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CLINICAL STUDY

Changes in the inflammatory markers with advancing stages of diabetic nephropathy and the role of pentraxin-3

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ABSTRACT

Background: Immunological and inflammatory mechanisms have been shown to have role in both the development and progression of diabetic nephropathy (DNP). There is need for more specific markers for inflammation as the ones commonly used are influenced by many factors. Pentraxin-3 (PTX-3) seems to be a potential candidate. We aimed in our study to evaluate the changes of PTX-3 levels in different stages of DNP and its relationship with other inflammatory markers.

Methods: This is a cross sectional study in which patients with DNP at different stages were involved. Patient were divided into three groups according to estimated glomerular filtration rate (eGFR), microalbuminuria and proteinuria levels: Group-1: eGFR >60 mL/min and microalbuminuria, Group-2: eGFR >60 mL/min and macroalbuminuria, Group-3: eGFR <60 mL/min and macroalbuminuria. Besides the routine biochemical parameters, levels of PTX-3, high sensitivity C-reactive protein (hsCRP), interleukin (IL)-1 and tumor necrosis factor (TNF)-α was measured. Groups were compared with each other regarding the study parameters and correlation of PTX-3 with other markers was evaluated.

Results: The mean PTX-3 level in Group-2 (0.94 ± 0.26 ng/mL) and -3 (1.35 ± 1.55 ng/mL) were higher than in Group-1 (0.81 ± 0.25 ng/mL) ($p = 0.009$ and $p = 0.012$). There was a significant correlation of PTX-3 with proteinuria ($r = 0.266$, $p = 0.016$), microalbuminuria ($r = 0.304$, $p = 0.014$) and hypoalbuminemia ($r = 0.197$, $p = 0.043$). PTX-3 was not correlated with other markers of inflammation (IL-1, TNF-α and hsCRP) and diabetic metabolic parameters (hbA1c, C-peptide, insulin and HOMA-IR). PTX-3, IL-1 and TNF-α levels increased with the advancing stage of DNP while hsCRP level did not change.

Conclusion: PTX-3 that increases similar to other markers of inflammation (IL-1, TNF-α) is a better inflammatory marker than hsCRP. Furthermore, there is a relationship between PTX-3 and proteinuria independent from eGFR.

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C-reactive protein; cytokines; diabetic nephropathy; inflammation; pentraxin-3; proteinuria

Introduction

Diabetic nephropathy (DNP), one of the most important microvascular complications of diabetes mellitus (DM), is one of the most important and frequent causes of end-stage renal disease.[1] The current knowledge shows that factors other than the traditional ones, namely immunological and inflammatory mechanisms, genetic and environmental factors[2–4] play role in the pathogenesis of DNP. Chronic low-grade inflammation resulting from activation of innate immune system plays role in the pathogenesis of DNP and other microvascular complications of DM.[5–7] The elucidation of the mechanisms of this effect may provide more effective strategies for the diagnosis, follow-up and treatment of DNP.

Interleukin (IL)-1 and tumor necrosis factor (TNF)- α which have key roles in every step of inflammation have been related with many histopathological changes seen in DNP, and are regarded as markers predicting the development and progression of DNP.[4,5] Vestra et al.[4] detected parallel increases in the thickness of glomerular basal membrane and levels of serum C-reactive protein (CRP) and IL-6 as the stage of DNP progresses. There are other studies showing the relationship of DM and DNP with classical markers of inflammation like CRP and fibrinogen.[4,8,9] But levels of these markers may be interfered with many factors other than inflammation. So, there is need for more specific markers related to DNP.

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Pentraxins are a group of protein family active in acute phase inflammatory response.[10] They are divided into two groups being long pentraxins and short pentraxins. CRP, that is the prototype of short pentraxins is synthesized in the liver in response to inflammatory cytokinesis mainly IL-6. Pentraxin-3 (PTX-3) is a member of long pentraxins, and is synthesized by many types of cells including endothelial cells, mononuclear phagocytes, dendritic cells, neutrophils, smooth muscle cells, fibroblasts, adipocytes, renal fibroblasts and proximal tubular cells in response to lipopolysaccharides, TNF-α, IL-1, IL-6 and stimulation of Toll-like receptors.[10–13] It has properties similar to antibodies including opsonization and complement activation.[13,14] It is thought to be a direct marker of disease activity and is related with endothelial dysfunction as it is synthesized directly at the site of inflammation. PTX-3 has been shown to be related to mortality in many cases mainly ischemic heart disease.[15]

There is need for more convenient inflammatory markers that enlighten the pathophysiological changes, and is concordant with the clinical findings. We aimed in this study to evaluate the role of PTX-3 in diabetic patients by analyzing PTX-3 levels in different stages of DNP, and its relationship with other inflammatory markers.

Materials and methods

Patients with DNP secondary to type-2 DM have been included in the presented study. There was no limit of GFR or proteinuria for inclusion into the study except for exclusion of patients with end-stage renal disease. Criteria proposed by American Diabetes Association were used for diagnosis of DM.[16] Exclusion criterion were as follows: patients aged <18 or >65 years, type 1 DM, acute renal dysfunction renal diseases other than DNP, advanced liver disease, patients with increased transaminase levels, autoimmune diseases, malignant diseases, advanced cardiac or respiratory diseases, active systemic infectious or inflammatory disease or ischemic vascular disease The study was approved by the local ethical committee. Informed consent form was obtained from all participants.

Patients were divided into three groups according to estimated glomerular filtration rate (eGFR), microalbuminuria and proteinuria levels:

Group 1: eGFR >60 mL/min and albuminuria between 30 and 300 mg/day on two of the three measurements within the last 3 months

Group 2: eGFR >60 mL/min and albuminuria >300 mg/day on two of the three measurements within the last 3 months.

Group 3: eGFR <60 mL/min and albuminuria >300 mg/day on two of the three measurements within the last 3 months.

Age, gender, weight, height, body mass index (BMI), waist and hip circumferences, DM duration, the presence of renal failure and its duration if present and the medications used by the patients were recorded for each patient.

Venous blood samples were obtained after 12 h of fasting. Serum and plasma samples were kept at −80 °C until the time of analysis for measurement of glucose, HbA_{1c}, urea, creatinine, uric acid, sodium (Na), potassium (K), calcium (Ca), phosphorus (P), total protein, albumin, parathyroid hormone (PTH), total cholesterol, (high-density lipoprotein) HDL-cholesterol, (low-density lipoprotein) LDL-cholesterol, VLDL-cholesterol, triglyceride, aspartate transaminase (AST), alanine transaminase (ALT), hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), ferritin, transferrin saturation, high sensitivity CRP, insulin (in the patients not using insulin), C-peptide (in the patients using insulin), IL-1, TNF-α and PTX-3 levels and total leukocyte and platelet counts. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with "(fasting plasma glucose (mg/dL)×insulin (mIU/L)/405" formula. GFR was calculated by "Chronic Kidney Disease Epidemiology Collaboration" (CKD-EPI) formula.[17] Proteinuria and microalbuminuria levels were determined by dividing corresponding levels in spot urine sample to creatinine level in the same sample[18] at three different occasions, and were regarded significant if at least two of them were concordant. PTX-3, TNF-α and IL-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) method using commercially available kit (Adipo Bioscience Inc., Santa Clara, CA). Measurement range of PTX-3 was 0.219–14 ng/mL.

SPSS (Statistical Package for Social Sciences) for Windows 16.0 standard version was used for statistical analysis. Numerical parameters with normal distribution were expressed as mean ± standard deviation (SD). Those with abnormal distribution were presented as median, minimum and maximum levels. Student's *t*-test and Mann–Whitney *U*-test were used for comparison of the groups. Chi-squared test or Fisher's exact test was used for comparison of nonnumeric variables. Pearson and Spearman's ρ correlation analyzes were used to analyze correlation between parameters with or without normal distribution, respectively. Analysis of variance (ANOVA) or Kruskal–Wallis H-variance analysis was used for comparison of more than two groups for parameters with normal or abnormal distribution, respectively. *Post-hoc* comparisons were performed by Tukey HSD. $p < 0.05$ was accepted as statistically significant.

Parameters found to be correlated with PTX-3 by univariate analysis were evaluated by linear regression analysis (stepwise method).

Results

One hundred and six patients (61 female, 45 male, mean age: 55.88 ± 8.7 years) were included in the study. The numbers of patients in groups were 37, 34 and 35 in Group 1, 2 and 3, respectively. There was no statistically significant difference between groups regarding gender, age, DM duration (Table 1). The mean duration of renal failure in Group 3 was 2.83 ± 1.24 years. Groups were similar regarding weight, height, BMI, body surface area (BSA), waist circumference, hip circumference, waist/hip ratio as presented in Table 1.

Basal biochemical data of the patients are presented in Table 1. Glucose and HbA_{1c} levels were similar in all groups. Renal functions were similar in Group 1 and Group 2, while Group 3 was different from the other two. The mean albumin level of Group 3 was significantly lower than both Group 1 and Group 2. There was no difference between groups regarding lipid parameters (Table 1). On the other hand the data related to the insulin and insulin resistance was significantly different between the groups (Table 1). The medications used by patients in the three grouped are presented in Table 2. The number of patients using insulin was highest and that using metformin was lowest in Group 3.

PTX-3, hsCRP, IL-1 and TNF-α levels are presented in Table 3. hsCRP levels were similar in all groups. IL-1, TNF-α and PTX-3 levels were highest in Group 3 followed by Group 2 and Group 1. Among the inflammatory markers, only PTX-3 and IL-1 were correlated negatively with eGFR (PTX-3: $r = -0.19$, $p = 0.042$, hsCRP: $r = -0.063$, $p = 0.59$, IL-1: $r = -0.22$, $p = 0.023$, TNF-α: $r = -0.038$, $p = 0.70$). PTX-3 was negatively correlated with albumin levels while others were not correlated (PTX-3: $r = -0.197$, $p = 0.043$, hsCRP: $r = -0.212$, $p = 0.065$, IL-1: $r = -0.005$, $p = 0.95$, TNF-α: $r = -0.157$,

Table 1. Demographic, antropometric and laboratory data of the groups.

	Group 1 ($n = 37$)	Group 2 ($n = 34$)	Group 3 ($n = 35$)	p-Value
Age (years)	54.5 ± 10.5	54.4 ± 8.2	58.8 ± 7.3	NS
Female/male	19/18	22/12	20/15	NS
DM duration (years)	9.2 ± 7.0	11.6 ± 9.3	13.8 ± 8.2	NS
Height (cm)	163 ± 8	163 ± 8	161 ± 6	NS
Weight (kg)	84 ± 15	82 ± 15	81 ± 12	NS
BMI (kg/m^2)	31.6 ± 4.9	30.6 ± 5.0	31.0 ± 5.2	NS
Body surface area (m^2)	1.90 ± 0.19	1.86 ± 0.20	1.85 ± 0.14	NS
Waist circumference/hip circumference	0.97 ± 0.04	0.93 ± 0.06	0.98 ± 0.12	NS
Hemoglobin (g/dl)	13.5 ± 1.3	13.0 ± 1.3	11.0 ± 1.5	<0.001*
Hematocrit (%)	41.3 ± 3.83	39.5 ± 3.7	33.9 ± 4.6	<0.001*
Leukocyte (×1000/mm^3)	7.95 ± 1.76	8.68 ± 2.46	8.61 ± 2.56	NS
Thrombocyte (×1000/mm^3)	277 ± 49	283 ± 83	282 ± 70	NS
Mean corpuscular volume (fl)	85 ± 4	87 ± 4	87 ± 3	NS
Transferrin saturation (%)	0.20 ± 0.09	0.19 ± 0.07	0.21 ± 0.07	NS
Ferritin (ng/ml)	62 ± 47	47 ± 39	145 ± 135	<0.001*
eGFR (ml/min)	95 ± 15	87 ± 24	33 ± 15	<0.001*
Proteinuria (mg/day)	197	1326	2626	<0.001*
Albuminuria (mg/day)	57	483	501	<0.001
Glucose (mg/dl)	181 ± 80	210 ± 88	221 ± 98	NS
$HemoglobinA_{1C}$ (%)	8.3 ± 1.7	8.9 ± 1.9	8.9 ± 1.8	NS
Urea (mg/dl)	31 ± 9	36 ± 13	94 ± 37	<0.001*
Creatinine (mg/dl)	0.77 ± 0.16	0.84 ± 0.25	2.24 ± 1.02	<0.001*
Sodium (mmol/L)	138 ± 3	138 ± 4	138 ± 3	NS
Potassium (mmol/L)	4.5 ± 0.4	4.7 ± 0.6	4.9 ± 0.4	0.001*
Calcium (mg/dl)	9.7 ± 0.5	9.7 ± 0.5	9.4 ± 0.6	NS
Phosphorus (mg/dl)	3.7 ± 0.4	3.5 ± 0.5	4.2 ± 0.9	<0.001*
Parathyroid hormone (pg/ml)	53 ± 20	58 ± 34	135 ± 149	0.002*
Uric acid (mg/dl)	4.8 ± 1.1	5.3 ± 1.8	6.3 ± 1.3	<0.001*
Total protein (g/dl)	7.5 ± 0.4	7.3 ± 0.5	7.2 ± 0.6	NS
Albumin (g/dl)	4.3 ± 0.3	4.1 ± 0.4	3.8 ± 0.5	<0.001*
Alanine transaminase (U/L)	24 ± 14	31 ± 27	21 ± 14	NS
Aspartate transaminase (U/L)	22 ± 9	25 ± 10	22 ± 28	NS
Total cholesterol (mg/dl)	221 ± 40	224 ± 66	225 ± 71	NS
Triglyceride (mg/dl)	203 ± 76	257 ± 249	222 ± 98	NS
LDL-cholesterol (mg/dl)	138 ± 34	139 ± 54	141 ± 60	NS
HDL-cholesterol (mg/dl)	43 ± 11	43 ± 11	41 ± 09	NS
VLDL-cholesterol (mg/dl)	40 ± 15	52 ± 49	44 ± 19	NS
Insulin (mIU/L)	10.2 ± 6.9	14.2 ± 7.4	15.6 ± 10.8	0.044**
C-peptide (ng/mL)	2.9 ± 1.1	2.49 ± 1.0	4.06 ± 2.2	0.003*
HOMA-IR	4.1 ± 2.9	6.9 ± 4.1	7.9 ± 5.5	0.012**

Notes: NS, not significant.
*Group 3 is different significantly from Group 1 and Group 2.
**Group 1 is different significantly from Group 2 and Group 3.

Table 2. The medications used by the patients.

	Group 1 ($n = 37$) (%)	Group 2 ($n = 34$) (%)	Group 3 ($n = 35$) (%)	p-Value
Angiotensin-converting enzyme inhibitors	10 (27)	15 (44)	8 (23)	0.130
Angiotensin receptor blockers	12 (32)	13 (38)	14 (40)	0.784
Diltiazem	0 (0)	4 (12)	8 (23)	0.009*
Sulphonylurea	13 (35)	3 (9)	3 (9)	0.003*
Insulin secretagogues	3 (8)	2 (6)	1 (3)	0.627
Glitazones	1 (3)	2 (6)	2 (6)	0.773
Insulin	18 (48)	20 (59)	29 (83)	0.009**
Metformin	31 (84)	20 (59)	7 (20)	<0.001**
Acarbose	11 (30)	7 (21)	3 (9)	0.079

Notes: *Group 1 is different from Group 2 and Group 3.
**Group 3 is different from Group 1 and Group 2.

Table 3. Levels of inflammatory markers in the groups.

	Group 1 ($n = 37$)	Group 2 ($n = 34$)	Group 3 ($n = 35$)	p-Value
PTX-3 (ng/ml)	0.81 ± 0.25	0.94 ± 0.26	1.35 ± 1.55	a = 0.009, b = 0.012
hs-CRP (mg/l)	0.45 ± 0.33	0.97 ± 1.21	0.75 ± 0.70	NS
IL-1 (pg/ml)	29.95 ± 14.20	48.66 ± 14.97	68.31 ± 50.36	a < 0.001, b <0.001, c = 0.013
TNF-α (pg/ml)	8.30 ± 7.98	15.42 ± 14.01	17.16 ± 11.00	a = 0.007, b < 0.001

Notes: NS, not significant.
a = Group 1 versus Group 2; b = Group 1 versus Group 3; c = Group 2 versus Group 3.

$p = 0.11$). On the other hand there were no any correlation between PTX-3 and glucose, hbA1c, C-peptide, insulin and HOMA-IR ($r = -0.11$, $p = 0.47$; $r = 0.07$, $p = 0.64$; $r = -0.12$, $p = 0.53$; $r = -0.15$, $p = 0.44$ and $r = -0.15$, $p = 0.44$, respectively). Male and female patients had similar levels of inflammatory markers. There was no statistically significant difference between patents using or not using statin, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor antagonists (ARB) and acetylsalicylic acid. Among the inflammatory markers, only PTX was correlated with proteinuria ($r = 0.266$, $p = 0.016$) and microalbuminuria ($r = 0.304$, $p = 0.014$).

Linear regression model was formed by age, gender, eGFR and proteinuria. The only parameter related to PTX-3 was proteinuria ($B = 0.089$, $\beta = 0.28$, $p = 0.01$).

Discussion

We evaluated hsCRP that is in common clinical use, IL-1 and TNF-α which are known to have important roles in the early steps of inflammation, and a newer marker, PTX-3, in three different groups of diabetic patients. Groups were well matched for age, gender, DM duration, BMI and other anthropometric measurements (Table 1). The laboratory data and the medications recorded were appropriate for the degree of renal impairment in each group (Tables 1 and 2).

There were three main results gained by our study. Firstly, levels of PTX-3, IL-1 and TNF-α increased as the stage of DNP progresses while hsCRP level did not change significantly. Second, only PTX was shown to be correlated with proteinuria and microalbuminuria while there was no correlation with other inflammatory markers. Third, serum albumin level was negatively correlated with only serum PTX-3 levels but not with other inflammatory markers.

So, only PTX-3 was correlated with proteinuria and hypoalbuminemia which are important predictors of disease progression and complications. There are studies supporting our findings. Suliman et al.[19] found a relationship between PTX-3 level, proteinuria and endothelial dysfunction in patients with stage 1 DNP and patients with stage-5 CKD due to various etiologies. The major difference from our study is lack of patients with different stages of DNP. Tong et al.[20] reported higher PTX-3 levels in patients with CKD compared to healthy control subjects. In this study, PTX-3 was found to be negatively correlated with eGFR, and positively correlated with protein-energy wasting, cardiovascular disease and mortality. Both of the mentioned studies included patients with CKD due to various causes without a subgroup analysis of patients with DNP. Moreover, the relationship between PTX-3 and proteinuria was not studied. Our study has been carried on with a more homogenous group including patients with varying stages of DNP. This is an important point considering exclusion of other inflammatory factors that may affect proteinuria. Herein, the relationship of PTX-3 and other inflammatory markers with proteinuria and other biochemical parameters. The major difference of our study from the previous ones is the finding of correlation of PTX-3 with the stage of DNP, the degree of proteinuria, hypoalbuminemia and progression of proteinuria. This is an important finding considering that proteinuria is

among the most important prognostic markers of DNP. Another difference of our study is the finding that CRP is related with neither disease stage nor the degree of proteinuria; and IL-1 and TNF-α increases in parallel with only the stage of the disease.

The finding that means PTX-3 level in Group 1 was significantly lower than that in Group 2 gains importance considering the similar eGFR values in these two groups. When Group 1 was compared with Group 3, PTX-3 was significantly higher in the latter. But it is striking that Group 2 and Group 3 with overt proteinuria had similar PTX-3 levels in spite of different mean eGFR values. PTX-3 was found to be correlated with proteinuria in early stages of DNP in which GFR loss has not occurred yet. This finding is different from other studies claiming increased level of PTX-3 correlated with eGFR loss due to its pentameric structure.[20,21] Our findings of the correlation of PTX-3 with proteinuria in all stages of DNP and similar levels in Group 2 and Group 3 show that static accumulation due to decreased GFR is not the only cause. Moreover, multivariate analysis showed that the relationship between PTX-3 and proteinuria is independent from eGFR.

IL-1 and TNF-α levels increased with advancing stages of DNP, but they did not show correlation with proteinuria. It is known that their level increase as CKD progresses.[22] They have been held responsible for mesangial proliferation, extracellular matrix accumulation and increased endothelial permeability associated with DNP.[23,24] They also have effects on the progression of disease not just with inducing proteinuria.[25,26]

Some of the previous studies showed different responses to inflammation of CRP and PTX-3.[27,28] There are studies reporting that PTX-3 is a better indicator of inflammation and endovascular damage in diabetic patients.[29,30] It was striking that there was no correlation of hsCRP with other inflammatory markers, disease stages and laboratory parameters. CRP is synthesized in the liver and is a sign of systemic inflammation. PTX-3, IL-1 and TNF-α are synthesized by various cells and tissues including kidney specific ones. So, they may be more specific and sensitive indicators of renal damage, and may be more useful to provide information about the early recognition, staging and prognosis of the disease.[13,24,25] On the other hand IL-1 and TNF-α behaved different from PTX-3 in that they were not correlated with other laboratory parameters although all three followed similar courses though the stages of DNP. So, PTX-3 was the only parameter related to the disease stage and proteinuria in our study by mechanisms that we could not be able to explain.

Our study also supports the studies showing increased insulin resistance in CKD patients since serum insulin, C-peptide and HOMA-IR were significantly increased in lower GFR groups[31] (Table 1).

The major limitations of our study was the cross sectional nature and the limited number of patients involved. Although these 106 patients were classified into three groups, there has been opportunity to involve all in multivariate analysis as the three groups included patients with that same disease at different stages. Another shortcoming of the study seems to be the lack of a control group of nondiabetic subjects. But the control group would have to involve both uremic and nonnumeric subjects, and other heterogenous causes of CKD would complicate the results. So this factor may be accepted as a neglectable one.

Conclusion

The levels of markers of inflammation increase as DNP progresses. PTX-3, the level of which increases parallel to the central inflammatory markers, IL-1 and TNF-α, seems to be a better inflammatory marker than hsCRP. Moreover, PTX-3 is related to proteinuria independent from GRF. The only inflammatory marker related to proteinuria and hypoalbuminemia was found to be PTX-3. There is need for further studies about the role of PTX-3 on mechanisms of inflammation and damage in DNP.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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