Journal of Hypertension: Open Access

Parlak et al., J Hypertens 2014, 3:4
DOI: 10.4172/2167-1095.1000158

Research Article Open Access

Investigation of Pentraxin 3 Levels in Hypertensive Patients with Stroke, Retinopathy and Nephropathy

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Received date: April 16, 2014; **Accepted date:** July 03, 2014; **Published date:** July 08, 2014

Abstract

Background: In this study, we aimed to determine PTX3 levels in hypertensive patients with nephropathy, retinopathy and stroke.

Methods: This study is considering totally 135 patients including normotensives and newly diagnosed hypertensive and hypertensive with nephropathy, retinopathy and stroke. Blood samples were extracted to perform biochemical tests and PTX3 levels.

Results: It is observed that PTX3 levels in the normotensive patients, isolated hypertensive patients and hypertensive patients have complication resulted with statistically differences (0.19 ± 0.15 ng/Ml, 37.15 ± 8.02 ng/Ml, 451.28 ± 244.39 ng/mL, p<0.00001). This arises from the differences between the PTX3 levels which belong the patient group has complication along with other groups and isolated hypertensive group along with normotensive group by the performed Post Hoc analyze. If the patients have complication are compared with each other, it is observed PTX3 level in the retinopathy group is statistically higher with reference to other groups (In retinopathy, neuropathy and nephropathy groups' 710.90 ± 254.6 ng/mL, 408.14 ± 65.56 ng/mL, 253.61 ± 62.66 ng/mL, p<0.0001 respectively). It was established PTX3 levels in the complicated hypertensive patients is associated with BMI and LDL/HDL by the performed multivariate regression analysis (For BMI, LDL/HDL is respectively R square=0.085, F=5.84 and p=0.019 versus R square=0.153, F=5.61 and p=0.006).

Conclusion: It is observed in the present study that in hypertensive patients with stroke and retinopathy and nephropathy, and isolated hypertensive, PTX3 levels are elevated. It is also found BMI and LDL/HDL is associated with PTX3 levels.

Keyword:

Pentraxin 3; Hypertension; Complications; Multivariate regression analysis

Introduction

Hypertension is one of the most common reasons around the world which lead to mortality and morbidity. Early diagnosis and end organ damage severity and secondary disorders are crucial to detect the cardiovascular prognosis in the patients who suffer from the arterial hypertension [1,2]. Hypertensive end organ damage is an atherosclerosis which includes differentiation such as vascular and hemorrhagic stroke, retinopathy, cardiac disorder/myocardial infarction, heart failure, proteinuria and renal failure, stenos and aneurism [3]. Higher arterial blood pressure leads organ damages via hemodynamic load [4]. Not only high arterial pressure load but also a lot of factors which are associated with pathogenesis may influence the severity of the end organ damages [5]. The main reason of the vascular inflammation and cardiovascular disorders associated with hypertension could be the relationship between high blood pressure which leads mortality all around the world and atherosclerosis. Mechanical stress variety and activation of the humoral factors such as renin angiotensin aldosterone system could increase oxidative stress resulted from endothelial dysfunction and could also cause inducing the inflammatory procedure related with hypertension [6].

In a similar way to CRP, pentraxin 3 (PTX3) is a marker of the atherosclerosis which is a part of the progression of vascular events [7,8]. A variety of cells which suffers from primer inflammatory signal such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), oxidized low density lipoprotein (LDL) and microbial particules could produce PTX3 [1,2]. This cell group which includes macrophage, endothelial cells and venous smooth muscles could give more information about growing and improving of the atherosclerosis by releasing a marker called PTX3 which is more specific to vascular damages than other non-specific markers like CRP [9]. In our study about isolated hypertensive patients, it was established that PTX3 levels are higher than normal [10]. In addition to this, it was reported that there is a relationship between high blood pressure and PTX3 levels [11]. It is considered that the PTX3 levels may also increase in relation to vascular damages in patients who have nephropathy, retinopathy and stroke associated with hypertension. In this study, we aimed to determine PTX3 levels in complicated hypertensive patients.

Materials and methods

Study population

This study includes hypertensive patients and healthy volunteers who applied Gulhane Military Medical Academy, Department of Internal Medicine out-patients' clinic at the time between November 2010-May-2012. Totally 135 individuals including 35 normotensive healthy volunteers, 35 isolated and newly diagnosed hypertensive patients, 23 hypertensive patients who have nephropathy, 21 hypertensive patients who have stroke and 21 hypertensive patients with retinopathy were present in this study. Patients who have acute infection, diabetes mellitus, infertility history, cardiac failure, angina pectoris, psoriasis, rheumatoid arthritis and dementia were excluded. Patients whose serum creatinine increased (for men 1.3-1.5 mg/dl, for women 1.2-1.4 mg/dl), elevated albumin excretion (micro-albuminuria: 30-300 mg/24 hours, albumin: normal to 10 mg/g creatinine), calculated GFR rate <60 mL/minute/1.73 m^2 or creatinine clearance <60 mL/minute were accepted hypertensive nephropathy, also hypertensive patients with stage 3 or 4 retinopathy were accepted as hypertensive retinopathy. Patients who suffer from stroke are also included in hypertensive with stroke group.

All the individuals who were present in this study were informed about the study. After this information, complete blood count (CBC) test, liver and kidney functions test, lipid profile, fasting blood glucose and PTX3 levels were studied with the blood sample which is taken after 10 hours fasting at 08:00 am. In addition to this test, socio-demographic data such as length, weight, body mass index (BMI) was recorded.

This study is approved (confirmed) by Gulhane Military Medical Academy, Local Ethical Committee Presidency (GEK 1491–1054–10/1539).

Determination of PTX3 levels

PTX3 levels measured with serum samples which were obtained from venous blood sample by 4000 route per minute centrifuge during 10 minutes. All samples were held at -80° C to operate all the PTX3 measures at the same time. PTX3 levels were analyzed by an immunoassay method by using human quantitative Pentraxin Enzyme Immunoassay kits (Quantakine DPTX 30; R&D Systems Inc., Minneapolis, MN) via Bio-Tec reader at the same time. PTX3 levels were studied in accordance with description (using explanation) of the producer. The minimum detectable dose (MDD) for the used kit is 0.007-0.116 ng/mL, the average dose is 0.25 ng/mL.

Biochemical analyses

Contributors' liver function and kidney function tests, fasting blood glucose test and lipid profile were studied with the instrument called Olympus AU2700 chemistry Analyzer (Beckman coulter, California, USA).

Statistical Analysis

Statistical calculations of the data about this study were done via microprocessor by using commercial statistic software (SPSS ver. 15.0, SPSS Inc., Chicago, Illinois, USA). Firstly, Kolmogorov-Smirnov test utilized for the normality analyses of the data. The differences between the groups were investigated with chi square test, unpaired Student's t-test and Anova test. After math of the determination of the statistical variation between the groups, sub group investigation was operated with post hoc analyses. Multiple comparison tests were operated for the data which is considered to influence the PTX3 levels. The relevant data was calculated as mean ± standard deviation. P value which was calculating with 0.05 degree of freedom and by accepting confidence interval 95% is smaller than 0.05 is accepted as significant.

Results

No statistically difference was identified between the normotensive, hypertensive and complicated hypertensive groups in terms of length, weight and age (for all the relevant parameters, p>0.05, Table 1).

*Chi square test, † Anova test, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FBG: Fasting Blood Glucose, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TC: Total Cholesterol, TG: Triglyceride, AST: Aspartat Amino Tansferase, ALT: Alanin Amino Transferase, PTX3: Pentraxin 3, NS: Nonsignificant.

No differences between groups were observed related with glucose, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC), aspartate aminotransferase (**AST**), alanine aminotransferase (ALT) levels (p>0.05 for all parameters, Table 1).

	Normotensive group	Isolated hypertensive group	Complicated hypertensive group	P
Sex, women (%)	57.14	54.28	53.84	NS*
Age (year)	52.02 ± 5.85	54.31 ± 7.47	54.12 ± 2.43	NS†
Length (cm)	164.57 ± 2.71	164.40 ± 5.22	169.75 ± 9.00	NS†
Weight (kg)	77.71 ± 7.08	76.25 ± 8.42	78.64 ± 1.26	NS†
BMI (kg/m^2)	28.45 ± 2.78	28.66 ± 2.89	27.62 ± 2.71	NS†
SBP (mmHg)	110.50 ± 5.15	145.35 ± 4.87	148.25 ± 9.05	<0.0001†
DBP (mmHg)	78.00 ± 8.25	94.65 ± 6.45	98.15 ± 5.75	<0.0001†
FBG (mg/dl)	84.82 ± 9.68	89.15 ± 8.23	91.22 ± 3.45	NS†
HDL (mg/dl)	43.24 ± 5.08	40.05 ± 3.28	42.64 ± 6.14	NS†

LDL (mg/dl)	137.44 ± 25.58	140.52 ± 22.35	143.51 ± 29.51	NS†
TC (mg/dl)	209.88 ± 27.37	214.85 ± 39. 09	206.21 ± 40.52	NS†
TG (mg/dl)	139.31 ± 46.07	144.45 ± 52.39	143.49 ± 55.36	NS†
AST (U/L)	28.23 ± 5.45	25.33 ± 3.12	28.05 ± 7.21	NS†
ALT (U/L)	26.11 ± 9.47	21.16 ± 5.56	23.53 ± 4.87	NS†
PTX3 (ng/Ml)	0.19 ± 0.15	37.15 ± 8.02	451.28 ± 244.39	<0.0001†

Table 1: Demographic and clinical characteristics of the participants,

It was observed that PTX3 levels in normotensive volunteers and isolated hypertensive patients and hypertensive patients who have complication resulted in statistically significant differences (p<0.00001).

The result of the post hoc analysis shows that the difference is originated from the patient group who has complications with other groups (with both normotensive group and isolated hypertensive group comparisons, p<0.0001) and isolated hypertensive group (37.15 ± 8.02 ng/mL) with normotensive group (0.19 ± 0.15 ng/mL). Addition to this, it was observed that the PTX3 level in the patients who have retinopathy is statistically higher than in others (retinopathy, neuropathy, nephropathy is respectively 710.90 ± 254.6 ng/mL, 408.14 ± 65.56 ng/mL, 253.61 ± 62.66 ng/mL, p<0.0001). In the subgroup Post hoc analysis, it is established that there is statistically significant differences between retinopathy group with neuropathy and nephropathy groups (respectively p<0.0001 and p<0.0001, Figure 1).

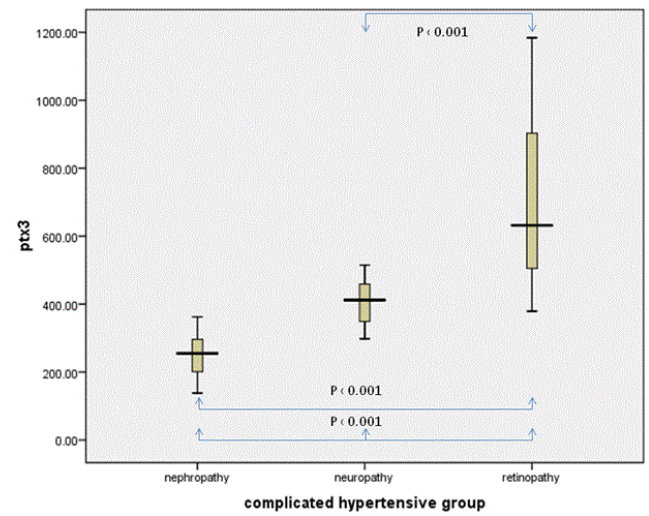

Figure 1: Comparation of the PTX3 levels in the hypertensive patient with developed complication

Moreover, the statistically differences between the neuropathy group and nephropathy group were also identified (p=0.004). By the applied Stepwise multivariate regression analysis, it was determined that differentiation of the PTX3 level 8.5% originate from BMI and 15.3% BMI and LDL/HDL ratio (Table 2).

	R	R square	F	p
BMI	0.29	0.085	5.84	0.019
BMI, LDL/HDL	0.39	0.153	5.61	0.006

Table 2: Assessment of the parameters may affect the PTX3 levels in the complicated hypertensive patients by stepwise multivariate regression analyses

PTX3: Pentraxin 3, BMI: Body Mass Index, LDL/HDL: Low Density Lipoprotein/High Density Lipoprotein. It was found that there is a correlation between PTX3 levels with BMI and LDL/HDL ratio in patients with complicated hypertension.

Discussion

In the present study, PTX3 levels are determined higher in the hypertensive patients and hypertensive ones with developed stroke, retinopathy and nephropathy related with hypertension. By developing retinopathy and neuropathy, PTX3 levels get advanced. Also, it has been found that BMI and LDL /HDL ratio are associated with PTX3 levels.

Evidences support that PTX3 levels could be an indicator which may be used in various clinical cases in order to show inflammation and the tissue damages [9]. Primary pro-inflammatory signals could increase the PTX3 releasing from the monocyte/macrophage and endothelial cells [12,13]. Literatures show PTX3 molecule help the mechanism which enhanced the inflammation and this molecule is associated with endothelial cells' function [14]. The PTX3 molecule is considered as a marker for atherosclerosis and founded associated with the evolving vascular events [6,9].

It is reported that PTX3 molecule indicate the local activation of the inflammation due to blood vessel wall unit produce high incidence of PTX3. The PTX3 levels could increase quickly from <2 ng/mL to 200-800 ng/mL during the active illness [1].

Large amount of study about hypertension are associated with disturbed endothelial function related with periphery, coroners and renal circulation. It is reported that decreasing of nitric oxide (NO) synthesis or increased inactivation of NO by free oxygen radicals lead enhancing the vascular resistance and vascular and/or cardiac hypertrophy related with hypertension, and coronary arterial disorders and stroke [15]. PTX3 is an independent risk factor for endothelial dysfunctions was considered due to the fact that PTX3 may produce in the inflammation area out of the liver [9]. It is established with the studies depend on this hypothesis that PTX3 levels increase in the

patients who have stroke, retinopathy and chronic renal failure [16-21]. In this study, higher PTX3 levels were detected in the patients who have developed complication. It was detected that PTX3 level increases with hypertension and/or developing hypertensive complication when considering the isolated hypertensive patients and normotensive volunteers who are the other participant of this study.

Some kind of mediators like interleukin, lipopolysaccharides, tumor necrosis factor alpha stimulate mRNA synthesis which is associated with PTX3, while at some case T and B lymphocytes, natural killer cells and polymorph nuclear leucocytes don't allow the PTX3 secretion signal [22]. Based on this, it was established that PTX3 levels are associated with cardiovascular disorders [9]. In complicated hypertensive group; development of retinopathy increases PTX3 level more than development of nephropathy or stroke. PTX3 level may be release more than other tissue in hypertensive patients with retinopathy.

The relationship between the cardiovascular risk factors and PTX3 levels in both healthy ones and patients who have some kind of cardiovascular disorders was studied. Ogava and et al. determine a negative relationship between the PTX3 levels and BMI, TG and weight while a similar relationship between BMI and TG was identified by Yamasaki K. and et al. [23,24]. In contrast, Alberti and et al. adduced that the PTX3 levels have positive correlation with BMI, HDL, HDL/LDL ratio and TG levels [25]. In this study, it was observed that BMI and LDL/HDL ratio are associated with PTX3. No association was found in the sense of other parameters. Observing inconsistent results in operated studies may due to the differences between patient groups which included, possibility of be present disturbing factors which can increase or suppresses PTX3 secretion or operating studies with different patient numbers.

There are some limitations in the present study. Firstly it could not be possible to prove a cause and effect relationship since this study is a cross sectional study. In addition to this fact, in order to determine the PTX3 level in the patients, blood sample was taken only once, however, it could be more suitable for this study to receive the blood sample more than once during the experiment time. Nevertheless, the quality of the study is tried to be enhanced by deciding the criteria of the exception accurately and avoiding the confounding factors.

In this study, it is observed that PTX3 levels increase in the patients who have stroke and retinopathy and nephropathy which are related with hypertension and isolated hypertensive individuals. In addition, it was found that BMI and LDL/HDL ratio are correlated with PTX3 levels. This indicator which is at the normal range in the normotensives while at high range in isolated hypertensive and hypertensive with developed complications is considered to be a marker to monitor a hypertension in the future. It may be beneficial to operate broader participation prospective studies in order to investigate PTX3 levels' alterations and developing complications in newly diagnosed hypertensive individuals by monitorizing them for many years.

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