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Associations of pentraxin 3 with presence and severity of coronary artery disease in type 2 diabetes patients

[Tip 2 diyabet hastalarında koroner arter hastalığı varlığının ve şiddetinin pentraxin 3 ile ilişkisi]

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ABSTRACT

Objective: Pentraxin 3 (PTX3) and C-reactive protein (CRP) may be associated with development of diabetic vascular complications. In the current study we evaluated the relationship between PTX3 levels and the presence and severity of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM). Furthermore, we compared the sensitivity and specificity of PTX3 and CRP for detection of CAD.

Methods: In 275 T2DM patients, coronary angiography revealed CAD (stenosis ≥ 50% at least in one vessel) in 140 patients and 135 patients without CAD. Gensini score was used to assess the severity of CAD. Demographic parameters and biochemical characteristics were measured in all participants.

Results: Log-transformed mean plasma PTX3 levels were higher in T2DM patients with CAD than in T2DM patients without CAD (2.42 ng/mL vs 1.98 ng/mL, $p<0.001$). Pearson correlation showed PTX3 levels highly correlated with systolic blood pressure, diastolic blood pressure, low-density lipoprotein-cholestrol and age. However, in multivariate linear regression analysis only age and hypertension was significantly related to PTX3 levels. Simple linear correlation in CAD patients group showed that Gensini score significantly related to PTX3($r=0.421$, $p<0.001$) and CRP ($r=0.187$, $p<0.05$). The area under the receiver-operating characteristic curve for PTX3 (0.0780, $p<0.001$) was superior to that for hs-CRP (0.683, $p<0.001$).

Conclusion: The PTX3 is associated with the presence and severity of CAD in patients with T2DM. Futhermore, PTX3 is a better biomarker for detection of CAD thanCRP.

Key Words: Type 2 diabetes mellitus, coronary artery disease, pentraxin3, C-reactive protein, Gensini score

Conflict of Interest: The authors have no conflict of interest.

ÖZET

Amaç: Diyabetik vasküler komplikasyonların gelişimi pentraksin 3 (PTX3) ve C-reaktif protein düzeyleri ile ilgilidir. Bu çalışmada tip 2 diyabetes mellitus hastalarında (T2DM) koroner arter hastalığı (CAD) varlığı ve şiddeti ile PTX3 düzeyleri arasındaki ilişki değerlendirildi. Buna ek olarak CAD varlığının tespitinde PTX3 ve CRP'nin duyarlılık ve özgünlüğünü karşılaştırdık.

Metod: Toplam 275 T2DM hastasından 140'ında koroner anjiyografi ile CAD varlığı (en az bir damarda %50'den≥stenoz) ve CAD olmayan 135 hasta tespit edildi. CAD şiddetini değerlendirmek için Gensini skorlaması kullanıldı. Tüm hastaların demografik parametreleri ve biyokimyasal karakteristikleri ölçüldü.

Bulgular: Koroner arter hastalığı olan T2DM hastaları, olmayanlar ile karşılaştırıldığında logaritması alınan ortalama plazma PTX3 düzeyleri CAD hastalığı olan grupta yüksek bulundu (2.42 ng/ml vs 1.98 ng/ml, $p<0.001$). PTX3 düzeyleri Pearson korelasyon analizinde sistemik kan basıncı, diastolic kan basıncı, düşük dansiteli lipoprotein-kolesterol ve yaş ile yüksek korele idi. Ancak çok değişkenli lineer regresyon analizinde PTX3 düzeyleri ile sadece yaş ve hipertansiyon anlamlı olarak ilişkiliydi. CAD olan hasta grubunda basit korelasyon ile PTX3 ($r=0.421$, $p<0.001$) ve CRP ($r=0.187$, $p<0.05$) düzeyleri Gensini skoru ile anlamlı olarak ilişkiliydi. PTX3 (0. 0.780, $p<0.001$) için ROC eğrisi altında kalan alan hs-CRP'ye (0.683, $p<0.001$) göre daha üstündü.

Sonuç: Tip 2 diyabet hastalarında CAD varlığı ve şiddeti PTX3 ile ilişkilidir. Ayrıca PTX3 CAD varlığının tespitinde CRP'den daha iyi bir biyobelirteçtir.

Anahtar Kelimeler: Tip 2 diyabetes mellitus, koroner arter hastalığı, pentraxin3, C-reaktif protein, Gensini skoru

Çıkar Çatışması: Yazarların çıkar çatışması yoktur.

Introduction

Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) are the main public health challenge for the 21st century [1]. Diabetes mellitus increases the risk of developing coronary heart disease (CHD) 2 to 3-fold, compared with individuals without diabetes [2]. Epidemiological studies indicate that diabetes mellitus can accelerate atherosclerotic processes and increase the incidence of cardiovascular events and strokes [3].

The mechanism through which the enhanced risk of atherosclerosis expressed is poorly understood but numerous observations support the theory that chronic low-degree inflammation is involved in the progression of atherosclerosis [4]. The innate immune system plays an important role in the development of CAD [5-8]. Recently, C-reactive protein (CRP) and pentraxin 3 (PTX3), two member of pentraxin family have been introduced as potential atherosclerotic biomarkers, because slightly increase in its blood levels has been associated with cardiovascular events [5-9].

PTX3 was more sensitive and specific to vascular inflammation than other proteins in the pentraxin family such as CRP [5]. For example, in the case of myocardial infarction (MI), the PTX3 concentration has been reported to peak more rapidly than the CRP concentration [10], which could indicate the higher sensitivity of PTX3 in response to vascular damage. PTX3 have a local production in various cells. All of these cells such as endothelical cells, monocytes, macrophages, fibroblasts ,dentritic cells and epithelial cells exist in vascular wall of heart and increase in atherosclerotic conditions. So, PTX3 could be a suitable biomarker of inflammation and atherosclerotic changes in this tissue [11-13].

Pentraxin 3 is structurally related but distinct from the classic short pentraxins, C-reactive protein and serum amyloid protein, differing in gene organization and localization, ligand recognition, producing cells, and inducing signals. PTX3 is expressed in response to primary proinflammatory signals such as bacterial products, interleukin-1, and tumor necrosis factor-alpha (TNF-a), oxidized low density lipoprotein (ox-LDL), microbial moieties [14], and serum amyloid A [15], but not interleukin-6 [16].

Pentraxin 3 levels are high in diseases characterized by persistent vascular inflammation, including systemic small vessel vasculitis [17] and chronic heart failure [7,8]. In both conditions, PTX3 levels are independent of those of CRP and identify patients with more severe disease and worse clinical outcome. Acute vascular injuries also cause the overexpression of PTX3 [18]. Jenny et al, reported that, PTX3 levels in apparently healthy older adults could independently of other cardiovascular risk factors predict cardiovascular disease [19].

However, there have been no sufficient studies presented so far that specifically evaluated the relationship between plasma PTX3 levels and coronary artery disease in type 2 diabetic patients. Furthermore, these studies often indirectly related to atherosclerosis. For instance, in two studies [20,21], researchers revealed that PTX3 concentration had significant positive correlation with carotid intima media thickness (CIMT) and significant negative correlation with flow-mediated dilation (FMD). CIMT and FMD are two markers of endothelial dysfunction.

So, in the present study we focused on more specific population of type 2 diabetes mellitus and followed three aims: First, to compare plasma PTX3 levels between patients with and without coronary artery disease. Second, to evaluate the correlation between plasma PTX3 levels and the severity of coronary artery disease assessed by coronary angiogram, using the Gensini score. Third, to compare the sensitivity and specificity of PTX3 and CRP for the diagnosis of the presence and severity of coronary artery disease in patients.

Materials and Methods

Study population

We evaluated all T2DM patients (n=853) with chest pain, who underwent coronary angiography at the Department of Cardiology, Ahvaz Imam Khomeini Hospital of Jondi Shapour University of Medical Sciences between August 2011 and December 2012. The Regional Ethics Committee for Medical Research (Tabriz University of Medical Sciences) approved the study protocol. The study complied with the declaration of Helsinki, and all of the patients gave written informed consent.

The inclusion criteria were: established T2DM and aged 40–60 years. Otherwise, Exclusion criteria were, body mass index >30, current smoking, diagnosed MI during the previous 3 months, and treatment for inflammatory or chronic infectious disease or malignancy. Individuals with CRP values above 10 mg/mL were excluded from the analyses due the possibility of an acute infection. For every participant, baseline information was conducted by trained research assistants and included questionnaires related to social and medical history and physical examination. Thus, 275 patients with complete data were included in the final analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with oral anti-hypertension drugs. Hyperlipidemia was diagnosed according to the guideline of the National Cholesterol Education Program (ATP III). T2DM was diagnosed according to the American Diabetes Association criteria [22].

Coronary Angiography

Coronary artery angiography was performed by using standard Judkins technique. Angiographic analysis was carried out by experienced cardiologists who were blinded to the study protocol. Angiography results were divided into CAD (≥50% obstruction in ≥1 coronary artery) group and non-CAD group. Gensini score assesses the

Table 1. Patient characteristics

	T2DM/CAD (n=140)	T2DM/non-CAD (n=135)	*P**
Age (years)	53.9±5.1	49.4±5.8	<0.001
Men	72(51.4)	51(37.7)	0.023
Duration of Diabetes (years)	7.9±7.2	6.9±6	0.22
Duration of CAD (years)	2.2±3.4	-------	
History of myocardial infarction	35(25)	-------	
Hypertention	84(61.3)	48 (36.6)	<0.001
Dyslipidemia	88(65.6)	74 (56.4)	0.13
Family history of CAD	30(29.4)	25 (20.4)	0.12
Body mass index (kg/m^2)	26.0±2.6	26.2±2.7	0.6
Systolic blood pressure (mmHg)	132.3±23.9	128.8±18.1	0.007
Diastolic blood pressure (mmHg)	82.4±13.8	77.6±10.8	0.003
Current use			
Lipid lowering drug	69(47.9)	50 (40.6)	<0.001
Acetyl Salisilic Acid	88(82.2)	42 (34.4)	<0.001
ACE inhibitors	41(40.1)	18(15)	<0.001
FPG (mg/dL)	151±53	147±51	0.18
Ln Triglyceride (mg/dL)**	5.0±0.5	5.2±0.5	<0.001
Ln Cholestrol (mg/dL)**	5.3±0.3	5.3±0.2	0.76
Ln CRP (mg/L)**	1.64±0.56	1.25±0.6	<0.001
HDL-c (mg/dL)	41.5±9.8	46.2±10.7	<0.001
LDL-c (mg/dL)	126.5±52.4	107.3±39.4	<0.001

Values presented are means±SD or numbers (%). Numbers may not add up to the expected total due to missing data for some variables. CRP: C-reactive protein; T2DM: Type 2 diabetes mellitus; CAD: Coronary artery disease; ACE: Angiotensin-converting enzyme; FPG: Fasting plasma glucose; HDL-c: High density lipoprotein-cholestrol; LDL-c: Low density lipoprotein-cholestrol; *Chi –Square or unpaired -sample t-test; **Ln-Transformed variables.

severity of coronary artery disease; it grades narrowing of the lumen of the coronary artery and scores it as 1 for 1-25% narrowing, 2 for 26-50% narrowing, 4 for 51-75%, 8 for 76-90%, 16 for 91-99% and 32 for a completely occluded artery. This score is then multiplied by a factor according to the importance of the coronary artery. The multiplication factor for a left main stem (LMS) lesion is 5. It is 2.5 for proximal left anterior descending artery (LAD) and proximal circumflex artery (CX) lesions, 1.5 for a mid-LAD lesion, and 1 for distal LAD, mid/distal CX and right coronary artery lesions. The multiplication factor for any other branch is 0.5.

Blood collection and biochemical analyses

In each case, 8 mL of blood was drawn in K-EDTA tubes for PTX3 and other biochemical marker measurement and 2 mL into tubes without additives for CRP determination. Phlebotomy was performed after an overnight fasting, serum and plasma were frozen at

-20°C. PTX3 levels were measured by commercially available sandwich ELISA (Glory Science Co., Del Rio, TX, USA). CRP levels were measured by commercially available sandwich ELISA (Labor Diagnostica Nord Gmbh & Co, KG). High-density lipoprotein cholesterol (HDL-c), Low-density lipoprotein cholesterol (LDL-c), total cholesterol, triglyceride (TG) and plasma glucose concentrations were determined enzymatically with a clinical chemistry analyzer (Vital Scientific, Spankeren, Netherlands).

Statistical analysis

Analysis of normality of the continuous variables was performed with the Kolmogorov–Smirnov test. The distribution of the CRP, PTX3, TG and cholestrol were not normal. These variables were logarithmically transformed and obtained a normal distribution. Data were expressed as means±Standard Deviation (SD), unless indicated otherwise. Significance between 2 groups was determined by unpaired Student's t test for continuous variables and by chi-square test for discrete variables. We used matched paired t-test for compare mean differences in PTX3 levels between groups after individually age-adjustment.

Pearson's correlation coefficients were used to evaluate the relationships between plasma PTX3 level and other variables. Linear regression analyses were used to look for associations between serum PTX3 levels and selected laboratory and clinical parameters. The predictive values of PTX3 and CRP for the presence of CAD were calculated by constructing receiver-operating characteristic (ROC) curves. P values <0.05 were considered significant, and all statistical tests were 2-sided. Statistical

analysis was performed using the SPSS software package (SPSS 16.0; SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of study subjects

Characteristics of the two diabetic patient groups are shown in Table 1. Diabetic patients with CAD were older, hypertensive and more were male compared with the patients without CAD. The CAD group had significantly higher levels of CRP, LDL-C and lower levels of TG and HDL-c. CAD patients had longer duration of diabetes. There was also no significant difference in the hyperlipidemia, BMI, FPG, Family history of CAD and total cholesterol levels between two groups. In addition, diabetic patients in the CAD group receiving all three medications were significantly higher (Table 1).

After log transformation, PTX3 concentrations in the CAD and non-CAD patients were 2.42 and 1.98 ng/mL, respectively, revealing a significant increase in PTX3 concentrations in CAD patients compared with non-CAD patients (p<0.001). After adjustment for age this difference remained significant (p<0.001) (Fig 1).

Associations of PTX3 with CVD Risk Factors

Pearson correlation analysis showed that PTX3 levels was closely related to age (r=0.230, p<0.001), systolic blood pressure (r=0.238, p<0.001), diastolic blood pressure (r=0.228, p<0.001), LDL-c(r=0.141, p=0.020) and somewhat with duration of diabetes (r=0.109, p=0.086), but not with CRP (r=0.092, p=0.127) and other risk factors (Table 2).

In the final multivariate linear regression analysis model that explained 39% (adjusted multiple R2=0.390) of the variation in PTX3 levels, the independent determinants were age (p<0.001), diabetes duration (p=0.439), history of hypertension (p<0.001), SBP (p=0.383), DBP (p=0.761), number of damaged vessels (p<0.001) and LDL-c (p=0.576) (Table 3).

Comparison PTX3 andCRP in Predicting presence and severity of CAD

The Gensini score ranged from 0 to 158 with a mean of 21.1±30.3. Simple linear correlation in CAD patients group showed that Gensini score significantly related to PTX3 (r=0.421, p<0.001) and CRP (r=0.187, p<0.05) (Fig 2). No significant correlations with the PTX3 concentration were observed in non-CAD patients group (not shown). The area under the ROC curve for PTX3 (0.780, 95% CI 0.726 to 0.834, p<0.001) was superior to that for CRP (0.683, 95%CI 0.620 to 0.746, p<0.001) (Fig 3).

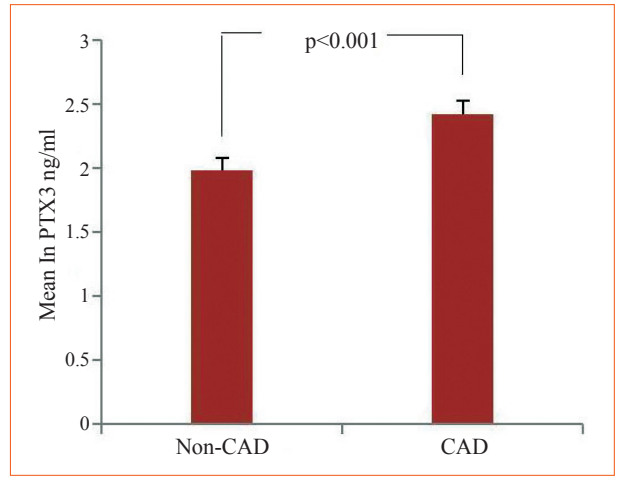

Figure 1. Mean ln plasma PTx3 levels in the diabetic patients with and without CAD. CAD=Coronary artery disease.

Discussion

To the best of our knowledge, no previous study has investigated PTX3 in T2DM patients with angiography-proven CAD. In the present study, we found significantly higher levels of PTX3 in T2DM-CAD patients compared to T2DM- nonCAD patients.

In the several studies PTX3 levels in healthy non-diabetic volunteers were <2ng/mL [23]. There are no sufficient studies for determination of PTX3 levels in exclusively type 2 diabetic patient population. Yilmaz et al, revealed that PTX3 levels were significantly higher in T2DM than non-diabetic in chronic kidney disease subjects [24]. Inoue et al, demonstrated that the plasma PTX3 levels were significantly higher in patients with UAP than a normal group. Further, diabetic patients in this study had higher PTX3 levels than non-diabetic patients. Knoflach et al, in the Bruneck Study analyzed plasma PTX3 levels in patients with coronary artery disease and showed similar results [25]. Jylhävä et al. demonstrated that the plasma PTX3 levels were significantly higher in insulin-resistant patients than control subjects [26]. Our results are consistent with all of those studies. In our study, plasma

Table 2. Pearson's correlations for (ln) PTX3

age	DM duration	BMI	hsCRP*	TG*	TC*	LDL	HDL	DBP	SBP
r=0.230	0.109	0.006	0.092	-0.071	0.049	0.141	-0.086	0.228	0.238
P<**0.001**	0.086	0.923	0.127	0.240	0.423	**0.020**	0.157	**<0.001**	**<0.001**

Statistically significant correlations (*P*<0·05) are shown in bold type; *Ln-Transformed variables; DM: diabetes mellitus; BMI: body mass index; CRP: C-reactive protein; TG: triglyceride; TC: total cholestrol; PTX3: pentraxin 3; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

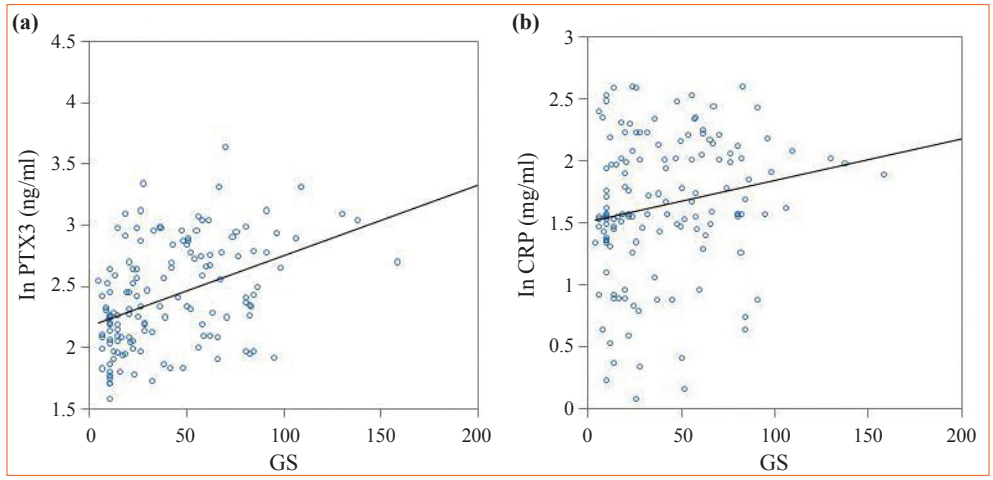

Figure 2. A,B Simple linear correlation of Gensini score and PTX3(a) and CRP (b) in patients with type 2 diabetes. GS=Gensini score.

PTX3 and CRP concentrations were significantly correlated with Gensini scores only in T2DM-CAD patients. Although, PTX3 concentrations had stronger correlation with Gensini scores than did CRP. Few studies investigated association between PTX3 and Gensini score. Soeki et al, demonstrated that concentrations of PTX3 in coronary sinus and peripheral plasma correlated with Gensini scores as an index of severity of coronary atherosclerosis [27]. Also, several studies investigated association between PTX3 and carotid intima media thickness (CIMT), as early stage atherosclerosis. PTX3 levels were associated with CIMT in advanced human atherosclerosis but not in CVD-free individuals with early atherosclerotic lesions [19,25,28], all of which are consistent with our findings.

In the present study, Pearson correlation analysis showed that PTX3 was significantly and positively related to, age, SBP, DBP, LDL-c and weakly related to diabetes duration. Meanwhile, plasma PTX3 non-significantly had inverse correlation with triglyceride (TG) and low HDL cholesterol levels. We observed no correlation between plasma PTX3 andCRP and other risk factors. Among cardiovascular risk factors examined in multiple regression modal, only age, history of hypertension and number of damaged vessels were significantly related to PTX3 levels. However, no strong significant relationship between PTX3 levels and none of factors were observed. A possible reason is that we deal with highly selected population and all subjects are diabetic. So, large scale studies are needed in this regard to get the actual correlation levels for this population. PTX3 levels differences between two study groups remained significant after adjustment for age and hypertension. In the several studies, there seems to be a consensus that advancing age is associated with higher PTX3 levels [6,19,29,30], a notion that was also verified in our study. Results on the associations of PTX3 with CRP and other risk factors [6,16,29] also seem to be contradictory. Yamasaki et al, have found inverse correlations between PTX3 levels and triglyceride and between plasma PTX3 and BMI [29]. In contrast, Zanetti et al, revealed direct correlation of plasma PTX3 levels with triglyceride levels and inverse with HDL cholesterol levels [31]. In rheumatic and non-rheumatic patients with CVD lack of association between the levels of PTX3 and all plasma lipids have also been reported [19,30]. Alberti et al. detected correlation between expression of PTX3 in adipose tissue and BMI, HDL, HDL/LDL ratio, triglyc-

Table 3. Relationship between PTX3 levels and clinical and laboratory variables

		age	SBP	DBP	LDL-c	VD	FH	HTN	Gender
PTX3***	P*	**0.013**	0.383	0.761	0.576	**<0.001**	0.926	**0.001**	0.845
	Beta	0.190	0.081	0.028	0.037	0.492	0.007	0.230	-0.014
	95%CI**								
	Upper limit	0.001	0.008	0.006	0.002	0.223	0.117	0.317	0.073
	Lower limit	0.005	-0.002	-0.008	0.000	0.141	0.142	0.106	0.156

*Multivariate regression analysis; Dependent variable: PTX3; Independent variables: age, SBP, DBP, LDL-c, DM-duration, VD, FH, HTN, Gender; DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-c: Low density lipoprotein-cholestrol; FH: Familial history of CAD; HTN: Hypertension; VD: Number of damaged vessels; **95% confidence interval; ***Ln-Transformed variables.

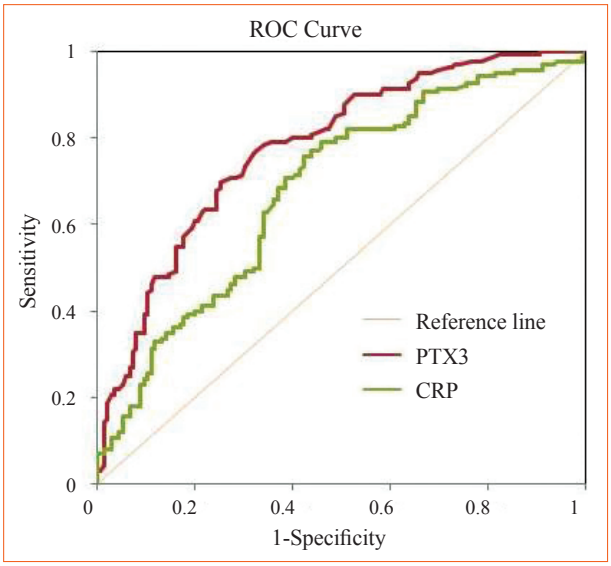

Figure 3. Receiver-operating characteristic (ROC) curve for PTX3 and CRP in predicting coronary artery disease. (CAD) in patients with type 2 diabetes (T2DM).

erides and CRP [32]. Whereas they did not find a correlation between the levels of PTX3 and LDL cholesterol, glucose, insulin or blood pressure. Bosutti et al. showed that PTX3 mRNA levels in adipose tissue in non-diabetic subjects are associated with plasma LDL-cholesterol [33]. Some of the inconsistency among studies may reflect the different sociodemographic composition of the samples, different accompanied disorders and the different inclusion and exclusion criteria. As shown in Figure 2, PTX3 has higher correlation with Gensini score than CRP. On the other hand we revealed that, the area under the ROC curve for PTX3 was superior to that for CRP. Thus, PTX3 exhibits higher sensitivity and specificity for detection of CAD than CRP. This superiority was consistent with several studies [5,34]. This prognostic superiority of PTX3 over CRP may because CRP is derived from hepatocytes, while PTX3 is synthesized in several cell types found in atherosclerotic lesions. This locally produced PTX3 may show more closely related than CRP to cardiac injuries.

Although *in vitro* and *in vivo* studies have demonstrated a direct association between PTX3 expression and atherosclerosis, several recent studies reported that PTX3 has cardioprotective and atheroprotective function through the modulation of the immunoinflammatory balance in the cardiovascular system [35,36]. These observations also propose that the protective physiologic response proportional to the severity of cardiovascular disease (CVD) may be cause of increased levels of PTX3 in these patients.

We use the gold standard of diagnosis, which is, coronary angiography to determine the stenosis. This is one of the powers of our study because other methods may overestimate the extent of stenosis due to artifact caused by extensive calcification or imaging modalities like computed tomography angiography. A few limitations of this study should be recognized. First, the sample size was relatively small in this study, so that some subgroup comparisons may have lacked power to detect significant differences for selected variables. Second, type 2 diabetes patients were highly selected and may not be representative of most patients with type 2 diabetes. Third, the present study was a cross-sectional design, our results only show the association between PTX3 levels and prevalent CAD rather than incident CAD. Finally, the mean age of two patient groups were not equal because finding completely healthy elderly subjects were not easy. However, the age of two groups were in same range and we matched two groups for age using statistical methods before analysis.

Conclusion

Our findings, irrespective of available evidence on the role of PTX3 as cardiovascular biomarker or as atheroprotective agent, suggests that the increased levels of PTX3 in T2DM patient could reflect a coronary artery damage that correlates with the severity of the disease.

Furthermore, PTX3 is a better biomarker for detection of CAD than CRP. However, further large-scale studies are still needed to confirm our results and to determine the other factors involved in the regulation of PTX3 in T2DM patients.

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Authors' contributions

NR Participated in the study design, analyzed the data and assessment final version of the manuscript. MG Designed the experiment and contributed reagents/materials/analysis tools.

SA Collected data, performed the experiments, analyzed the data and wrote the manuscript.

GM Checked the statistical methods used in the study. SM Participated in Patient selection and Gensini score calculation,

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Conflict of Interest

There are no conflicts of interest among the authors.

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