

Copyright © 2012 S. Karger AG, Basel

Introduction

The incidence and prevalence of chronic kidney disease (CKD) – a disease state with high morbidity and mortality – is rising, and CKD has become a major public health problem [1]. The pathophysiology of CKD is in-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 S. Karger AG, Basel
0250–8095/12/0353–0288\$38.00/0

Accessible online at:
www.karger.com/ajn

Prof. Murielle Bochud
Service de Néphrologie
Rue du Bugnon 17
CH–1011 Lausanne (Switzerland)
Tel. +41 21 314 1154, E-Mail murielle.bochud@chuv.ch

completely understood. Chronic low-grade inflammation is increasingly considered to be one of the main pathways leading to the development and progression of CKD [2]. Over the last decade, several studies reported elevated concentrations of ultrasensitive C-reactive protein (hsCRP), tumor necrosis factor- α (TNF- α) and interleukin (IL)-6 in CKD patients as compared to healthy controls, yet associations varied across studies [3–9]. This is partly explained by the fact that some data were derived from selected groups (elderly, high cardiovascular risk groups), while data from the general population remain sparse [3, 8, 9]. Besides, early markers of renal dysfunction such as microalbuminuria (MAU) and/or glomerular hyperfiltration (GHF) were often not assessed in these studies. A better knowledge of the association of proinflammatory biomarkers across all ranges of kidney function and MAU in a general population may help to unravel a potential role in this association.

The aim of this study was to analyze the associations of TNF- α , IL-1 β , IL-6, and hsCRP levels with all levels of kidney function and MAU in the general adult population.

Subjects and Methods

Recruitment

The CoLaus Study is a cross-sectional study aimed at assessing the prevalence and deciphering the molecular determinants of cardiovascular risk factors in the Caucasian population of Lausanne, a town of 117,161 inhabitants in Switzerland. The sampling procedure of the CoLaus Study has been described previously [10]. Briefly, a simple, non-stratified random sampling of 19,830 participants, corresponding to 35% of the source population, was drawn, and a letter inviting to participate was sent to these individuals. Eventually, 6,184 participants were included in the CoLaus Study cohort, after having excluded the non-responders and non-eligible people. Inclusion criteria included a written informed consent, age between 35 and 75 years and Caucasian origin. The participation rate was 41%. The CoLaus Study was approved by the Institutional Ethics Committee of the University of Lausanne. Recruitment began in June 2003 and ended in May 2006.

All participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast. They were asked to continue their usual medication intake. Data were collected by trained field interviewers in a single visit lasting about 60 min.

The examination included a detailed questionnaire, anthropometric measures and laboratory testing. Smoking was defined as present if the participant reported to be current smoker at the time of examination. Blood pressure was measured three times on the left arm using a clinically validated automatic oscillometric device (Omron HEM-907; Omron, Matsusaka, Japan) after a period of 10 min rest in the sitting position and using the appropri-

ate cuff size. The average of the second and third values was used for analysis. Hypertension was defined as mean systolic blood pressure (SBP) ≥ 140 mm Hg and/or mean diastolic blood pressure (DBP) ≥ 90 mm Hg or presence of antihypertensive medication. Body weight was measured in kilograms to the nearest 100 g using a Seca® scale, which was calibrated regularly. Height was measured to the nearest 5 mm using a Seca height gauge. Fat mass was assessed by electrical bioimpedance using the Bodystat® 1500 analyzer (Douglas, Isle of Man, British Isles). A diagnosis of diabetes was made if fasting plasma glucose was ≥ 7.0 mmol/l and/or presence of oral hypoglycemic or insulin treatment.

Biological Data

Venous blood samples were drawn after an overnight fast. Creatinine was measured using Jaffe kinetic compensated method (Roche Diagnostics, Switzerland, intra-assay variability 0.7–2.9%). Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI formula. CKD was defined as eGFR ≤ 60 ml/min/1.73 m² [9]. GHF was defined as eGFR ≥ 140 ml/min [14]. Plasma cytokine levels were measured using a multiplexed particle-based flow cytometric cytokine assay, as previously described [11]. Milliplex kits were purchased from Millipore (Zug, Switzerland). The analysis was conducted using a conventional flow cytometer (FC500 MPL; Beckman Coulter, Nyon, Switzerland). Lower detection limits for IL-1 β , IL-6 and TNF- α were 0.2 pg/ml. Intra- and interassay coefficients of variation were 15 and 16.7% for IL-1 β , 16.9 and 16.1% for IL-6 and 12.5 and 13.5% for TNF- α , respectively. The following results were found for the reproducibility of the duplicate cytokine assessments (n = 80): Spearman rank correlations for IL-1 β , IL-6 and TNF- α were 0.914, 0.963 and 0.891, respectively; Lin's correlation coefficients were 0.969, 0.971 and 0.945, respectively, and intra-class correlation coefficients were 0.970, 0.972 and 0.946 (all p < 0.005), indicating a good reproducibility.

MAU adjusted for creatinine [urinary albumin/creatinine ratio (UACR)] was measured on spot morning urine, using quantitative immunonephelometry; to define MAU, a gender-related cut-off value was used (UACR ≥ 2.5 mg/mmol for men, and ≥ 3.5 mg/mmol for women) [12].

Statistical Analysis

Statistical analysis was conducted using STATA 11.0 (Stata-Corp, College Station, Tex., USA). Quantitative variables were expressed as mean \pm SD, and qualitative variables as number of participants and (percentage). Cytokines were presented as median and interquartile range of measured values and by percentage of values within each distribution quintile. When performing quantitative analyses, the value of 0.133 pg/ml was attributed to undetectable values of IL-1 β , TNF- α and IL-6, which corresponds to two thirds of the lower detection limit [13]. In separate analyses, undetectable values of cytokines were included in the first quartile. Multivariable logistic regression, adjusting for age, sex, smoking, body mass index (BMI), waist circumference, diabetes, hypertension, HDL and LDL cholesterol, lipid lowering and antihypertensive treatment, was used to determine the independent association of each log-transformed biomarker with CKD. In a separate analysis, further adjustment was performed for the other inflammatory biomarkers. Similarly, we used multivariable linear regression to analyze the associations of the log-transformed cytokines (independent variable of interest) with

Table 1. Baseline characteristics according to the presence of CKD

	No CKD	CKD
Participants	5,784 (95.3)	283 (4.7)
Age, years	52.5 ± 10.5	64.9 ± 8.9
Female, %	52.2	60.4
Smoking, %	27.6	14.5
Antihypertensive drug, %	16.9	45.6
Lipid treatment, %	10.8	26.5
Diabetes, %	6.3	13.8
Waist circumference, cm	89.1 ± 13.3	93.5 ± 14.2
SBP, mm Hg	128 ± 11	136 ± 21
DBP, mm Hg	79.3 ± 10.8	80.2 ± 11.4
Creatinine, µmol/l	78.2 ± 13.2	118.3 ± 71.2
CKD-EPI eGFR, ml/min/1.73 m ²	87.2 ± 13.6	51.9 ± 8.8
BMI	25.8 ± 4.5	27.1 ± 4.7
MAU, %	8.8	21.9
hsCRP, mg/l	1.3 (0.6–2.6)	1.6 (0.8–3.1)
TNF-α, pg/ml	2.84 (1.8–4.5)	3.72 (2.5–5.4)
IL-1β, pg/ml	0.40 (0.1–1.8)	0.24 (0.1–1.1)
IL-6, pg/ml	1.31 (0.6–3.2)	1.52 (0.8–3.3)

Results are expressed as n (%), mean ± SD or medians (interquartile range), as appropriate.

kidney function (eGFR, dependent variable) or MAU (dependent variable).

Results of the logistic multivariate analysis are presented as odds ratio (OR) and 95% confidence interval (95% CI), and of linear regression as β -coefficients (β) and their 95% CIs. Statistical significance was considered for a two-sided $p < 0.05$.

Results

Clinical Characteristics

Of the 6,184 initial participants, 6,067 (98.1%) had their cytokines assessed. Their clinical characteristics, according to the presence of hypertension and/or CKD, are summarized in table 1. Overall, mean age was 53.1 ± 11 years (range 35–75), 52.5% were women, 27% active smokers, 9.6% had MAU, 6.6% suffered from diabetes, 1.8% from coronary artery disease, 1.1% had a history of stroke, and 35.9% had hypertension. Of the 283 subjects with CKD, 6 (2.1%) had an eGFR between 15 and 29 ml/min/1.73 m² (CKD stage IV), and 3 (1.0%) an eGFR <15 ml/min/1.73 m². Subjects with CKD had a history of stroke in 2.1% and of coronary artery disease in 4.3% of cases; 14.5% were treated with ACE inhibitors, 17.0% with angiotensin receptor blockers, 19.8% with diuretics, and 17.3% with aspirin.

Distribution of Cytokine Levels

Among the 6,067 participants, 2,280 (37.6%), 446 (7.4%) and 39 (0.6%) had IL-1β, IL-6 and TNF-α levels below detection limits, respectively. The distribution of hsCRP, IL-1β, IL-6 and TNF-α plasma values across levels of kidney function are shown in table 2. Plasma concentrations of hsCRP, TNF-α and IL-6 were higher at lower eGFR, while IL-1β concentrations were lower.

Relations between Inflammatory Markers and Kidney Function

In adjusted linear regression analysis analyzing eGFR as a continuous variable, TNF-α was associated negatively with eGFR [coefficient $\beta = -0.54$ (95% CI $-0.91; -0.16$), $p = 0.004$], whereas the associations between hsCRP [$\beta = 0.10$ ($-0.24; 0.43$), $p = 0.57$], IL-6 [$\beta = -0.08$ ($-0.30; 0.15$), $p = 0.51$] and IL-1β [$\beta = 0.04$ ($-0.17; 0.24$), $p = 0.73$] with eGFR were no longer significant. Results were similar in men and women. In sensitivity analyses, excluding subjects with inflammatory markers ≥ 95 th percentile, similar results were found.

Results of multivariable logistic regression analysis, with CKD as dichotomized dependent variable [<60 (n = 283) or ≥ 60 ml/min/1.73 m² (n = 589)] are shown in table 3A. log-transformed TNF-α was independently associated with CKD (OR 1.17; 1.01–1.35; $p = 0.027$), whereas IL-1β, IL-6, and hsCRP were not (table 3A). Concurrent adjustment for IL-1β, IL-6 and/or hsCRP did not alter the association between TNF-α and CKD. Broadly, we found similar results with the MDRD formula and with CKD-EPI, although the association of TNF-α with eGFR_{MDRD} was slightly weaker than with eGFR_{CKD-EPI}: adjusted OR 1.13 (1.01–1.30) versus 1.17 (1.01–1.35), respectively.

Associations between inflammatory markers and GHF were analyzed separately. For this analysis, GHF was defined as eGFR ≥ 140 ml/min [14]. Levels of hsCRP and IL-6 tended to be higher in the GHF group as compared to the groups with eGFR between 60 and 139 ml/min, whereas levels of IL-1β were slightly lower (fig. 1). In logistic regression analysis, adjusted for age and sex and with the group of eGFR 60–139 ml/min as base outcome, hsCRP (OR 2.07; 95% CI 1.55–2.76, $p < 0.001$) and IL-6 (OR 1.24; 1.02–1.49; $p = 0.027$) were positively associated with GHF. In multivariable logistic regression analysis, with a further adjustment for BMI, smoking and diabetes, IL-6 levels (OR 1.09; 0.85–1.38; $p = 0.66$) and hsCRP levels (OR 1.34; 0.91–1.97; $p = 0.13$) were no longer associated with GHF.

Table 2. Plasma levels of hsCRP, IL-1 β , IL-6, and TNF- α across quintiles of kidney function

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p trend
eGFR, ml/min/1.73 m ²	66 (60–70)	78 (75–80)	86 (84–88)	95 (92–97)	106 (102–109)	<0.001
hsCRP, mg/l	1.50 (0.7–2.9)	1.2 (0.6–2.5)	1.2 (0.6–3.4)	1.2 (0.6–3.2)	1.1 (0.5–2.6)	<0.001
IL-6, pg/ml	1.37 (0.7–3.1)	1.33 (0.6–3.2)	1.37 (2.7)	1.23 (0.6–3.2)	1.30 (0.5–3.4)	0.04
IL-1 β , pg/ml	0.29 (0.1–1.3)	0.45 (0.1–1.8)	0.39 (0.1–1.9)	0.40 (0.1–1.8)	0.47 (0.1–2.0)	<0.001
TNF- α , pg/ml	3.11 (2.0–4.9)	2.96 (1.9–4.5)	2.98 (1.8–4.5)	2.67 (1.7–4.3)	2.67 (1.7–4.4)	<0.001

Results are expressed as medians (interquartile range).

Relationship between Inflammatory Markers and Microalbuminuria

The distributions of hsCRP, IL-1 β , IL-6 and TNF- α plasma values across quintiles of UACR are shown in table 4. Plasma concentrations of hsCRP, TNF- α and IL-6 were higher at higher UACR levels, while IL-1 β concentrations were lower.

In logistic regression analysis adjusted for age and sex, with MAU as dichotomized dependent variable, including 583 participants (9.4%) with and 5,484 participants without MAU, log-transformed hsCRP, TNF- α and IL-6 were associated with MAU (table 3B), whereas IL-1 β was not. In multivariable logistic regression analysis adjusting for all confounders including kidney function, log-transformed hsCRP and IL-6 remained associated with MAU, whereas the slight association between MAU and TNF- α was no longer significant after correction for BMI or fat mass (online suppl. table 1, www.karger.com/doi/10.1159/000335934). Similar trends were observed when analyzing UACR as continuous variable: in adjusted linear regression analysis, hsCRP (β = 0.21; 0.03–0.38; p = 0.02) and IL-6 (β = 0.17; 0.05–0.29; p = 0.005) were associated positively with UACR; TNF- α and IL-1 β were no longer significantly associated with UACR in adjusted linear regression analysis.

Discussion

The main findings of this population-based study were that: (1) TNF- α levels are associated negatively with renal function, independently of major confounding factors; (2) no such association was found for hsCRP, IL-1 β and IL-6 levels, and (3) plasma levels of IL-6 and hsCRP were positively associated with MAU, whereas IL-1 β and TNF- α were not. This is, to the best of our knowledge, one of the largest community-based studies so far that

Table 3. Multivariable logistic regression using CKD (A) or MAU (B) as the dependent variable

Variables	Age- and sex-adjusted	Fully adjusted
A. CKD		
hsCRP, mg/l	1.05 (0.94–1.19)	Fully adjusted ¹ 1.01 (0.88–1.14)
IL-1 β , pg/ml	0.96 (0.89–1.04)	0.97 (0.89–1.05)
IL-6, pg/ml	1.05 (0.96–1.15)	1.04 (0.95–1.14)
TNF- α , pg/ml	1.17 (1.02–1.35)*	1.17 (1.01–1.35)*
B. MAU		
hsCRP, mg/l	1.30 (1.20–1.41)*	Fully adjusted ² 1.21 (1.10–1.32)*
IL-1 β , pg/ml	0.97 (0.92–1.02)	0.98 (0.93–1.04)
IL-6, pg/ml	1.11 (1.04–1.18)*	1.09 (1.02–1.16)*
TNF- α , pg/ml	1.12 (1.02–1.24)*	1.09 (0.98–1.20)

Results are expressed as OR (95% CI) per unit increase of variable. CKD defined as eGFR <60 ml/min/1.73 m².

Statistical analysis by logistic regression. * p < 0.05.

¹ Adjusted for age, sex, smoking, BMI, waist circumference, diabetes, hypertension, HDL and LDL cholesterol, lipid-lowering and antihypertensive treatment.

² Adjusted for the same confounders, plus eGFR according to the CKD-EPI formula.

has examined the relationship between biomarkers of inflammation and kidney function in a Caucasian population, across a large range of age, socio-economical background and health status.

The lack of association between kidney function and hsCRP, IL-1 β and IL-6 contrasts with previous population-based studies that reported strong associations between inflammatory markers and kidney function [3, 4, 6]. Nevertheless, the negative findings in this study are in line with some longitudinal studies, which did not find any association between hsCRP, IL-6 and the risk for the development and/or progression of CKD [15, 16]. There

Fig. 1. Levels of hsCRP, TNF- α , IL-6 and IL-1 β in subjects with GHF eGFR (≥ 140 ml/min according to CKD-EPI formula; $n = 52$) as compared to eGFRs between 90 and 140 ml/min ($n = 3,007$), 60 and 90 ml/min ($n = 2,725$) and <60 ml/min ($n = 283$).

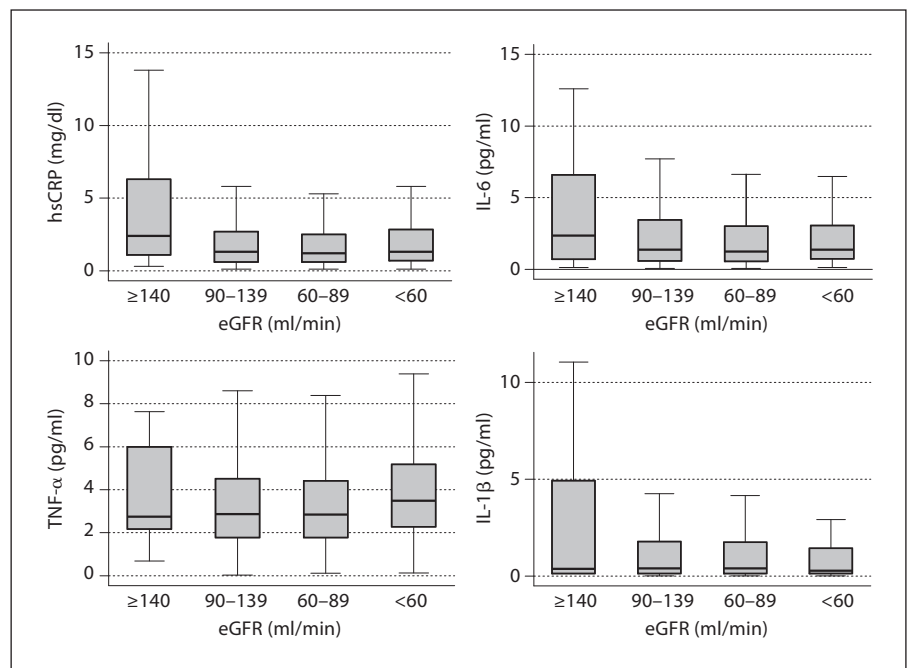


Table 4. Plasma levels of hsCRP, IL-1 β , IL-6, and TNF- α across quintiles of UACR

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p trend
UACR, mg/mmol	0.28 (0.2–0.3)	0.42 (0.4–0.5)	0.58 (0.5–0.6)	0.88 (0.78–1.03)	2.21 (1.6–4.0)	<0.001
eGFR, ml/min/1.73 m ²	85 (75–95)	87 (77–96)	88 (76–97)	87 (76–97)	85 (72–97)	0.89
hsCRP, mg/l	1.00 (0.6–2.3)	1.10 (0.6–2.4)	1.20 (0.6–2.5)	1.3 (0.6–2.8)	1.70 (0.8–3.4)	<0.001
IL-6, pg/ml	1.33 (0.6–3.1)	1.18 (0.5–3.0)	1.19 (0.5–3.0)	1.25 (0.6–3.3)	1.60 (0.7–3.8)	<0.001
IL-1 β , pg/ml	0.50 (0.1–2.1)	0.36 (0.1–1.7)	0.40 (0.1–1.8)	0.44 (0.1–1.8)	0.33 (0.1–1.6)	0.02
TNF- α , pg/ml	2.91 (1.9–4.5)	2.82 (1.8–4.5)	2.82 (1.8–4.5)	2.76 (1.7–4.4)	3.11 (1.9–4.8)	0.47

Results are expressed as medians (interquartile range).

are several putative explanations for these discrepancies. First, different parameters (creatinine, cystatin C) and different formulas (MDRD, Cockcroft-Gault) were used to assess eGFR; as in our study, this might have changed the (strength of) cytokine-kidney function associations. Second, sample size tended to be smaller. Third, the number of participants with CKD was rather low in this study, and only a minority of them had eGFR values <30 ml/min/1.73 m². Further, different laboratory techniques were used for cytokine assessment, with differing lower detection limits (ranging from 0.15 to 10 pg/ml) [17, 18]. Finally, a rather high proportion of participants had undetectable (<0.2 pg/ml) levels of IL-1 β , thus limiting the interpretation of the results for this cytokine. In this

study, an arbitrary value of 0.133 (two thirds of the lower detection limit) was attributed to subjects with undetectable levels [13], while in other studies, the issue of undetectable values has not always been clearly discussed, thus further compromising between-study comparisons. Taken together, a larger uniformity in eGFR assessment and in laboratory techniques used for cytokine dosing might improve between-study comparisons and our ability to understand the relationships between serum levels of inflammatory cytokines and associated disease states.

Of interest, higher TNF- α concentrations were associated with lower eGFR, suggesting that the TNF- α pathway is implicated in the pathophysiology of CKD. Indeed, in experimental models, TNF- α causes direct glomerular

injury, by inducing expression of adhesion molecules, promoting the influx of monocytes and macrophages, and by stimulating the proliferation of mesangial cells, thus leading to glomerulosclerosis and interstitial fibrosis [19].

In human studies, the reported associations between TNF- α and kidney function were in general stronger than associations between kidney function and other biomarkers, including hsCRP [3, 9]. As such, this study confirms previous findings in a slightly younger population. Moreover, a post-hoc analysis of the CARE study found that high levels of TNF- α were associated with faster kidney function decline [7].

In this study, serum levels of IL-6 and hsCRP were positively associated with MAU, independently of kidney function (eGFR). MAU is generally considered as a marker of vascular inflammation and/or kidney damage [20], and the associations found between inflammatory markers and MAU are in line with this hypothesis. Most previous studies reporting associations between cytokines and MAU were performed in diabetics [21], or focused on hsCRP only [22]. To the best of our knowledge, only two studies – the Framingham Offspring cohort and the MESA (Multi-Ethnic Study on Atherosclerosis) study – assessed associations between several inflammatory markers and MAU in the general population [3, 23]. In the Framingham Study, serum levels of IL-6 and TNF- α were associated independently with MAU, whereas hsCRP was not; in the MESA study, hsCRP and pentraxin-3 were associated with MAU in univariate, but not in multivariate analyses. In our study, the association between serum levels of TNF- α and MAU was weak, and no longer significant upon adjustment for BMI and more precisely fat mass. Adipose tissue is the main source of TNF- α , and obesity is linked to MAU, which might partly explain the influence of BMI on the association between MAU and TNF- α [24].

It is actually unclear to what extent the high levels of cytokines reported in CKD are the result of increased production of cytokines, decreased renal clearance, or both [2]. Of interest, the distribution of cytokine levels across different stages of eGFR observed in this study was somewhat U-shaped, with higher concentrations in participants with eGFR <60 ml/min/1.73 m² or with GHF. GHF is considered by some authors as a preliminary stage of CKD, especially in the context of diabetes [25]. The observed U-shaped distribution could thus indicate that high cytokine levels in early CKD are merely the result of an increased production. As for TNF- α and MAU, the associations between hsCRP, IL-6 and GHF disappeared

after adjustment for BMI, suggesting that obesity leads to an inflammatory state, GHF, or both. This hypothesis is in line with cross-sectional data from the PREVENT study, which reported an association between CRP and GHF [8]. However, the number of subjects with GHF in this study was too low to draw definite conclusions. Besides, GHF might have been a transient state in these individuals, due to for example subclinical infection.

The strengths of this study include the large sample size, the availability of detailed information on numerous possible confounders, including drugs capable of lowering plasma levels of inflammatory markers, and the high quality and reproducibility of cytokine assessments. The limitations of this study are its cross-sectional nature, which limits causal inferences and the relatively high number of undetectable values for IL-1 β , which hampered the analysis of this cytokine in continuous models. Besides, serum creatinine was used for kidney function estimations, and cystatin C might be a more sensitive marker in this relatively healthy population. Finally, we cannot exclude that some of the higher cytokine levels were explained by (subclinical) infections, although participants were instructed to postpone their appointment in case of (suspected) infection.

Conclusion

This study underlines the possibly important role of the TNF- α pathway in kidney disease, which merits further study in experimental models, and confirms the association between inflammation and MAU. The absence of an association of the other inflammatory markers with renal function suggests either that these markers do not play a major role in the development and progression of CKD in the general population, or that actual dosing techniques are not refined enough to detect small differences in concentrations in a relatively healthy population. More longitudinal population-based studies are needed to assess the role of cytokines in CKD, and efforts should be made to increase uniformity in dosing techniques of cytokines and kidney function measurements.

Acknowledgements

The CoLaus Study was supported by research grants from the Swiss National Science Foundation (grant No. 33CSGO-122661), from GlaxoSmithKline and the Faculty of Biology and Medicine of Lausanne, Switzerland. The authors also express their gratitude to the participants in the Lausanne CoLaus Study and to the in-

investigators who have contributed to the recruitment, in particular Yolande Barreau, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection. M. Bochud is supported by the Swiss School of Public Health Plus (SSPH+). M.P. and B.P. are supported by the Swiss National Science Foundation (SPUM): FN 33CM30-124087.

Disclosure Statement

P.V. and G.W. received grant money from GlaxoSmithKline to build the CoLaus Study.

References

- Glasscock RJ: The rising tide of end-stage renal disease: what can be done? *Clin Exp Nephrol* 2004;8:291–296.
- Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z: Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol* 2008;3:505–521.
- Upadhyay A, Larson MG, Guo CY, Vasan RS, Lipinska I, O'Donnell CJ, Kathiresan S, Meigs JB, Keaney JF Jr, Rong J, Benjamin EJ, Fox CS: Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. *Nephrol Dial Transplant* 2011;26:920–926.
- Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 2003;107:87–92.
- Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ, Chaves P, Furberg C, Kuller L, Newman A: Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. *J Am Soc Nephrol* 2004;15:3184–3191.
- Keller CR, Odden MC, Fried LF, Newman AB, Angleman S, Green CA, Cummings SR, Harris TB, Shlipak MG: Kidney function and markers of inflammation in elderly persons without chronic kidney disease: the health, aging, and body composition study. *Kidney Int* 2007;71:239–244.
- Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G: Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int* 2005;68:237–245.
- Staveland EM, Hillege HL, Bakker SJ, Gans RO, de Jong PE, de ZD: C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int* 2003;63:654–661.
- Keller C, Katz R, Cushman M, Fried LF, Shlipak M: Association of kidney function with inflammatory and procoagulant markers in a diverse cohort: a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis (MESA). *BMC Nephrol* 2008;9:9.
- Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P: The CoLaus Study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008;8:6.
- Marques-Vidal P, Bochud M, Bastardot F, Luscher T, Ferrero F, Gaspoz JM, Paccaud F, Urwyler A, von Känel R, Hock C, Waeber G, Preisig M, Vollenweider P: Levels and determinants of inflammatory biomarkers in a Swiss population-based sample (CoLaus Study). *PLoS One* 2011;6:e21002.
- Mattix HJ, Hsu CY, Shaykevich S, Curhan G: Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002;13:1034–1039.
- Glass DC, Gray CN: Estimating mean exposures from censored data: exposure to benzene in the Australian petroleum industry. *Ann Occup Hyg* 2001;45:275–282.
- Vora JP, Dolben J, Dean JD, Thomas D, Williams JD, Owens DR, Peters JR: Renal hemodynamics in newly presenting non-insulin dependent diabetes mellitus. *Kidney Int* 1992;41:829–835.
- Keller C, Katz R, Sarnak MJ, Fried LF, Kestenbaum B, Cushman M, Shlipak MG: Inflammatory biomarkers and decline in kidney function in the elderly: the Cardiovascular Health Study. *Nephrol Dial Transplant* 2010;25:119–124.
- Sarnak MJ, Poindexter A, Wang SR, Beck GJ, Kusek JW, Marcovina SM, Greene T, Levey AS: Serum C-reactive protein and leptin as predictors of kidney disease progression in the Modification of Diet in Renal Disease Study. *Kidney Int* 2002;62:2208–2215.
- Bautista LE, Vera LM, Arenas IA, Gamarra G: Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF- α) and essential hypertension. *J Hum Hypertens* 2005;19:149–154.
- Chrysoshoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C: Association between prehypertension status and inflammatory markers related to atherosclerotic disease: The ATTICA Study. *Am J Hypertens* 2004;17:568–573.
- Bertani T, Abbate M, Zoja C, Corna D, Perico N, Ghezzi P, Remuzzi G: Tumor necrosis factor induces glomerular damage in the rabbit. *Am J Pathol* 1989;134:419–430.
- Glasscock RJ: Is the presence of microalbuminuria a relevant marker of kidney disease? *Curr Hypertens Rep* 2010;12:364–368.
- Navarro JF, Mora C, Maca M, Garca J: Inflammatory parameters are independently associated with urinary albumin in type 2 diabetes mellitus. *Am J Kidney Dis* 2003;42:53–61.
- Nakamura M, Onoda T, Itai K, Ohsawa M, Satou K, Sakai T, Segawa T, Sasaki J, Tonari Y, Hiramori K, Okayama A: Association between serum C-reactive protein levels and microalbuminuria: a population-based cross-sectional study in northern Iwate, Japan. *Intern Med* 2004;43:919–925.
- Dubin R, Shlipak M, Li Y, Ix J, de Boer IH, Jenny N, Peralta CA: Racial differences in the association of pentraxin-3 with kidney dysfunction: the Multi-Ethnic Study of Atherosclerosis. *Nephrol Dial Transplant* 2011;26:1903–1908.
- Wisse BE: The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004;15:2792–2800.
- Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy – an 8-year prospective study. *Kidney Int* 1992;41:822–828.