

Association between levels of pentraxin 3 and incidence of chronic kidney disease in the elderly

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Abstract. Sjöberg B, Qureshi AR, Heimbürger O, Stenvinkel P, Lind L, Larsson A, Bárány P, Ärnlöv J. (Karolinska Institutet, Stockholm; Uppsala University, Uppsala; Dalarna University, Falun, Sweden). Association between levels of pentraxin 3 and incidence of chronic kidney disease in the elderly. *J Intern Med* 2016; **279**: 173–179.

Objective. Higher levels of the novel inflammatory marker pentraxin 3 (PTX3) predict cardiovascular mortality in patients with chronic kidney disease (CKD). Yet, whether PTX3 predicts worsening of kidney function has been less well studied. We therefore investigated the associations between PTX3 levels, kidney disease measures and CKD incidence.

Methods. Cross-sectional associations between serum PTX3 levels, urinary albumin/creatinine ratio (ACR) and cystatin C-estimated glomerular filtration rate (GFR) were assessed in two independent community-based cohorts of elderly subjects: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS, $n = 768$, 51% women, mean age 75 years) and the Uppsala Longitudinal Study of Adult Men (ULSAM, $n = 651$, mean age 77 years). The longitudinal association between PTX3 level at baseline and incident CKD (GFR < 60 mL min⁻¹ 1.73 m⁻²) was also analysed (num-

ber of events/number at risk: PIVUS 229/746, ULSAM 206/315).

Results. PTX3 levels were inversely associated with GFR [PIVUS: B-coefficient per 1 SD increase -0.16 , 95% confidence interval (CI) -0.23 to -0.10 , $P < 0.001$; ULSAM: B-coefficient per 1 SD increase -0.09 , 95% CI -0.16 to -0.01 , $P < 0.05$], but not ACR, after adjusting for age, gender, C-reactive protein and prevalent cardiovascular disease in cross-sectional analyses. In longitudinal analyses, PTX3 levels predicted incident CKD after 5 years in both cohorts [PIVUS: multivariable odds ratio (OR) 1.21, 95% CI 1.01–1.45, $P < 0.05$; ULSAM: multivariable OR 1.37, 95% CI 1.07–1.77, $P < 0.05$].

Conclusions. Higher PTX3 levels are associated with lower GFR and independently predict incident CKD in elderly men and women. Our data confirm and extend previous evidence suggesting that inflammatory processes are activated in the early stages of CKD and drive impairment of kidney function. Circulating PTX3 appears to be a promising biomarker of kidney disease.

Keywords: chronic kidney disease, community, glomerular filtration, pentraxin 3, risk factor.

Introduction

Accelerated atherosclerosis associated with an increase in cardiovascular morbidity and mortality is observed in patients with chronic kidney disease (CKD), compared to the general population [1, 2]. The prevalence of both microalbuminuria and decreased glomerular filtration rate (GFR) is increasing, partly explained by diabetes and

hypertension but other unknown factors may contribute to this global phenomenon [3]. Both GFR and urinary albumin/creatinine ratio (ACR) should be assessed to diagnose, classify and monitor CKD and the associated risks in clinical practice [4].

Inflammation is thought to play a relevant role in both atherogenesis and the development of CKD [5–7]. The most commonly used marker of inflammation is C-reactive protein (CRP) which predicts all-cause and cardiovascular mortality in the general population [8, 9], as well as in patients with CKD [10–12].

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Pentraxin 3 (PTX3) belongs to the same superfamily of acute-phase reactants as CRP. We recently reported that PTX3 is a rapid and sensitive marker of inflammation in patients with CKD [13]. High systemic PTX3 levels are associated with increased risk of cardiovascular morbidity and mortality in patients with CKD [14–17] and in nonrenal patients [18–20]. In haemodialysis (HD) patients, PTX3 levels vary more than CRP levels, and a persistently high serum PTX3 concentration over 3 months is associated with increased mortality [21]. Yet, at present, the role of PTX3 in the early stages of CKD is incompletely understood. Therefore, we aimed to investigate the cross-sectional associations between PTX3 and both GFR and ACR, as well as the longitudinal association between PTX3 and the incidence of CKD over a 5-year period, in two independent community-based cohorts of elderly men and women.

Methods

Study samples

The prospective investigation of the vasculature in uppsala seniors. From 2001 to 2004, all 70-year-old men and women living in Uppsala, Sweden, were invited to participate in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (for details, see: <http://www.meds-ci.uu.se/pivus/>) [22]. A total of 2025 individuals were invited and 1016 agreed to participate. From 2006 to 2009, a second examination cycle of PIVUS was performed, when the participants were 75 years old. Of 964 invited participants for this second examination cycle, 827 accepted (86%), and data on PTX3 were available for 768 individuals. In the first examination cycle (PIVUS 70), data from individuals with $\text{GFR} > 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ ($n = 746$) were used as the baseline for longitudinal analyses of the association between PTX3 and the development of CKD. Follow-up data from the second examination cycle were used for longitudinal studies of relation between PTX3 and GFR and cross-sectional analyses between PTX3 and ACR.

The Uppsala longitudinal study of adult men. In 1970, all 50-year-old men living in Uppsala were invited to participate in a study to identify cardiovascular disease risk factors (for details, The Uppsala Longitudinal Study Of Adult Men (ULSAM) see: <http://www.2.pubcare.uu.se/ULSAM>) [23]. The first examination cycle was performed during the period 1970–1974 when men born in 1920–1924 were 50 years old. In this study, we used the fourth examination cycle (1998–2001), when the

participants were 77 years old (ULSAM 77), as the baseline. Of 1398 invited men, 838 (60%) agreed to participate and data on serum PTX3 levels were available for 651 individuals. The fourth examination cycle was used as the baseline for the longitudinal analyses and in all cross-sectional analyses. The fifth examination cycle (2003–2005) was performed when participants were 82 years old, and was used to identify individuals who had progressed to CKD. For the fifth examination cycle, the 952 men still alive were invited to participate and 530 men (56%) accepted the invitation; we included 315 individuals for whom data on GFR were available.

The studies were conducted in accordance with the Declaration of Helsinki. All participants in both studies provided written informed consent, and the Ethics Committee of Uppsala University approved the study protocols.

Baseline investigations

In both the PIVUS and ULSAM studies, the investigations were performed using similar standardized procedures, including blood sampling, determination of blood pressure and use of questionnaires to obtain information about medical history, medication, smoking habits, physical activity level and socio-economic status [22, 23]. Blood samples were collected after an overnight fast and kept frozen at -70°C until analysis. A morning urine sample was collected from the PIVUS participants, and 24-h urine samples were collected from the ULSAM participants.

High-sensitivity CRP was measured by latex-enhanced reagent with the BN ProSpec analyser (Siemens, Global Siemens Healthcare, Erlangen, Germany). Diabetes mellitus was diagnosed in individuals with fasting plasma glucose $\geq 7.0 \text{ mmol L}^{-1}$ ($\geq 126 \text{ mg dL}^{-1}$) or those receiving insulin or antidiabetic medication [24].

Serum PTX3. Serum PTX3 concentration was determined using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) (DY1926, R&D Systems, Minneapolis, MN, USA). The total coefficient of variation (CV) for the PTX3 ELISA was 7%, and the intra-assay CV was 5%.

Calculation of GFR. In the ULSAM cohort, GFR was estimated from serum cystatin C using latex-enhanced reagent (N Latex Cystatin C and a BN ProSpec analyser, Siemens) according to the formula: estimated $\text{GFR} = 77.24 * \text{cystatin C}^{-1.2623}$. In the PIVUS

cohort, GFR was estimated using Gentian reagents (Moss, Norway) according to the formula: estimated GFR = $79.901 \times \text{cystatin C}^{-1.4389}$ in PIVUS. Both formulas for the calculation of GFR are closely correlated with plasma iohexol clearance [25, 26].

Statistical analysis

Baseline characteristic data are presented as mean \pm SD, median (10th–90th percentiles) or number (%).

Cross-sectional analyses. Multivariable linear regression models were used to assess cross-sectional associations between PTX3 and both GFR and ACR (expressed per 1 SD increase).

The following multivariable models were used: (i) model A, adjusted for age and gender (gender is only relevant in the PIVUS cohort); (ii) model B, additionally adjusted for the inflammation marker CRP; and (iii) model C, additionally adjusted for the cardiovascular disease risk factors smoking, body mass index, systolic blood pressure, HDL cholesterol, total cholesterol, diabetes mellitus and anti-hypertensive and lipid-lowering treatment.

Longitudinal analyses. The longitudinal association between PTX3 levels at baseline and, in patients with incident CKD (defined as GFR $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$), at re-examination after 5 years was investigated in both cohorts using the same multivariable models A–C. Data from individuals with CKD at baseline were excluded in these models. In both cohorts, we also investigated whether baseline PTX3 level predicted change in GFR after 5 years in multivariable regression models adjusted for age at baseline and at follow-up, and baseline GFR. In the PIVUS cohort, with available data on PTX3 and GFR both at baseline and follow-up, we investigated the association between the change in PTX3 and change in GFR between baseline and follow-up after 5 years using multivariable linear regression models adjusted for age at baseline and at follow-up and baseline GFR (to avoid regression towards the mean). The statistical software package STATA 12.1 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

Results

Baseline characteristics

A summary of the baseline characteristics of the PIVUS and ULSAM study cohorts is presented in Table 1.

Cross-sectional analyses

The regression coefficient of the association between PTX3 and markers of declining kidney function and kidney damage (GFR and ACR, respectively) in the PIVUS and ULSAM cohorts is shown in Table 2. There were inverse associations between PTX3 and GFR in both cohorts that remained significant after adjustments for age, gender, inflammation and established cardiovascular disease risk factors. Conversely, PTX3 was not significantly associated with ACR in any tested model in either cohort (Table 2).

Longitudinal analyses

In the ULSAM cohort, the serum concentration of PTX3 in individuals with GFR $>60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ at baseline ($n = 315$) was significantly associated with a 33% increased risk of incident CKD (GFR $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$) after 5 years of follow-up [odds ratio 1.33, 95% confidence interval (CI) 1.05–1.70, $P < 0.05$]. These results remained significant after adjustment for age, gender, inflammation and established cardiovascular disease risk factors (models A–C). In the PIVUS cohort ($n = 746$), there was no significant association between PTX3 and risk of incident CKD after adjustment for age and the presence of inflammation, but the association became significant after further adjustment for cardiovascular disease risk factors (Table 3).

In the ULSAM cohort, a 1 SD increase in baseline serum PTX3 was significantly associated with a decrease in GFR of $2.5 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ over 5 years after adjustment for GFR at baseline and age at baseline and at follow-up (regression coefficient 2.47, 95% CI -4.0 to -0.9 , $P = 0.002$); however, this association was not statistically significant in the PIVUS cohort (regression coefficient 0.3, 95% CI -0.5 to 1.1, $P = 0.44$). By contrast, in the PIVUS cohort, a 1 ng mL^{-1} increase in serum PTX3 levels during the 5-year follow-up was associated with a decrease in GFR of $0.25 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ after adjustment for baseline PTX3, baseline GFR and age at baseline and at follow-up (regression coefficient -1.2 , 95% CI -1.8 to -0.6 , $P < 0.001$).

Discussion

Main study findings

In the present study, a higher serum concentration of PTX3 was associated with a lower GFR in

Table 1 Baseline characteristics of the PIVUS and ULSAM cohorts

Variable	PIVUS	ULSAM
Number of subjects, <i>n</i>	768	651
Female, <i>n</i> (%)	393 (51)	0 (0)
Age, years	75.3 ± 0.2	77.5 ± 0.8
C-reactive protein, mg L ⁻¹	2.1 (2.8)	1.8 (3.3)
Pentraxin 3, µg L ⁻¹	2.4 (1.5)	2.1 (1.3)
Cardiovascular disease, <i>n</i> (%)	157 (20)	175 (27)
Estimated glomerular filtration rate, mL min ⁻¹ 1.73 m ⁻²	68 ± 19	74 ± 17
Urinary albumin/creatinine ratio, mg mmol ⁻¹	1.3 (2)	0.8 (1.8)
Body mass index, kg m ⁻²	26.8 ± 4.3	26.3 ± 3.5
Systolic blood pressure, mmHg	149 ± 19	151 ± 21
Antihypertensive treatment, <i>n</i> (%)	370 (48)	313 (48)
Cholesterol, mmol L ⁻¹	5.5 ± 1.1	5.4 ± 1.0
HDL, mmol L ⁻¹	1.5 ± 0.5	1.3 ± 0.3
Lipid-lowering treatment, <i>n</i> (%)	206 (27)	118 (18)
Smoking, <i>n</i> (%)	47 (6)	45 (7)
Diabetes, <i>n</i> (%)	106 (14)	92 (14)

Normally distributed continuous variables are presented as mean ± sd, skewed continuous variables as median (interquartile range) and categorical variables as *n* (%). PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ULSAM, Uppsala Longitudinal Study of Adult Men.

cross-sectional analyses in two community-based cohorts of elderly individuals. Moreover, in longitudinal analyses, higher PTX3 predicted CKD incidence in both cohorts. In the ULSAM cohort, baseline PTX3 also predicted GFR decline, and in the PIVUS cohort, there was a close association between longitudinal changes in PTX3 and changes in GFR over 5 years. By contrast, there was no association between PTX3 levels and albuminuria in either of the cohorts.

Comparisons with previous findings

Our findings are in accordance with those of previous studies that found an association between PTX3 and advanced CKD [16, 17], but there are limited data on PTX3 and declining renal function in community-based cohorts. The present results are consistent with those of a North American cross-sectional study including a large multi-ethnic cohort of 2824 men and women [median age 61 (range 45–84) years] without cardiovascular disease or CKD (cystatin C-estimated GFR >60 mL min⁻¹ 1.73 m⁻²). It was found that high PTX3 levels were associated with lower GFR even after adjustment for demographic characteristics, comorbidities and IL-6 level, but this association was strongest amongst Blacks and nonsignificant

amongst Whites [27]. We are not aware of any previous study of the longitudinal association between PTX3 levels and CKD incidence in a community-based setting.

Possible mechanisms underlying the observed associations

The mechanisms underlying the inverse association between PTX3 levels and kidney function in the present study remain unclear; however, several potential mechanisms may explain how high PTX3 levels mirror impaired kidney function. First, PTX3 activates and regulates the complement cascade and is an important factor in the regulation of inflammation and, because PTX3 is produced and stored in the vasculature, rapid release is possible in response to stimulation by cytokines [28–30]. Therefore, PTX3 is thought to have a protective counter-regulatory role in the acute-phase reaction. Secondly, as PTX3 is involved in tuning the immune system, it seems to protect not only against certain infections, but also against the development of atherosclerotic lesions. It has been shown that PTX3 knock-out mice develop more pronounced atherosclerosis than mice expressing PTX3, which indicates that deficiency of PTX3 promotes vascular inflammation [31]. In a Japanese clinical study, circulating

Table 2 The cross-sectional associations between PTX3, GFR and ACR: linear multivariate regression models in the ULSAM and PIVUS cohorts

	PIVUS			
	Model A	Model B	Model C	Model C
GFR	-0.12 (-0.19 to -0.04)**	-0.10 (-0.18 to -0.02)*	-0.09 (-0.16 to -0.02)*	-0.16 (-0.23 to -0.10)***
ACR	0.08 (0.0 to 0.15)	0.05 (-0.02 to 0.12)	0.05 (-0.02 to 0.12)	0.05 (-0.03 to 0.11)

Data are presented as B-coefficients per 1 SD increment of PTX3 (95% confidence intervals) * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. GFR, estimated glomerular filtration rate (cystatin C); ACR, urinary albumin/creatinine ratio; Models: A, adjusted for age and gender (PIVUS only); B, additionally adjusted for C-reactive protein; C, additionally adjusted for smoking, body mass index, systolic blood pressure, diabetes mellitus, HDL, cholesterol and antihypertensive and lipid-lowering treatment; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ULSAM, Uppsala Longitudinal Study of Adult Men; PTX3, pentraxin 3; GFR, glomerular filtration rate; ACR, albumin/creatinine ratio.

Table 3 Longitudinal analyses: multivariate logistic regression of the association between PTX3 and the development of CKD in the ULSAM and PIVUS cohorts

	Odds ratios with 95% confidence intervals	
	ULSAM	PIVUS
Model A	1.33 (1.05 to 1.70)*	1.13 (0.96 to 1.34)
Model B	1.33 (1.04 to 1.69)*	1.13 (0.96 to 1.34)
Model C	1.37 (1.07 to 1.77)*	1.21 (1.01 to 1.45)*

* $P < 0.05$.

Models: A, adjusted for age (at baseline and follow-up examinations) and gender (PIVUS only); B, additionally adjusted for C-reactive protein; C, additionally adjusted for body mass index, smoking, systolic blood pressure, HDL, cholesterol, diabetes and antihypertensive and lipid-lowering treatment.

PTX3 levels were higher in endurance-trained healthy young men (19–26 years) than in sedentary control subjects, indicating a cardioprotective role of PTX3 [32].

However, whether PTX3 initiates or reflects endovascular inflammation is not clear. Several clinical studies have shown that high PTX3 levels predict different cardiovascular outcomes independently of CRP [33]. Based on the findings of studies of atherosclerosis, it has been proposed that high levels of PTX3 predict acute myocardial infarction [34] and higher mortality risk in patients with heart failure [35], unstable angina pectoris [36] and myocardial infarction [37]. PTX3 levels are increased in patients with CKD stages 3–5, but few studies have focused on PTX3 in patients in the early stages of CKD (stages 1–2). Studies are needed to investigate whether PTX3 has a detrimental role in endovascular inflammation, initiating microvascular damage in the kidneys leading to loss of nephrons.

A third possible explanation of our findings is that PTX3 has no protective or causal role in CKD pathology but that higher circulating PTX3 is merely due to decreased renal clearance. Cystatin C is a low molecular weight protein (13 kDa) which can pass through the glomerular barrier. Although PTX3 is a small molecule (42 kDa), it forms multimers of 440 kDa and passage through the glomerular membrane is impaired.

Clinical implications

There is a need for biomarkers to evaluate the risk of developing CKD stages 3–5 in healthy individuals as

even mild renal impairment increases the cardiovascular mortality risk [38]. The prevalence of CKD in Europe and the USA is above 10% in the general population [39] and much higher in the elderly [40]. Identifying individuals at risk of cardiovascular disease and progressive CKD in the population to initiate preventive treatment would be of value. Yet, further studies of PTX3 as a marker to predict CKD in community-based cohorts are needed. In a recent study, circulating PTX3 was found to be a marker of the renal protective effects of atorvastatin. A total of 117 patients with serum creatinine $>120 \mu\text{mol L}^{-1}$ were randomly assigned to receive atorvastatin 10 mg day^{-1} ($n = 56$) or placebo ($n = 61$) and were followed for 2.5 years. In patients with raised PTX3 levels at baseline, the decline in GFR during the trial was significantly less in those treated with atorvastatin compared to individuals in the placebo group [41].

Strengths and limitations

The main strength of this study is the use of two independent community-based cohorts with longitudinal data and detailed phenotype information for the subjects. Some limitations should be considered. First, even though the cohorts were large, only men were included in one and 51% were women in the other. Secondly, it is not known whether the results can be extrapolated to other age and ethnic groups. Thirdly, GFR values were calculated from cystatin C and these may differ from true GFR values. Moreover, in the PIVUS but not in the ULSAM cohort, the longitudinal association between PTX3 level and GFR decline was attenuated after adjusting for baseline GFR. However, adjustment for baseline GFR may represent an 'overadjustment' as GFR is cross-sectionally related to PTX3 and may therefore represent an intermediate state along the causal pathway from PTX3 to CKD. Finally, this is an observational study and, therefore, conclusions regarding causality cannot be drawn.

Conclusions

Our data suggest that PTX3 is a promising biomarker of kidney damage prior to the development of overt CKD. Further studies are needed to determine the clinical relevance of our findings.

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Author contributions

B.S. drafted the manuscript and contributed to data research. J.Ä. edited the manuscript and contributed to data research and discussion. P.B., P.S., A.R.Q. and O.H. reviewed the manuscript and contributed to discussion. L.L. collected the PIVUS data, reviewed the manuscript and contributed to discussion. A.L. measured PTX3 and cystatin C, reviewed the manuscript and contributed to discussion.

Conflict of interest statement

The authors of this manuscript have no conflict of interests to disclose.

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