Inverse Relationship between the Inflammatory Marker Pentraxin-3, Fat Body Mass, and Abdominal Obesity in End-Stage Renal Disease

Tetsu Miyamoto,† Abdul Rashid Qureshi,* Olof Heimbürger,* Peter Bárány,* Karin Carrero,* Bodil Sjöberg,* Bengt Lindholm,* Peter Stenvinkel,* and Juan Jesús Carrero*‡*

Summary

Background and objectives Pentraxin-3 (PTX3) belongs to the same pentraxin superfamily of acute-phase reactants as C-reactive protein (CRP). Abdominal fat accumulation in ESRD is considered a chronic inflammatory state, but the relationship of PTX3 to this phenomenon is unknown. This study assesses plausible associations between PTX3 and surrogates of fat mass deposits in dialysis patients.

Design, setting, participants, & measurements Circulating levels of PTX3, CRP, and IL-6 were cross-sectionally analyzed in relation to anthropometric and nutritional surrogate markers of fat tissue in two cohorts comprising 156 prevalent hemodialysis (HD) and 216 incident dialysis patients.

Results In both cohorts, PTX3 was negatively associated with body mass index (BMI) and fat body mass index (FBMI) derived from anthropometrics and leptin, whereas there was a positive association with adiponectin. In prevalent HD patients, those with larger waist circumference (above gender-specific median values) had lower PTX3, higher CRP, and higher IL-6 levels. This was also true in multivariate analyses. In both cohorts, multivariate regression analyses showed that PTX3 was negatively and CRP (or IL-6) was positively associated with FBMI.

Conclusions Although CRP and IL-6 were directly associated with body fat, PTX3 levels showed negative correlations with surrogates of adipose tissue in two independent cohorts of ESRD patients. Understanding the underlying reasons behind these opposite associations may have clinical relevance given the survival advantage described for obese patients on dialysis.

Clin J Am Soc Nephrol 6: 2785–2791, 2011. doi: 10.2215/CJN.02320311

*Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology and ‡Center for Gender Medicine and Center for Molecular Medicine: Karolinska Institutet, Stockholm, Sweden; and †Second Department of Internal Medicine, University of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan

Correspondence: Dr. Juan Jesús Carrero, Division of Renal Medicine, K56 Karolinska University Hospital at Huddinge, 141 86, Stockholm, Sweden. Phone: +46-8-58583982; Fax: +46-8-58583925; E-mail: juan.jesus.carrero@ki.se

Introduction

Obesity, specifically abdominal obesity, is nowadays regarded as a proinflammatory state that contributes to increased cardiovascular mortality in the general population (1,2). Some but not all studies indicate that this may also be the case in chronic kidney disease (CKD) patients and especially in ESRD (3–7). Pentraxin-3 (PTX3) is a multifunctional soluble pattern recognition receptor modulating the immunoinflammatory response and it belongs to the same pentraxin superfamily of acute-phase reactants as C-reactive protein (CRP) (8,9). However, PTX3 and CRP are produced by different tissues and may be involved in different pathophysiological mechanisms (10). Whereas hepatocytes are the main source of CRP, PTX3 is produced at sites of inflammation by a wide range of different cell types, including endothelial cells and adipocytes (8,9,11). Thus, plasma PTX3, similar to CRP, is positively associated with adhesion molecules and endothelial dysfunction in CKD patients (12–15) and like CRP it is also linked to increased cardiovascular and overall mortality risk (12–15). However, the relationship between PTX3 and the chronic inflammatory state of obesity in CKD remains unknown. Because several different cell types within adipose tissue can produce PTX3 (11), we hypothesized that PTX3 could be a more sensitive marker of inflammation-induced obesity than systemic CRP. Against this background, we studied the association between PTX3 and fat-related parameters in two cohorts of patients: one treated with maintenance hemodialysis (HD) and another with CKD stage 5 patients starting dialysis.

Materials and Methods

Subjects and Study Design

This is a cross-sectional observational study performed in two patient cohorts. The first cohort is composed of 156 prevalent patients undergoing maintenance HD (HD patients, 89 men, median 67 [10th to 90th percentile, 44 to 80] years old, median dialysis vintage 28 [7 to 101] months). The protocol design of this patient material has been described elsewhere in

more detail (16,17); in the same patient cohort we observed an association between PTX3 and mortality (15). Patient recruitment was performed at five dialysis units in Stockholm and one at the Uppsala Academic Hospital in Uppsala, Sweden. From the 224 patients included in this cohort, the analysis presented here comprises the 156 patients in whom data on waist circumference (WC), fat body mass index (FBMI), PTX3, IL-6, and CRP were available. Data on WC were the main limiting factor. There were no major differences in clinical and demographic characteristics between the included and the 68 excluded patients (data not shown). The second cohort, with recruitment still ongoing (18,19), is composed of 216 CKD stage 5 patients (128 men, 56 [36 to 68] years old, median GFR 6.3 [3.7 to 9.0] ml/min) referred to start dialysis therapy at the Department of Renal Medicine at Karolinska University Hospital Huddinge in Stockholm, Sweden. In this patient cohort, we also found an association between PTX3 and mortality (12). Among 276 consecutive patients, the analysis presented here comprises the 216 patients in whom data on FBMI, PTX3, IL-6, and CRP were available. Data on FBMI were the main limiting factor. There were no major differences in clinical and demographic characteristics between the included and the excluded 60 patients (data not shown). Inclusion criteria in both cohorts were the absence of clinical signs of acute infection, active vasculitis, hepatitis, or HIV at the time of evaluation and willingness to participate in the study. Additionally, only subjects ≤70 years of age were included in the incident cohort, whereas no age limit was considered in the prevalent cohort. However, only patients on HD >3 months were included in the prevalent cohort. Most patients were on antihypertensive medications as well as phosphate and potassium binders, diuretics, and vitamins B, C, and D supplementation in accordance with the clinical judgment of the treating physician. All subjects gave written informed consent, and the local ethical committees of the involved hospitals approved the protocols.

Anthropometric Evaluation and Nutritional Status

Body weight, body mass index (BMI; in kg/m^2), and anthropometric measurements were taken on a dialysis day immediately after the dialysis session for the prevalent HD patients, and, for the incident dialysis patients, at the time of or within 1 week of blood sample collection. Fat mass was assessed according to the formula of Durnin *et al.* (20), which is based on the four skinfold thicknesses (biceps, triceps, subscapular, and suprailiac), and was measured with a skinfold caliper (Cambridge Scientific Instruments, Cambridge, MD). Fat BMI (FBMI, in kg/m^2) was calculated from these values. WC was measured at a level midway between the lowest lateral border of the ribs and the uppermost lateral iliac crest. Subjective global nutritional assessment (21) was done on the same occasion as blood sampling and used as a surrogate of protein-energy wasting (defined as a subjective global nutritional assessment score ≥2).

Blood Sampling and Biochemical Measurements

Blood samples were collected before the HD session after the longest interdialytic period for the prevalent HD patients or under fasting conditions early in the morning for the incident dialysis patients and stored at −70°C if not analyzed immediately. In both cohorts, plasma PTX3 was determined from frozen samples by and ELISA kit (Perseus Proteomics, Tokyo, Japan). The intra-assay coefficient of variation was 4.1%, and the interassay coefficient of variation was within 4.3%. Cross-reactivity with CRP and serum amyloid protein was <0.1 ng/ml. High-sensitivity CRP was measured by the nephelometry method. IL-6 was quantified in serum by an immunometric assay on an Immulite Analyzer according to the instructions of the manufacturer (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Determinations of serum albumin (bromcresol purple), cholesterol, triglycerides, and HDL cholesterol were performed by routine procedures in the Department of Clinical Chemistry at Karolinska University Hospital or Uppsala Academic Hospital. Additionally, serum leptin levels in both cohorts and plasma adiponectin levels in the cohort of HD patients were measured by a RIA kit (Linco Research, Inc., Saint Charles, MO). Plasma adiponectin levels in the cohort of incident dialysis patients were determined by ELISA (Linco Research, Inc.). GFR in incident dialysis patients was calculated by the mean of renal urea and creatinine clearances from a 24-hour urine correction.

Statistical Analyses

Values are expressed as median (10th to 90th percentile) or percentage, as appropriate. Statistical significance was set at the level of $P < 0.05$. Spearman rank correlation analysis was used to determine associations between two parameters. Comparisons between two groups were assessed with a nonparametric Mann–Whitney test for continuous variables and a chi-squared test for nominal variables. Differences among four groups were analyzed by a nonparametric Kruskal–Wallis test. Linear regression models were fitted to assess determinants of FBMI and WC. These models included PTX3, CRP, or IL-6 and potential confounders of their association with fat deposits. Other possible confounders considered are age and gender (both influencing FBMI and WC) as well as cardiovascular disease and diabetes (influencing both inflammation and body composition) and finally GFR or dialysis vintage, depending on the patient material. CRP, IL-6, and PTX3 values were $\log_2$ transformed. All analyses were performed using STATA version 11.1 (Stata Corporation, College Station, TX).

Results

General characteristics and laboratory data for the two cohorts studied are depicted in Table 1 with univariate correlates of PTX3. The median levels of plasma PTX3 were 10.5 (5.7 to 22.9) ng/ml in prevalent HD patients and 5.5 (2.3 to 15.1) ng/ml in the incident dialysis cohort. In univariate analysis, PTX3 showed significant negative associations with BMI, FBMI, leptin, and serum albumin, whereas it was positively associated with adiponectin in both cohorts. Additionally, WC also negatively associated with PTX3 in the prevalent HD cohort. In both cohorts, PTX3 associated positively with CRP and IL-6 levels.

Table 1. General characteristics and univariate Spearman correlations with circulating PTX3

	Prevalent Hemodialysis Patients		Incident Dialysis Patients	
	$n = 156$	ρ (P)[a]	$n = 216$	ρ (P)[a]
Age (years)	67 (44 to 80)	0.14 (0.09)	56 (36 to 68)	0.16 (0.02)
Gender (% men)	57	–	59	–
Diabetes mellitus (%)	22	–	32	–
Cardiovascular disease (%)	61	–	39	–
Dialysis vintage (months)	28 (7 to 101)	0.04 (0.63)	NA	NA
GFR (ml/min)	NA	NA	6.3 (3.7 to 9.0)	−0.10 (0.16)
Body mass index (kg/m^2)	23.9 (18.8 to 31.1)	−0.35 (<0.001)	24.0 (19.8 to 29.9)	−0.14 (0.04)
Fat body mass index (kg/m^2)	7.9 (4.4 to 12.4)	−0.28 (<0.001)	5.7 (4.5 to 12.0)	−0.17 (0.01)
WC (cm)	100 (84 to 117)	−0.23 (0.004)	NE	NE
Wasting (SGA ≥ 2, %)	47	–	29	–
Serum albumin (g/L)	35 (29 to 40)	−0.38 (<0.001)	33 (26 to 40)	−0.39 (<0.001)
Cholesterol (mmol/L)	4.3 (3.0 to 5.7)	0.03 (0.70)	4.9 (3.4 to 7.2)	−0.05 (0.50)
Triglyceride (mmol/L)	1.5 (0.8 to 3.3)	−0.20 (0.01)	1.8 (0.9 to 3.5)	−0.10 (0.15)
HDL cholesterol (mmol/L)	1.3 (0.9 to 2.1)	0.28 (<0.001)	1.3 (0.8 to 2.0)	0.05 (0.46)
Leptin (ng/ml)	17.1 (3.7 to 113.9)	−0.25 (0.002)	12.0 (2.7 to 54.8)[b]	−0.18 (0.02)
Adiponectin (ng/ml)	20.7 (9.6 to 37.5)	0.25 (0.002)	25.0 (11.4 to 74.3)[c]	0.24 (0.01)
PTX3 (ng/ml)	10.5 (5.7 to 22.9)	–	5.5 (2.3 to 15.1)	–
CRP (mg/L)	6.0 (0.9 to 34.6)	0.19 (0.02)	4.8 (0.6 to 43.2)	0.36 (<0.001)
IL-6 (pg/ml)	8.5 (3.3 to 24.7)	0.24 (0.002)	6.7 (2.2 to 18.6)	0.37 (<0.001)

Data presented as median (10th to 90th percentile); NA, not applicable; NE, nonexistent; PTX3, pentraxin-3; CRP, C-reactive protein; WC, waist circumference.
[a]Spearman univariate correlation with PTX3 levels.
[b]$n = 159$.
[c]$n = 125$.

Measurements of WC were only available in the prevalent HD material. In univariate analysis, PTX3 associated negatively with WC ($\rho = -0.23$; $P = 0.004$), whereas CRP showed a positive nonsignificant trend ($\rho = 0.15$; $P = 0.08$) and IL-6 presented a positive significant association ($\rho = 0.19$; $P = 0.01$). When patients were dichotomized according to gender-specific median values of WC, individuals with a large WC (≥101 cm [for men], ≥97 cm [for women]) presented at the same time significantly lower PTX3 ($P = 0.01$; Figure 1), higher CRP ($P = 0.03$; Figure 1), and higher IL-6 ($P = 0.01$; Figure 1) levels. The opposing associations between PTX3 and CRP (or IL-6) with WC persisted after adjustment for age, gender, diabetes mellitus, cardiovascular disease, and dialysis vintage in multiple regression models (Table 2).

In each patient cohort, FBMI was concomitantly associated with lower PTX3 and higher CRP levels in univariate analysis (Table 1), which also held true in multivariate models including both markers as well as age, gender, presence of diabetes and cardiovascular disease, and GFR or dialysis vintage (Table 3). As a sensitivity analysis, when multivariate models were repeated including IL-6 instead of CRP, the statistically significant inverse association between FBMI and PTX3 was maintained (data not shown).

Discussion

PTX3 is produced by various types of cells and increases rapidly in response to primary local activation of inflammation and innate immunity (8–11). This specificity opposes that of its homologous CRP, which is exclusively synthesized by the liver mainly in response to IL-6 and reflecting the overall inflammatory status. Because abdominal adipose tissue serves as a crucial site in the generation of inflammatory responses and mediators, we expected to find a positive association between PTX3 and fat-related markers in CKD patients. Instead, and contrary to our hypothesis, this study reports inverse relationships between PTX3 and BMI, FBMI, and WC. Given the presumed proinflammatory nature of PTX3, such results were unexpected, although mathematically it is in the nature of mutual correlations that, in the case of three factors, the correlation between two pairs could be positive and one pair negative. Such novel observation in ESRD patients is nevertheless in line with previous small studies in nonrenal populations: Yamasaki *et al.* (22) reported an inverse association between PTX3 and BMI in healthy Japanese individuals, and a brief report (23) in healthy populations describes opposed associations of PTX3 and CRP in relation to components of the metabolic syndrome. Our study adds the value of confirming our findings in two independent CKD patient cohorts and demonstrating these inverse associations with different surrogates of total and abdominal adiposity, even in multivariate models that include, among others, the inflammatory marker CRP. Interestingly, during 2 weeks of bed rest in healthy volunteers, longitudinal changes in fat mass directly correlated with CRP and IL-6 but inversely correlated with changes in PTX3 (24). However, this evidence is opposed by the findings of Shim *et al.* (25), who assessed markers of total, visceral, and abdominal fat by anthropometrics and computed tomography in 40 subjects with ST-segment elevation myocardial infarction. Although BMI or WC did not associate with PTX3 in that study, visceral and abdominal fat by computed tomography were positively associated

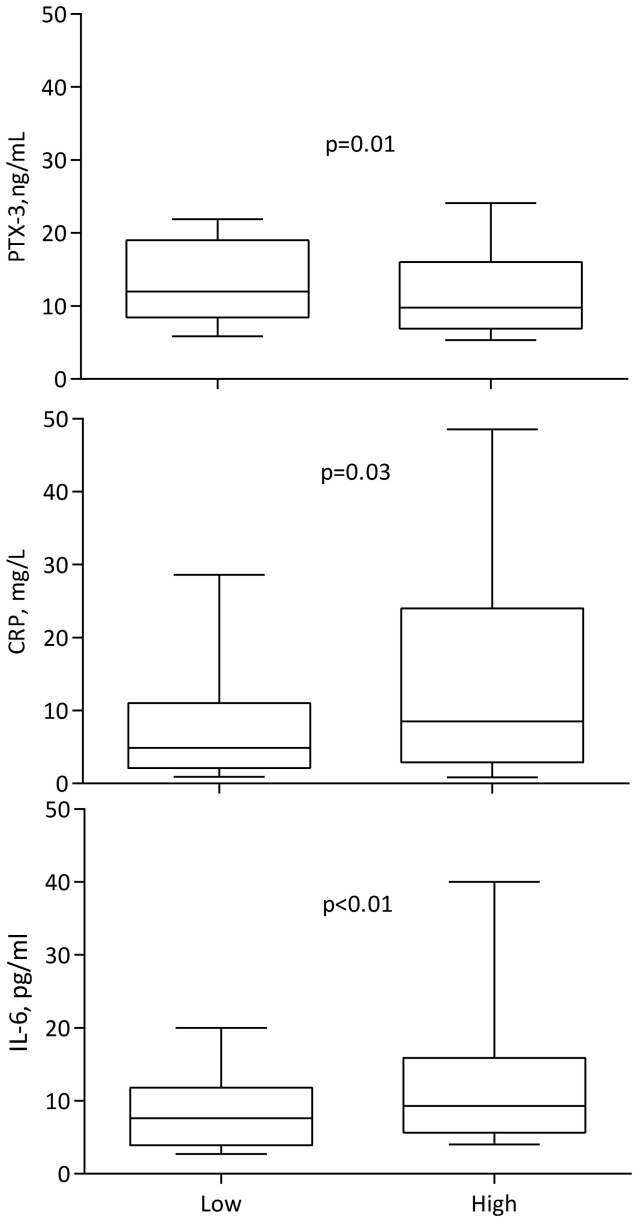

Figure 1. | Plasma pentraxin-3 (PTX3), C-reactive protein (CRP), and IL-6 levels in relation to gender-specific waist circumference (WC) categories (≤101 cm [men], and ≤97 cm [women]) in 156 prevalent hemodialysis patients. Seventy-one patients were included in the low WC group and 85 in the high WC group.

with circulating PTX3 levels in univariate analysis. No association was seen with subcutaneous fat. The lack of multivariate adjustment in that study raises the question of whether other factors may have confounded the reported associations. It is also possible that the association of this acute-phase protein with fat deposits may have been influenced by the blood sampling during the acute phase of myocardial infarction. Altogether, this evidence illustrates that we still do not understand the mechanisms that regulate PTX3 or the biologic role of PTX3.

Cross-sectional studies in patients with CKD have shown that PTX3 levels increase along with renal function loss and share strong independent links with endothelial dysfunction and albuminuria (12–15,26). In dialysis patients, increased PTX3 levels strongly predicted outcome and did so independently of traditional risk factors and CRP (12–15). Pharmacologically, short-term angiotensin converting enzyme inhibitor treatment significantly improved flow-mediated dilation while normalizing PTX3 and urinary protein excretion in patients with type 2 diabetes with proteinuria (27), whereas the improvement in flow-mediated dilation after treatment with antihypertensive drugs in diabetic CKD stage 1 patients with hypertension was independently associated with PTX3 normalization (28). Altogether, these results suggest that increased PTX3 may play a role in the pathogenesis of endothelial dysfunction/cardiovascular disease.

Interestingly, recent observations have led some authors to postulate that the increase in PTX3 should be regarded as an attempt to counterbalance the overactivation of the proinflammatory cascade rather than as a harmful response. Indeed, mice with induced PTX3 genes are more resistant to endotoxic shock induced by lipopolysaccharide and to polymicrobial sepsis caused by cecal ligation and puncture (29). PTX3-deficient mouse models of acute myocardial infarction caused by coronary artery ligation developed more myocardial damage, and this phenotype was reversed by exogenous PTX3 (30). Double knockout mice lacking ApoE and PTX3 displayed an increment in aortic lesion size and a higher inflammatory response as compared with ApoE knockout mice expressing PTX3 (31). Taken together, PTX3 may play tissue-protective and anti-inflammatory roles. In human studies, endurance exercise, which has been shown to improve cardiovascular profile, was also associated with an acute increase in systemic PTX3 in healthy volunteers (32). HDL cholesterol stimulated PTX3 mRNA expression and protein release in endothelial cells, leading the authors to speculate on an involvement of PTX3 in the atheroprotective effects of HDL cholesterol (33). The positive correlation between HDL cholesterol and PTX3 observed in our study may agree with this. Also, and consistent with a previous report in healthy men (23), our study shows a direct relationship between PTX3 and adiponectin, an adipokine with purported antiatherosclerotic properties (34,35). In the general population, systemic clinical hypoadiponectinemia is closely associated with obesity, type 2 diabetes, and coronary artery disease, and the increased oxidative stress in adipose tissue that accumulates in obesity associates with decreased adiponectin production (36). In CKD patients, reduction in oxidative stress through blockade of the angiotensin II type 1 receptor ameliorates adiponectin concentration (37), and oxidative stress is an important determinant of low fat adiponectin expression (38). A similar oxidative stress-related mechanism might also, at least in part, affect PTX3 production in adipocytes. Whether these reported effects may contribute to explain the observed negative associations with surrogates of fat mass in our study requires further investigation. We hope that the description of this unexpected but robust finding may trigger further mechanistic studies on the topic.

Although confirmation of our findings in two carefully phenotyped materials strengthens the analysis, the cross-sectional study design cannot denote causality in the observed associations. The lack of WC data in the incident dialysis

Table 2. Multiple regression model predicting waist circumference (per centimeter of increase) in 156 prevalent hemodialysis patients including either CRP or IL-6

	β	Coefficient (95% CI)	*p-values*
Including CRP (adjusted $r^2 = 0.16$)			
age, per year	0.065	0.07 (−0.09;0.23)	0.40
gender, male	0.069	2.06 (−2.30;6.42)	0.35
diabetes, presence	0.338	11.90 (6.64;17.29)	<0.0001
cardiovascular disease, presence	0.010	0.26 (−4.43;4.96)	0.91
dialysis vintage, months	−0.037	−0.01 (−0.05;0.03)	0.62
PTX3, per doubling ng/ml	−0.208	−3.52 (−6.72;−0.28)	0.008
CRP, per doubling mg/L	0.138	0.99 (−0.10;2.01)	0.060
Including IL-6 (adjusted $r^2 = 0.19$)			
age, per year	0.037	0.04 (−0.12;0.20)	0.63
gender, male	0.064	1.91 (−2.38;6.21)	0.38
diabetes, presence	0.318	11.26 (5.98;16.53)	<0.0001
cardiovascular disease, presence	−0.022	−0.67 (−5.40;4.04)	0.77
dialysis vintage, months	−0.051	−0.01 (−0.06;0.03)	0.49
PTX3, per doubling ng/ml	−0.227	−3.84 (−7.07;−0.61)	0.004
IL-6, per doubling pg/ml	0.222	2.68 (0.98;4.38)	0.007

PTX3, IL-6, and CRP were $\log_2$ transformed in both models. CI, confidence interval; CRP, C-reactive protein; PTX3, pentraxin-3.

Table 3. Multiple regression model predicting fat body mass index (per kg/m^2 of increase) in prevalent and incident dialysis patients

	β	Coefficient (95% CI)	*P*
Prevalent hemodialysis, $n = 156$ (adjusted $r^2 = 0.30$)			
age, per year	−0.060	−0.01 (−0.04; 0.01)	0.40
gender, male	−0.403	−2.63 (−3.51; −1.75)	<0.0001
diabetes, presence	0.269	2.08 (1.02; 3.15)	<0.0001
cardiovascular disease, presence	0.084	0.55 (−0.39; 1.50)	0.24
dialysis vintage, months	−0.094	−0.01 (−0.01; 0.01)	0.17
PTX3, per doubling ng/ml	−0.289	−1.08 (−1.68; −0.48)	<0.0001
CRP, per doubling mg/L	0.162	0.26 (0.02; 0.50)	0.02
Incident dialysis, $n = 216$ (adjusted $r^2 = 0.31$)			
age, per year	0.344	0.08 (0.05; 0.11)	<0.0001
gender, male	0.325	1.94 (1.20; 2.67)	<0.0001
diabetes, presence	0.168	1.05 (0.26; 1.85)	0.09
cardiovascular disease, presence	0.006	0.04 (−0.81; 0.88)	0.93
GFR, ml/min	−0.005	−0.01 (−0.16; 0.15)	0.92
PTX3, per doubling ng/ml	−0.212	−0.61 (−0.98; −0.25)	0.002
CRP, per doubling mg/L	0.147	0.20 (0.01; 0.40)	0.031

PTX3 and CRP were $\log_2$ transformed. CI, confidence interval; PTX3, pentraxin-3; CRP, C-reactive protein.

cohort is a limitation, and in future studies it would be interesting to assess these relationships in cohorts with alternative methods to estimate abdominal fat, such as a dual-energy x-ray absorptiometry scan or computed tomography. Finally, and to conclude, this study shows that although CRP and IL-6 were directly associated with body fat, PTX3 levels exhibited negative correlations with surrogates of adipose tissue in two independent cohorts of ESRD patients. Understanding the mechanisms behind this observation may have clinical and/or therapeutic relevance given the survival advantage described for obese patients on dialysis.

Acknowledgments

We thank the patients and participants in this study. We are indebted to our research staff at KBC (Annika Nilsson, Ann-Christin Emmoth, and Ulrika Jensen) and the KFC (Björn Anderstam, Monica Eriksson, and Ann-Christin Bragfors-Helin). The collection of the prevalent HD patient material was supported by an unrestricted grant from Amgen. We further acknowledge the support from the Osterman and Westman Foundations as well as the Swedish Medical Research Council. Baxter Novum is the result of a grant to the Karolinska Institute from Baxter Healthcare Corporation.

Disclosures

Baxter Healthcare Corporation employs Bengt Lindholm. Peter Stenvinkel is a member of the scientific advisory board of Gambro AB. The other authors have no conflicts of interest to declare.

References

1. de Koning L, Merchant AT, Pogue J, Anand SS: Waist circumference and waist-to-hip ratio as predictors of cardiovascular

events: Meta-regression analysis of prospective studies. *Eur Heart J* 28: 850–856, 2007
2. Hotamisligil GS: Inflammation and metabolic disorders. *Nature* 444: 860–867, 2006
3. Witasp A, Carrero JJ, Heimburger O, Lindholm B, Hammarqvist F, Stenvinkel P, Nordfors L: Increased expression of proinflammatory genes in abdominal subcutaneous fat in advanced chronic kidney disease patients. *J Intern Med* 269: 410–419, 2011
4. Zoccali C, Mallamaci F: Does adipose tissue have a key role in inflammation in CKD? *J Intern Med* 269: 407–409, 2011
5. Cordeiro AC, Qureshi AR, Stenvinkel P, Heimburger O, Axelsson J, Barany P, Lindholm B, Carrero JJ: Abdominal fat deposition is associated with increased inflammation, protein-energy wasting and worse outcome in patients undergoing haemodialysis. *Nephrol Dial Transplant* 25: 562–568, 2010
6. Carrero JJ, Stenvinkel P: Inflammation in end-stage renal disease—What have we learned in 10 years? *Semin Dial* 23: 498–509, 2010
7. Carrero JJ, Stenvinkel P: Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: A hypothesis proposal. *Clin J Am Soc Nephrol* 4[Suppl 1]: S49–S55, 2009
8. Mantovani A, Garlanda C, Doni A, Bottazzi B: Pentraxins in innate immunity: From C-reactive protein to the long pentraxin PTX3. *J Clin Immunol* 28: 1–13, 2008
9. Norata GD, Garlanda C, Catapano AL: The long pentraxin PTX3: A modulator of the immunoinflammatory response in atherosclerosis and cardiovascular diseases. *Trends Cardiovasc Med* 20: 35–40, 2010
10. Bottazzi B, Doni A, Garlanda C, Mantovani A: An integrated view of humoral innate immunity: Pentraxins as a paradigm. *Annu Rev Immunol* 28: 157–183, 2010
11. Alberti L, Gilardini L, Zulian A, Micheletto G, Peri G, Doni A, Mantovani A, Invitti C: Expression of long pentraxin PTX3 in human adipose tissue and its relation with cardiovascular risk factors. *Atherosclerosis* 202: 455–460, 2009
12. Tong M, Carrero JJ, Qureshi AR, Anderstam B, Heimburger O, Barany P, Axelsson J, Alvestrand A, Stenvinkel P, Lindholm B, Suliman ME: Plasma pentraxin 3 in patients with chronic kidney disease: Associations with renal function, protein-energy wasting, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* 2: 889–897, 2007
13. Suliman ME, Yilmaz MI, Carrero JJ, Qureshi AR, Saglam M, Ipcioglu OM, Yenicesu M, Tong M, Heimburger O, Barany P, Alvestrand A, Lindholm B, Stenvinkel P: Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. *Clin J Am Soc Nephrol* 3: 976–985, 2008
14. Yilmaz MI, Sonmez A, Ortiz A, Saglam M, Kilic S, Eyileten T, Caglar K, Oguz Y, Vural A, Cakar M, Egido J, Altun B, Yenicesu M, Blanco-Colio LM, Carrero JJ: Soluble TWEAK and PTX3 in nondialysis CKD patients: Impact on endothelial dysfunction and cardiovascular outcomes. *Clin J Am Soc Nephrol* 6: 785–792, 2011
15. Suliman ME, Qureshi AR, Carrero JJ, Barany P, Yilmaz MI, Snaedal-Jonsdottir S, Alvestrand A, Heimburger O, Lindholm B, Stenvinkel P: The long pentraxin PTX-3 in prevalent hemodialysis patients: Associations with comorbidities and mortality. *QJM* 101: 397–405, 2008
16. Carrero JJ, Qureshi AR, Axelsson J, Avesani CM, Suliman ME, Kato S, Barany P, Snaedal-Jonsdottir S, Alvestrand A, Heimburger O, Lindholm B, Stenvinkel P: Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. *Am J Clin Nutr* 85: 695–701, 2007
17. Snaedal S, Heimburger O, Qureshi AR, Danielsson A, Wikstrom B, Fellstrom B, Fehrman-Ekholm I, Carrero JJ, Alvestrand A, Stenvinkel P, Barany P: Comorbidity and acute clinical events as determinants of C-reactive protein variation in hemodialysis patients: Implications for patient survival. *Am J Kidney Dis* 53: 1024–1033, 2009
18. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55: 1899–1911, 1999
19. Carrero JJ, Witasp A, Stenvinkel P, Qureshi AR, Heimburger O, Barany P, Suliman ME, Anderstam B, Lindholm B, Nordfors L, Schalling M, Axelsson J: Visfatin is increased in chronic kidney disease patients with poor appetite and correlates negatively with fasting serum amino acids and triglyceride levels. *Nephrol Dial Transplant* 25: 901–906, 2010
20. Durnin JV, Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr* 32: 77–97, 1974
21. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN: What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr* 11: 8–13, 1987
22. Yamasaki K, Kurimura M, Kasai T, Sagara M, Kodama T, Inoue K: Determination of physiological plasma pentraxin 3 (PTX3) levels in healthy populations. *Clin Chem Lab Med* 47: 471–477, 2009
23. Ogawa T, Kawano Y, Imamura T, Kawakita K, Sagara M, Matsuo T, Kakitsubata Y, Ishikawa T, Kitamura K, Hatakeyama K, Asada Y, Kodama T: Reciprocal contribution of pentraxin 3 and C-reactive protein to obesity and metabolic syndrome. *Obesity* 18: 1871–1874, 2010
24. Bosutti A, Malaponte G, Zanetti M, Castellino P, Heer M, Guarnieri G, Biolo G: Calorie restriction modulates inactivity-induced changes in the inflammatory markers C-reactive protein and pentraxin-3. *J Clin Endocrinol Metab* 93: 3226–3229, 2008
25. Shim BJ, Jeon HK, Lee SJ, Kim SS, Park MY, Lee DH, Shin WS, Lee JM, Youn HJ, Chung WS, Seung KB: The relationship between serum pentraxin 3 and central obesity in ST-segment elevation myocardial infarction patients. *Korean Circ J* 40: 308–313, 2010
26. Boehme M, Kaehne F, Kuehne A, Bernhardt W, Schroder M, Pommer W, Fischer C, Becker H, Muller C, Schindler R: Pentraxin 3 is elevated in haemodialysis patients and is associated with cardiovascular disease. *Nephrol Dial Transplant* 22: 2224–2229, 2007
27. Yilmaz MI, Carrero JJ, Martin-Ventura JL, Sonmez A, Saglam M, Celik T, Yaman H, Yenicesu M, Eyileten T, Moreno JA, Egido J, Blanco-Colio LM: Combined therapy with renin-angiotensin system and calcium channel blockers in type 2 diabetic hypertensive patients with proteinuria: Effects on soluble TWEAK, PTX3, and flow-mediated dilation. *Clin J Am Soc Nephrol* 5: 1174–1181, 2010
28. Yilmaz MI, Axelsson J, Sonmez A, Carrero JJ, Saglam M, Eyileten T, Caglar K, Kirkpantur A, Celik T, Oguz Y, Vural A, Yenicesu M, Lindholm B, Stenvinkel P: Effect of renin angiotensin system blockade on pentraxin 3 levels in type-2 diabetic patients with proteinuria. *Clin J Am Soc Nephrol* 4: 535–541, 2009
29. Dias AA, Goodman AR, Dos Santos JL, Gomes RN, Altmeyer A, Bozza PT, Horta MF, Vilcek J, Reis LF: TSG-14 transgenic mice have improved survival to endotoxemia and to CLP-induced sepsis. *J Leukoc Biol* 69: 928–936, 2001
30. Salio M, Chimenti S, De Angelis N, Molla F, Maina V, Nebuloni M, Pasqualini F, Latini R, Garlanda C, Mantovani A: Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. *Circulation* 117: 1055–1064, 2008
31. Norata GD, Marchesi P, Pulakazhi Venu VK, Pasqualini F, Anselmo A, Moalli F, Pizzitola I, Garlanda C, Mantovani A, Catapano AL: Deficiency of the long pentraxin PTX3 promotes vascular inflammation and atherosclerosis. *Circulation* 120: 699–708, 2009
32. Miyaki A, Maeda S, Otsuki T, Ajisaka R: Plasma pentraxin 3 concentration increases in endurance-trained men. *Med Sci Sports Exerc* 43: 12–17, 2011
33. Norata GD, Marchesi P, Pirillo A, Uboldi P, Chiesa G, Maina V, Garlanda C, Mantovani A, Catapano AL: Long pentraxin 3, a key component of innate immunity, is modulated by high-density lipoproteins in endothelial cells. *Arterioscler Thromb Vasc Biol* 28: 925–931, 2008
34. Carrero JJ, Cordeiro AC, Lindholm B, Stenvinkel P: The emerging pleiotrophic role of adipokines in the uremic phenotype. *Curr Opin Nephrol Hypertens* 19: 37–42, 2010

35. Park SH, Carrero JJ, Lindholm B, Stenvinkel P: Adiponectin in chronic kidney disease has an opposite impact on protein-energy wasting and cardiovascular risk: Two sides of the same coin. *Clin Nephrol* 72: 87–96, 2009
36. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I: Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 114: 1752–1761, 2004
37. Kurata A, Nishizawa H, Kihara S, Maeda N, Sonoda M, Okada T, Ohashi K, Hibuse T, Fujita K, Yasui A, Hiuge A, Kumada M, Kuriyama H, Shimomura I, Funahashi T: Blockade of angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. *Kidney Int* 70: 1717–1724, 2006
38. Barazzoni R, Bernardi A, Biasia F, Semolic A, Bosutti A, Mucci M, Dore F, Zanetti M, Guarnieri G: Low fat adiponectin expression is associated with oxidative stress in nondiabetic humans with chronic kidney disease—Impact on plasma adiponectin concentration. *Am J Physiol Regul Integr Comp Physiol* 293: R47–R54, 2007

Received: March 11, 2011 **Accepted:** October 6, 2011

Published online ahead of print. Publication date available at www.cjasn.org.