Elevated pentraxin-3 levels are related to blood pressure levels in hypertensive patients: an observational study

Hipertansif hastalarda artmış pentraxin- 3 seviyelerinin kan basıncı seviyeleri ile ilişkisi: Gözlemsel bir çalışma

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ABSTRACT

Objective: In this study, relationship between systolic and diastolic blood pressure and pentraxin-3 (PTX3) levels in hypertensive patients was investigated.

Methods: Overall, 80 patients with stage 1 hypertension between 40-61 years of age without any disease and 80 healthy volunteers were included to the study. Blood samples obtained to measure PTX3 levels and biochemical analysis. Relationship between PTX3 levels and clinical and biochemical parameters were analyzed using multivariate regression analysis.

Results: Although systolic and diastolic blood pressures were significant different, there were no differences regarding age and gender between hypertensives and normotensives. In each group, significant statistical differences were found between PTX3 and CRP levels (PTX3 (ng/mL) 35.25±5.45 and 0.27±0.24, p<0.001; CRP (mg/dL) 10.03±5.81 and 4.30±3.38, p<0.001; in hypertensive and normotensive groups respectively). It was observed that increase in PTX3 levels accompanies the increase in systolic and diastolic blood pressures (r^2=0.78). It was observed that PTX3 levels are not effected from CRP, lipid levels and body mass index (p>0.05). On multivariate regression analysis PTX3 was found to strongly affect blood pressure (beta=0.82, 95% CI 0.644-0.799, p<0.001, and beta=0.84, 95% CI 0.422-0.799, p<0.001, respectively for systolic and diastolic blood pressures), CRP and total cholesterol are found to affect moderately (beta=0.115-0.265, 95% CI 0.101-0.572, p<0.05 and beta=0.107-0.141, 95% CI 0.041-0.110, p<0.05, respectively).

Conclusion: This study showed that PTX3 levels are higher in newly diagnosed hypertensive patients than in healthy individuals. In addition, it was noticed that increased PTX3 levels causes increase in systolic and diastolic blood pressures. *(Anadolu Kardiyol Derg 2012; 12: 298-304)*

Key words: Hypertension, pentraxin3, inflammatory mediators, regression analysis

ÖZET

Amaç: Bu çalışmada, hipertansif hastalarda sistolik ve diyastolik kan basınçları ile PTX3 düzeyleri arasındaki ilişki incelendi.

Yöntemler: Çalışmaya 40 ile 61 yaş arasında ek hastalığı olmayan evre 1 hipertansiyonlu 80 hasta ile 80 sağlıklı gönüllü dahil edildi. PTX3 düzey tayini ve biyokimyasal analizler için kan örnekleri alındı.

Bulgular: Hipertansif ve normotansiflerde sistolik ve diyastolik kan basınçları arasında fark olmasına rağmen cinsiyet ve yaş açısından fark saptanmadı. Her iki grupta PTX3 ve CRP düzeyleri arasında istatistiksel olarak anlamlı fark vardı [Hipertansif ve normotansiflerde sırasıyla PTX3 (ng/mL) 35.25±5.45 ve 0.27±0.24, p<0.001; CRP (mg/dL) 10.03±5.81 ve 4.30±3.38, p<0.001]. Sistolik ve diyastolik kan basınçlarındaki yükselmeye PTX3 seviyelerindeki artışın eşlik ettiği tespit edildi (r^2=0.78). PTX3'ün CRP, lipid düzeyleri ve VKİ'den etkilenmediği gözlendi (p>0.05). Sistolik ve diyastolik kan basınçlarını etkilediği değerlendirilen parametreler için çoklu regresyon analizi uygulandığında, PTX3'ün kan basıncını kuvvetli (sistolik ve diyastolik kan basınçları için sırasıyla, p<0.001, beta;0.82, %95 GA; 0.644-0.799 ve p<0.001; beta;0.84, %95 GA; 0.422-0.799), CRP ve TC düzeylerinin ise ılımlı etkilediği sonucuna ulaşıldı (sırasıyla p<0.05, beta; 0.115-0.265, %95 GA; 0.101-0.572 ve p<0.05, beta; 0.107-0.141, %95 GA; 0.041-0.110).

Sonuç: Bu çalışma, yeni tanı konulan izole hipertansiflerdeki PTX3 düzeylerinin normal tansiyonlu sağlıklı bireylere göre yüksek olduğunu gösterdi. Ayrıca yükselen PTX3 düzeylerinin sistolik ve diyastolik kan basınçlarında artışa yol açtığını saptadı.
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Anahtar kelimeler: Hipertansiyon, pentraxin 3, inflamatuvar medyatör, çoklu regresyon analizi

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Introduction

High blood pressure levels are associated with increase in circulating levels of inflammation markers, which can reflect vascular inflammatory processes, suggesting that hypertension is a low-grade inflammatory process. The vascular inflammation associated with hypertension could be the link between high blood pressure levels and the atherosclerotic process, which is the principal origin of cardiovascular disease, the leading cause of worldwide mortality.

Changes in mechanical stress and activation of humoral factors such as the rennin-angiotensin-aldosterone system can be underlying not only increases in oxidative stress (and consequently endothelial dysfunction) but also the development of the inflammatory process associated with hypertension (1).

Up regulation of inflammatory mediators in tissues, such as nuclear factor-kB (NF-kB), activator protein-1 (AP-1), the vascular and intracellular adhesion molecules (VCAM-1, ICAM-1), platelet endothelial cell adhesion molecule and tissue factor (2), has been demonstrated in experimental hypertension.

Evidence suggests that pentraxin 3 (PTX3) is a useful new serological marker, rapidly reflecting tissue inflammation and damage under diverse clinical conditions (3). Primary pro-inflammatory signals induce the expression of PTX3 in different cell types and, in particular, in monocyte/macrophages and endothelial cells (4, 5). Data indicate that PTX3 may serve as a mechanism of amplification of inflammation and innate immunity, tightly related to endothelial cell functions (6). PTX3 in humans, like CRP, is a marker of atherosclerosis and correlates with the risk of developing vascular events (3, 7). PTX3 may represent a candidate reactant by which to monitor local inflammatory involvement in patients with hypertension.

However, there are no studies on the levels of PTX3 levels in isolated hypertension patients and its clinical significance.

We aimed to study PTX3 levels in newly diagnosed hypertensive and to assess the relationship with clinical and laboratory variables in blood pressure.

Methods

Study design and sample size

Study was designed as a cross-sectional observational controlled study. If it was calculated that standard deviation for PTX3 as 1.8 ng/mL, alfa degree of freedom as 0.05, difference between the groups as 1.5 ng/mL, it was found that 80 patients should be included in each group for 99% study power.

Study population

This study included 80 patients with isolated hypertension who were admitted to the outpatient clinics of the Department for Internal Medicine at Gülhane Military of Medicine Faculty of Training and Research Hospital in Ankara between September 2009 and May 2010. The control group was composed of 80 healthy volunteers who did not have any disease and use any drugs, applied for routine control and were comparable to the patient group in terms of age and sex. Patients who were in stage 1 criteria according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) (8), and were newly diagnosed, having never been treated with antihypertensive medications and have no additional disease were included in this study.

Patients with secondary hypertension, renal failure, diabetes mellitus, acute infections, additional systemic disease, use of an angiotensin converting enzyme (ACE) inhibitor, beta-blocker or angiotensin receptor blocker (ARB), smokers or those taking additional medications that affect blood pressure were excluded from the study.

The study was approved by Gülhane Military Medical Academy Institutional Ethics Committee (protocol No: GEK 1491-674-09/1539).

Blood pressure measurement

Blood pressure of the patients measured by the same doctor after ten minutes rest, in sitting position from the right arm with mercury manometers. Mean of the three measurements after 5 minutes periods recorded as systolic and diastolic pressure. Each patient's data were noted in patient`s follow up charts. Since lipid levels, liver and kidney function tests were thought to effect systolic and diastolic blood pressures and PTX3 levels, these were also investigated and noted in patient charts.

Study variables

Predictor variable*:* hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg).

Primary outcome variable: PTX3.

Secondary outcome variable: C -reactive protein (CRP).

Confounding factors: fasting blood glucose (FBG), urea, creatinine, total cholesterol (TC), low-density lipoprotein (LDL), high- density lipoprotein (HDL), triglyceride (TG), alanine amino transferase (ALT), aspartate aminotransferase (AST).

Basal clinical variables: age, sex, body mass index (BMI).

Sample collection and measurement of biochemical markers

Blood pressures of the patients included in the study were measured and a detailed physical examination was performed. After hypertension was diagnosed, blood was drawn to assess complete blood count, liver and kidney functions, FBG and cholesterol levels after an overnight fasting. Same procedure was performed for control group. Biochemical analyses were performed with the OLYMPUS AU2700 Chemistry Analyzer (Beckman Coulter, California, USA).

Measurement of PTX3 and CRP

The levels of PTX3 were measured in the serum separated by centrifugation for 10 min at 4000 rpm from the whole venous

blood. Serum samples were kept in -80°C until the measurements were performed and PTX3 measurements were done at the same time for all the samples. Plasma concentrations of PTX3 were determined using a commercial enzyme-linked immunosorbent assay kit (Quantakine DPTX 30; R&D Systems Inc., Minneapolis, MN). The PTX3 assay was carried out according to the manufacturer's instructions. Briefly, standard or plasma samples assayed in duplicate and 20 µL of which were added to microtiter plate wells coated with a monoclonal antibody specific for PTX3, followed by incubation at room temperature for 2 hour. The wells were then washed four times with a buffered surfactant solution, and thereafter, 200 µL of anti-PTX3 polyclonal antibody conjugated to alkaline phosphatase was added to each well and incubated for 2 hour at room temperature. After appropriate washing, 200 µL of substrate solution was added to each well and incubated again for 30 min at room temperature. The reaction was then stopped by the addition of 2 N sulfuric acid to the wells, and absorbance was measured at 450 nm with corrections set at 540 nm using a microplate reader (BioTek's Synergy™ HT Multi-Mode Microplate Reader). The values of plasma PTX3 levels were extrapolated from a curve drawn using standard PTX3. Quantakine human pentraxin 3 / TSG-14 immunoassay / Catalog number DPTX30 and sensitivity: minimum detectable dose (MDD) from 0.007 to 0.116 ng/mL, the average dose 0.25 ng/mL.

CRP levels were measured by nephelometric method in RADIM Delta nephelometer (Radim Diagnostics, Pomezia, Italy). Values under 6 mg/dL were evaluated as normal.

Statistical analysis

The statistical analysis was performed using SPSS version 15.0 program (SPSS Inc., Chicago, Ill, USA). The analysis of normality was determined by primarily using Kolmogorov-Smirnov test for the analysis of continuous data. Parametric tests were performed for the data fit to the normal distribution and nonparametric tests were performed for the data which did not fit to a normal distribution.

The differentiation between the groups were investigated by using one of the following tests, Chi-square, Mann-Whitney U or unpaired Student's t-test according to the number of groups and the distribution of the data. The relation between the variables performed in the study was investigated by multivariate regression analysis. While dependent variables for multivariate regression analysis were PTX3, SBP and DBP, independent variables were CRP, FBG, TC, TG, HDL, LDL, urea, and creatinine. Data were presented as mean±standard deviation, median value with range, beta and 95% confidence interval. In all tests, Alpha, degree of freedom, was accepted as 0.05 and calculated p values lower than 0.05 were considered as significant.

Results

Clinical characteristics of patients and controls

The hypertensive group included 25 male (31.25%) and 55 female (68.75%) subjects, while the normotensive group consisted of 30 male (37.5%) and 50 female (62.5%) healthy volunteers. Although systolic (SBP) and diastolic (DBP) blood pressures were significantly different, there were no differences regarding age and gender between study and control groups. Besides the mean BMI value of the study group was slightly but significantly higher than the control group (p=0.038).

Analyses of general characteristics, biochemical parameters and PTX3 levels in hypertensive and normotensive groups are summarized in Table 1. There were no statistical differences between each group regarding biochemical parameters, except ALT.

Relationship of PTX3 with clinical and laboratory parameters

There was a linear relationship between PTX3 levels and rising blood pressure. This result showed that, normal blood pressure is associated with low PTX3 levels, but when blood pressure begin to rise, PTX3 levels similarly associate it (Fig. 1).

CRP and PTX3 levels were measured in blood samples of both hypertensive and normotensive groups, to demonstrate endothelial inflammation (Table 1). CRP and PTX3 levels were significantly different between both groups adjusted for BMI [CRP (mg/dL) 10.03±5.81 and 4.30±3.38, p<0.001; PTX3 (ng/mL) 35.25±5.45 and 0.27±0.24, p<0.001 in hypertensive and normotensive groups, respectively]. No correlation between PTX3 levels and CRP, FBG, TC, LDL, HDL, and BMI were confirmed by multivariate regression analysis (p>0.05 for all parameters, summarized in Table 2).

Relationship of SBP and DBP with laboratory parameters

Systolic and diastolic blood pressures were found to be affected from the levels of PTX3 (beta-0.819, 95% CI 0.644-0.799, p<0.001 and beta=0.843, 95% CI 0.422-0.526, p<0.001, respectively), CRP (beta; 0.115, 95% CI 0.370-0.572 p<0.001 and beta=0.265, 95% CI 0.101-0.280 p<0.001) and TC (beta=0.141, 95% CI 0.005-0.110, p=0.03, and beta=0.107, 95% CI 0.041-0.063, p=0.06, respectively). In addition, TG levels were observed to contribute to the high level of SBP (beta=0.068, 95% CI 0.064-0.176, p=0.01), (Table 3).

Discussion

In this study PTX3 levels were found high in newly diagnosed hypertension patients. Also, increase in PTX3 levels was accompanied by SBP and DBP increase.

PTX3 is produced outside of the liver at sides of inflammation, which is the reason why it is an independent determinant of endothelial dysfunction (9). Moreover, PTX3 is produced in healthy myocardial cells and increases during myocardial infarction (10). According to these reasons, PTX3 in hypertensive patients may be a useful marker for future cardiovascular events. When considering that our study group consisted of newly diagnosed hypertensive patients without any target organ damage, we can claim that PTX3 levels increased synchronically to elevated blood pressure.

Table 1. Comparison of sociodemographic, biochemical and inflammatory mediators in hypertensive and normotensive groups

Variables	Hypertensive Group (n=80)	Normotensive Group (n=80)	*p
Gender, M:F ratio	1:0.45	1:0.6	0.19
Age, years	50.07±5.75	49.01±4.73	0.20
BMI, kg/m^2	28.25±3.49	27.08±3.52	0.04
SBP, mmHg	150 (140-155)	120 (110-140)	<0.001
DBP, mmHg	95 (80-99)	75 (70-90)	<0.001
PTX3, ng/mL	36.41 (22.02-46.86)	0.17 (0.14-1.33)	<0.001
CRP, mg/dL	9.40 (1.00-25)	3.11 (0.80-16)	<0.001
FBG, mg/dL	94.82±7.90	92.83±9.69	0.16
Urea, mg/dL	30.95±8.44	28.54±7.01	0.06
Creatinine, mg/dL	0.91 (0.68-1.03)	0.91 (0.69-1.01)	0.77
TC, mg/dL	206.85±36.69	196.12±40.47	0.81
TG, mg/dL	167.30±77.92	144.26±75.28	0.06
HDL, mg/dL	46.95±8.72	47.20±16.44	0.90
LDL, mg/dL	132.28±29.49	124.1±34.84	0.15
AST, U/L	22.06±8.73	20.50±6.22	0.53
ALT, U/L	21 (6-35)	19 (4-33)	0.03
Red cells, e^6/µL	4.66 (3.77-5.99)	4.74 (3.87-5.65)	0.53
Hemoglobin, g/dL	13.80 (13.40-14.90)	13.90 (13.35-14.87)	0.19
Platelets, 10.e^3/ µL	264.98±58.28	257.13±55.85	0.38
White cells, e^3/ µL	7.00±1.73	6.60±1.45	0.12

Data are presented as mean±standard deviation for parametric test, median (min-max) value for nonparametric test and ratio

* Chi-square test; unpaired Student's t-test, Mann-Whitney U test.

ALT - alanine aminotransferase, AST - aspartate aminotransferase, BMI - body mass index, CRP- C reactive protein, DBP - diastolic blood pressure, FBG - fasting blood glucose, HDL - high -density lipoprotein, LDL - low density lipoprotein, M:F - male:female ratio, SBP - systolic blood pressure, PTX3 - pentraxin 3, TC - total cholesterol, TG - triglyceride

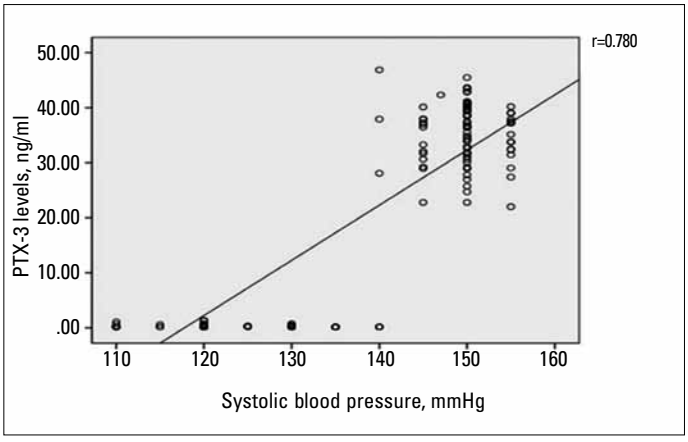

Figure 1. A linear relation between PTX-3 levels and increasing systolic blood pressure is shown on scatter diagram
PTX3 - pentraxin-3

Vessel wall elements produce high levels of PTX3 during inflammation. Thus, when compared to the liver-produced short-pentraxin CRP, PTX3 may represent a rapid marker for primary local activation of inflammation as well as of innate immunity. Indeed, blood levels of PTX3 rise dramatically in inflammatory conditions from <2 ng/mL up to 200-800 ng/mL during active disease (11). This occurs very rapidly when compared to the increase of CRP levels, consistent with the original identification of PTX3 as an immediate early gene (12).

It has been shown, that PTX3 levels slightly increase in psoriasis and unstable angina pectoris, moderately increase in febrile diseases and systemic inflammatory response syndrome, and severely increase in septic shock (13-17). Our study reveals that PTX3 levels increases up to 15 times than the upper limit of the normal range in hypertensive patients. Yılmaz et al. (18, 19) investigated PTX3 levels in type 2 diabetic patients with proteinuria and demonstrated a slight increase in both hypertensive and normotensive patients. Therefore it is interesting that PTX3 levels in diabetic patients of the mentioned study is lesser increased than the levels of isolated hypertensive patients in our study. Various conditions affect PTX3 levels by different biological molecules (20, 21). The reason for the less increase of PTX3 may be due to the fact that these patients suffer from a chronic illness and use several medical drugs.

Table 2. Relationship between PTX3 levels and clinical and laboratory variables

		CRP	FBG	TC	HDL	LDL	TG	BMI
PTX3	*p	0.49	0.66	0.69	0.70	0.45	0.11	0.14
	Beta	-0.119	-0.118	0.109	-0.06	-0.080	-0.037	-0.215
	**95% CI	-0.323-0.100	-0.239-0.076	-0.050-0.165	-0.132-0.208	-0.118-0.105	-0.005-0.068	-0.703-0.141

*Multivariate regression analysis. Dependent variable: PTX3; Independent variables: CRP, FBG, TC, HDL, LDL, TG and BMI. **95% confidence interval
BMI - body mass index, CRP - C reactive protein, FBG - fasting blood glucose, HDL - high density lipoprotein, LDL - low density lipoprotein, PTX3 - pentraxin 3, TC - total cholesterol, TG - triglyceride

Table 3. Relationship of SBP and DBP with biochemical and inflammatory mediators

		PTX3	CRP	FBG	Urea	Creatinine	TC	TG	HDL	LDL
SBP	*p	<0.001	<0.001	0.22	0.19	0.41	0.03	0.01	0.89	0.18
	Beta	0.819	0.115	0.003	-0.004	-0.010	0.141	0.068	0.003	-0.106
	**95% CI	0.644-0.799	0.370-0.572	-0.131-0.141	-0.164-0.147	-3.708-2.82	0.005-0.110	0.064-0.176	-0.094-0.102	-0.107-0.003
DBP	*p	<0.001	<0.001	0.16	0.25	0.34	0.06	0.10	0.56	0.18
	Beta	0.843	0.265	0.19	-0.016	-0.007	0.107	-0.036	0.034	-0.070
	**95% CI	0.422-0.526	0.101-0.280	-0.069-0.113	-0.124-0.084	-2.367-2.01	0.041-0.063	-0.017-0.008	-0.040-0.092	-0.059-0.015

*Multivariate regression analysis. Dependent variables: systolic and diastolic blood pressure. Independent variables: PTX3, CRP, FBG, urea, creatinine, TC, TG, HDL, LDL
**95% confidence interval
CRP - C reactive protein, DBP - diastolic blood pressure, FBG - fasting blood glucose, HDL - high density lipoprotein, LDL - low density lipoprotein, PTX3 - pentraxin 3, SBP - systolic blood pressure, TC - total cholesterol, TG - triglyceride

One of the most detailed studies on the molecular mechanisms of the role of CRP in angiogenesis and atherosclerosis was performed by Verma et al. (22). The correlation between CRP and hypertension was also introduced by several other studies (23-25). Bautista et al. (26) was the first who asserted that CRP increase has to be considered as an independent risk factor for hypertension. Hingorani et al. (27) demonstrated a significant correlation between moderate CRP increase and endothelial dysfunction. In our study we observed a moderate increase in CRP levels of newly diagnosed hypertensive. CRP levels of this study are similar with the other researches.

The American Heart Association pointed out that CRP is not a very suitable marker to be used in coronary heart diseases, because it is easily affected by other risk factors. On the other hand, they stated that it is needed to dwell on PTX3 from the same molecular family like CRP, because of its higher tissue-specify (25).

A study performed in 2009 stated that there is no detected relation between CRP and PTX3 levels in cardiovascular diseases (23). This study also revealed no significant relation between CRP and PTX3 levels in the hypertensive group.

It is also proclaimed that high HDL cholesterol levels or low LDL/HDL ratio adversely affects the release of PTX3 from adipose tissues, while high LDL cholesterol levels are correlated with high PTX3 levels (28, 29). It is also emphasized that this fact could be one of the secrets behind the development of atherosclerosis (28). Furthermore it is alleged that PTX3 levels are correlated to obesity, lipid levels, FBG, and blood pressure (22). Our study revealed no correlation between PTX3 and the factors proposed by Jenny et al. (23). except blood pressure, which showed a significant correlation to PTX3 levels. In this study, the correlation of PTX3 and blood pressure, as an independent parameter apart from investigated biochemical markers, can suggest us that it can be used as a useful marker in monitoring of hypertension in future.

In our study, systolic and diastolic blood pressures were found to be affected from the levels of PTX3, CRP, TC and TG. It is known that in hypertensives, CRP levels can be high and dyslipidemia can be found as a comorbid condition. We observed that the high level of PTX3 is one of the factors of increase blood pressure.

Study limitations

We consider that, not investigation of FMD, NOx, carotid intima-media thickness and other endothelial damage markers, which are used to show endothelial dysfunction, is the limitation of this study.

Conclusion

PTX3 levels are higher in hypertension patients. PTX3 levels are independent markers causing increase in blood pressure without being effected by other biochemical and inflammatory markers. PTX3 levels are investigated in many studies as endothelial injury marker but did not use routinely, we think that high levels of PTX3 in newly diagnosed hypertensive patients caused by endothelial injury of these patients.

Clinical implications

There are only a few studies, which investigated PTX3 levels and endothelial dysfunction. Studies with large numbers are needed to show this association. Researches with PTX3 and inflammation worked on diseases like myocardial infarction, renal failure, vasculities which many factors play a role as predisposing. Certain markers are found to be increased in inflammation and endothelial injury. Further research should be done to identify the position of PTX3 in this association.

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