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Pentraxin 3 (PTX3) is associated with cardiovascular risk factors: the Health 2000 Survey

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Summary

Pentraxin 3 (PTX3) is a novel candidate immunoinflammatory marker that has been reported to be associated with cardiometabolic risk factors and to predict adverse outcomes in individuals with cardiovascular disease (CVD). Despite being a member of the same pentraxin protein family as C-reactive protein (CRP), PTX3 probably reflects different aspects of CVD pathogenesis. In this study, we assessed plasma PTX3 correlates and determinants in the Health 2000 Survey population, which comprised $n = 403$ insulin-resistant subjects, $n = 845$ hypercholesterolaemic subjects and $n = 311$ hypertensive subjects, all aged between 46 and 76 years. In insulin-resistant subjects the PTX3 concentration was found to correlate directly with age, pulse pressure and indoleamine 2,3-dioxygenase (IDO) enzyme activity and inversely with total and low-density lipoprotein (LDL) cholesterol. In hypercholesterolaemic subjects, the PTX3 concentration correlated directly with HDL cholesterol, systolic blood pressure and pulse pressure, whereas in hypertensive subjects, the PTX3 concentration correlated directly with systolic blood pressure, pulse pressure and IDO activity. No correlation was observed between the concentrations of PTX3 and CRP, adiposity indicators or indicators of subclinical atherosclerosis in any of the subject groups. PTX3 concentration variations were attributed to variations in LDL cholesterol and IDO activity in insulin-resistant subjects and to pulse pressure in hypercholesterolaemic and hypertensive subjects. These results indicate that, in individuals at high risk of CVD, the PTX3 concentration is associated with cardiovascular risk factors but not with subclinical atherosclerosis.

Keywords: acute phase proteins, atherosclerosis, inflammation/inflammatory mediators including eicosanoids

Introduction

Immune response and inflammatory factors are known to be involved in the development of atherosclerosis from the point of endothelial injury to acute clinical manifestations. According to current understanding, chronic low-grade inflammation in the arterial wall can accelerate the accumulation of asymptomatic atherosclerotic changes, whereas an abrupt and more vigorous inflammatory activation precedes end-point plaque rupture [1]. However, it is unclear whether inflammatory mediators can act as causal agents in the pathogenesis of cardiovascular disease (CVD) or whether they merely emerge as indicators of ongoing vascular damage. Various players of the innate immune system, such as the traditional C-reactive protein (CRP) and a newer candidate of the same pentraxin family, pentraxin 3 (PTX3), have been presented as potential atherosclerotic biomarkers, as their low-level increase in plasma has been associated with cardiovascular events in a number of studies [2–7].

PTX3 is an acute-phase reactant that shares structural and functional homology with CRP, as it activates the complement system, binds microbial surfaces and apoptotic cells and aids in their clearance [8]. However, unlike CRP, which is synthesized mainly in the liver, PTX3 is produced at the site of inflammation by macrophages, dendritic cells, neutrophils, fibroblasts, endothelial cells and smooth muscle cells

(SMCs) [8]. Synthesized PTX3 can also be stored in neutrophil granules that, upon stimulation, release PTX3 rapidly into circulation [9]. Production of PTX3 is induced by interleukin (IL)-1, tumour necrosis factor (TNF)-α, oxidized low-density lipoprotein (ox-LDL) and microbial moieties, but is not induced by IL-6 [8]. It has been suggested that PTX3 plays the same role in the periphery that CRP does in circulation [10]. However, in the case of myocardial infarction (MI), the PTX3 concentration has been reported to peak more rapidly than the CRP concentration [2], which could indicate the higher sensitivity of PTX3 in response to vascular damage. Alternatively, the PTX3 concentration may reflect different and uncharacterized aspect(s) of inflammation because in mouse models of atherosclerosis and MI, PTX3 has been demonstrated to exert a cardioprotective function [11,12].

Despite the incompletely understood role of PTX3 in vascular biology, several lines of epidemiological and experimental evidence imply that PTX3 could be involved intimately in the pathogenesis of CVD. Elevated PTX3 plasma levels have been associated with adverse cardiovascular outcomes [2–4,6,7], and PTX3 expression has also been detected in atherosclerotic plaques [13,14]. Furthermore, PTX3-positive neutrophils can infiltrate atherosclerotic lesions, and their presence has been observed in coronary arterial thrombi originating from culprit lesions in MI patients [14]. However, no consensus currently exists as to whether plasma PTX3 is an independent risk factor in the pathophysiology of atherosclerosis or whether it is just an auxiliary signalling marker between vascular inflammation and tissue repair. To determine the usefulness of PTX3 as a marker of subclinical atherosclerosis in individuals free of clinical CVD, we studied the relationship between plasma PTX3 and the following factors: cardiovascular risk factors, indices of subclinical atherosclerosis and inflammatory measures, namely CRP and indoleamine 2,3-dioxygenase (IDO) enzyme activity.

Materials and methods

Study population

The study population was a subpopulation drawn from the Health 2000 Survey, a large Finnish cross-sectional health examination survey carried out from 2000 to 2001 [15]. The overall study cohort was a two-stage stratified cluster sample (8028 individuals) representing the entire Finnish population aged 30 years and older. To study cardiovascular risk and diabetes more thoroughly, a supplemental study was carried out (sample size 1867, 82% participation rate). The participants in this study consisted of those supplementary study subjects for whom clinical and metabolic cardiovascular risk factor data were available. The study population consisted of the following subject groups, based on clinical condition: 403 insulin-resistant subjects, 845 hypercholesterolaemic subjects, 311 hypertensive subjects and 108 healthy subjects, all aged between 46 and 76 years, and without a history of CVD, MI, stroke or heart failure. Please see the inclusion criteria for the subject groups in the following section (Clinical and biochemical analyses). Among the 403 insulin-resistant subjects, 355 individuals also had hypertension and/or hypercholesterolaemia; among the 845 hypercholesterolaemic subjects, 521 individuals also had insulin resistance and/or hypertension; and among the 311 hypertensive subjects, 284 individuals had also hypercholesterolaemia and/or insulin resistance. The study was conducted in five Finnish University Hospitals. The Health 2000 Survey protocol was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. All participants gave their written informed consent.

Clinical and biochemical analyses

Height and weight were measured, and body mass index (BMI) was calculated. Waist and hip circumferences were measured in the standing position using the standards created for population health studies. Waist circumference was not measured in the supplemental study; therefore, the waist circumference values measured for the Health 2000 Survey were used. Blood pressure was measured after at least 10 min of rest with the automatic Omron M4 manometer (Omron Matsusaka Co., Japan; Omron Healthcare Europe BV, Hoofddrop, the Netherlands) and the mean of three measurements was used in the analysis. Pulse pressure was calculated as the difference between the mean systolic pressure and the mean diastolic pressure.

Current smoking, diabetes, CVD history and CVD events, including coronary artery disease (CAD), were evaluated with a questionnaire. Those who were current smokers were defined as smokers, and the rest of the subjects were defined as non-smokers. Insulin resistance was assessed according to the International Diabetes Federation criteria [16], and hypercholesterolaemia (LDL cholesterol >3 mmol/l or total cholesterol >5 mmol/l) and hypertension (diastolic blood pressure >90 mmHg and systolic blood pressure ≥140) were assessed according to the Finnish Current Care guidelines, formulated on the basis of the European guidelines on cardiovascular disease prevention [17]. Subjects were classified as healthy based on the absence MI, CAD, heart failure, stroke, diabetes, hyperlipidaemia, hypercholesterolaemia and hypertension.

Venous blood samples were drawn after an overnight fast. High-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride and plasma glucose concentrations were determined enzymatically with a clinical chemistry analyser (Olympus, AU400, Hamburg, Germany). LDL cholesterol was calculated with the Friedewald formula. Plasma insulin concentrations were determined using a radioimmunoassay (Phadeseph Insulin RIA, Pharmacia Sweden). Homeostasis assessment of insulin resistance (HOMA-IR) was calculated

according to the formula: HOMA-IR = fasting glucose (mmol/l) × fasting insulin (mU/l)/22·5 [18]. Detailed descriptions of the methods used have been published elsewhere [19]. Plasma CRP concentrations were determined using a chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA). PTX3 concentrations were determined in ethylenediamine tetraacetic acid (EDTA)-plasma using a commercial enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer's instructions (Quantikine DPTX 30; R&D Systems Inc., Minneapolis, USA). According to the manufacturer, the mean detection limit for the assay is 0·025 ng/ml and it exhibits no cross-reactivity with either CRP or serum amyloid P. The enzymatic activity of IDO was assessed (data available in 759 individuals) using the plasma kynurenine/tryptophan ratio (μmol/mmol), as described previously [20].

Carotid artery studies

High-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to a standardized protocol using a 7·5-MHz linear array transducer. The examinations were performed by centrally trained and certified sonographers at six study locations throughout Finland. Carotid IMT measurements were performed off-line with the use of automated image processing software, and one researcher was responsible for reading all of the ultrasound images. Three summary measures of the carotid IMT were calculated: (i) the mean of the three average IMTs of the common carotid artery (mean CCA IMT), (ii) the mean of the three average IMTs of the carotid bulb (mean bulb IMT) and (iii) the mean of these two means (mean IMT). Mean IMT was used in the present study. This method has been described in detail previously [21]. Arterial elasticity was assessed as carotid artery compliance (CAC) according to the following formula:

$$\mathrm{CAC}\,(\%/10\ \mathrm{mmHg}) = 100 \times 10 \times [(\mathrm{ADC}/\mathrm{DAD})/\mathrm{PP}],$$

where ADC is the arterial diameter change, DAD is the diastolic arterial diameter and PP is pulse pressure. Arterial diameters were calculated as the mean of three average systolic and diastolic arterial diameters.

Statistical analyses

Individuals with CRP values above 10 mg/ml were excluded from the analyses ($n = 66$) due the possibility of an acute infection. The distributions of the PTX3, CRP, insulin, HOMA-IR and triglyceride values were skewed, hence the variables were transformed logarithmically prior to the analyses. Student's *t*-tests and Mann–Whitney's tests were used to analyse differences between sexes in the test variables, and χ^2 analyses with Fisher's exact tests were used to assess differences in smoking between sexes and prevalence of CVD events between sexes. The correlates for plasma PTX3 were estimated separately for each subgroup (insulin-resistant subjects, hypercholesterolaemic subjects, hypertensive subjects and healthy subjects) using Pearson's tests. Stepwise multivariate linear regression modelling was performed to assess the independent determinants for plasma PTX3 concentration. Regression modelling for the determinants of PTX3 was not, however, performed for the healthy subjects due to the lack of statistically significant correlates for the PTX3 concentration (Table 2). All statistical analyses were performed using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA) and *P*-values < 0·05 were considered statistically significant.

Results

The characteristics of the study population are presented in Table 1. The majority of the variables differed significantly between men and women; the only variables that did not deviate between the sexes were age, LDL cholesterol level, pulse pressure, CRP level, PTX3 level and IDO activity. Additionally, the prevalences of hypertension, hypercholesterolaemia, CAD, heart failure and stroke did not differ between the sexes. In insulin-resistant subjects, the PTX3 concentration correlated directly with age, pulse pressure and indoleamine 2,3-dioxygenase (IDO) enzyme activity and correlated inversely with total and LDL cholesterol (Table 2). In hypercholesterolaemic subjects, the PTX3 concentration correlated directly with HDL-cholesterol, systolic blood pressure and pulse pressure (Table 2). In hypertensive subjects, the PTX3 concentration correlated directly with systolic blood pressure, pulse pressure and IDO activity (Table 2). No significant correlations with the PTX3 concentration were observed in healthy subjects (Table 2). Smoking was not associated with plasma PTX3 concentration ($P = 0{\cdot}546$). The determinants, i.e. factors that explained the variation in plasma PTX3, were LDL cholesterol and IDO activity in insulin-resistant subjects, and pulse pressure in hypercholesterolaemic and hypertensive subjects (Table 3).

Discussion

In this study, we demonstrated that the plasma PTX3 concentration correlates with several cardiovascular risk factors in individuals at high risk of developing CVD. In insulin-resistant subjects plasma PTX3 correlated directly with age and pulse pressure, and inversely with total and LDL cholesterol. In hypercholesterolaemic subjects, we found that plasma PTX3 correlated directly with age, HDL cholesterol, systolic blood pressure and pulse pressure, whereas in hypertensive subjects PTX3 correlated directly with diastolic blood pressure and pulse pressure. In addition, we observed that PTX3 correlated directly with another inflammatory marker, IDO, in insulin-resistant and hypertensive subjects. The factors explaining the variation in plasma PTX3 were found

Table 1. Characteristics of the study population.

	All		Men		Women		*P* for difference between sexes
	Mean	s.d.	Mean	s.d.	Mean	s.d.	
Age (years)	58·21	8·03	57·90	7·75	58·47	8·246	0·223
BMI (kg/m^2)	27·13	4·35	27·49	3·97	26·82	4·62	0·006
Waist circumference (cm)	93·36	13·11	99·31	11·31	88·23	12·36	<0·001
Hip circumference (cm)	102·19	9·08	101·27	7·98	102·97	9·86	<0·001
Waist-to-hip ratio	0·91	0·09	0·98	0·06	0·85	0·06	<0·001
Heart rate (beats/min)	66·51	10·14	65·49	10·51	67·35	9·75	0·002
Systolic blood pressure (mmHg)	138·47	21·71	141·63	20·46	135·71	22·41	<0·001
Diastolic blood pressure (mmHg)	84·42	10·56	87·50	10·79	81·80	9·62	<0·001
Pulse pressure (mmHg)	54·02	15·00	54·15	13·76	53·91	15·99	0·798
Total cholesterol (mmol/l)	5·59	0·94	5·50	0·96	5·66	0·91	0·002
HDL cholesterol (mmol/l)	1·58	0·43	1·43	0·38	1·71	0·43	<0·001
LDL cholesterol (mmol/l)	3·40	0·87	3·41	0·88	3·38	0·86	0·626
Triglycerides (mmol/l)*	1·20	0·90–1·60	1·30	1·00–1·80	1·10	0·80–1·50	<0·001
Glucose (mmol/l)	5·85	1·19	6·13	1·35	5·61	0·97	<0·001
Insulin (mmol/l)*	7·80	5·70–11·10	8·50	5·93–12·28	7·30	5·40–10·20	<0·001
HOMA-IR*	1·98	1·37–2·96	2·23	1·49–3·36	1·80	1·29–2·69	<0·001
CRP (mg/l)*	1·44	0·79–2·87	1·47	0·82–2·81	1·38	0·76–2·95	0·332
PTX3 (ng/l)*	1·01	0·68–1·44	1·04	0·74–1·44	0·98	0·64–1·46	0·107
IDO (kyn/tryp)	31·65	8·27	31·36	8·02	31·89	8·48	0·379
IMT (mm)	0·93	0·23	0·96	0·24	0·90	0·21	<0·001
CAC (%/10 mmHg)	0·93	0·48	0·88	0·41	0·96	0·53	0·010
Smoking (%)†							
No	78·5		73·7		82·6		<0·001
Yes	21·5		26·3		17·4		
Hypertension (%)†							
No	71·8		71·5		72·0		0·845
Yes	28·2		28·5		28·0		
Insulin resistance (%)†							
No	58·1		52·4		62·7		0·001
Yes	41·9		47·6		37·3		
Hypercholesterolemia (%)†							
No	21·3		23·0		80·3		0·684
Yes	78·7		77·0		68·2		
Diabetes (%)†							
No	94·6		92·4		96·5		0·002
Yes	5·4		7·6		3·5		
CAD (%)†							
No	93·5		93·0		94·0		0·471
Yes	6·5		7·0		6·0		
Heart failure (%)†							
No	96·6		95·6		97·4		0·076
Yes	3·4		4·4		2·6		
MI (%)†							
No	96·0		93·9		97·7		0·001
Yes	4·0		6·1		2·3		
Stroke (%)†							
No	98·1		97·4		98·8		0·064
Yes	1·9		2·6		1·2		

*Median values and interquartile range (IQR): Mann–Whitney's *U*-test for difference between sexes. †χ^2 test for difference between sexes; *t*-test for difference between sexes. BMI: body mass index; CAC: carotid artery compliance; CAD: coronary artery disease; CRP: C-reactive protein; PTX3: pentraxin 3; HDL: high-density lipoprotein; HOMA-IR: insulin resistance index; IDO: indoleamine 2,3-dioxygenase (IDO) enzyme; IMT: intima-media thickness; LDL: low-density lipoprotein; MI: myocardial infarction; s.d.: standard deviation.

Table 2. Pearson's correlations for (log)pentraxin 3 (PTX3).

	Insulin-resistant subjects $n = 403$		Hypercholesterolaemic subjects $n = 845$		Hypertensive subjects $n = 311$		Healthy subjects* $n = 108$	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0·105	**0·034**	0·085	**0·013**	0·103	0·070	0·033	0·734
Body mass index (kg/m)	–0·059	0·236	–0·058	0·093	0·034	0·546	–0·069	0·475
Waist circumference (cm)	–0·014	0·783	–0·017	0·613	0·028	0·621	0·032	0·744
Hip circumference (cm)	–0·037	0·464	–0·009	0·805	0·074	0·192	–0·035	0·722
Waist-to-hip ratio	0·021	0·680	–0·019	0·574	–0·030	0·604	0·068	0·485
Heart rate (beats/min)	–0·023	0·652	0·038	0·273	0·079	0·167	–0·060	0·541
HDL cholesterol (mmol/l)	0·017	0·737	0·080	**0·019**	0·058	0·310	–0·048	0·623
LDL cholesterol (mmol/l)	–0·139	**0·006**	–0·061	0·079	0·040	0·487	–0·107	0·273
Total cholesterol (mmol/l)	–0·102	**0·040**	–0·012	0·721	0·063	0·270	–0·156	0·106
(log)Triglycerides (mmol/l)	0·034	0·498	–0·012	0·722	0·001	0·987	–0·019	0·844
Glucose (mmol/l)	0·041	0·408	0·053	0·126	0·018	0·748	0·074	0·448
(log)Insulin (mmol/l)	0·082	0·102	0·032	0·360	0·103	0·069	0·070	0·474
(log)HOMA-IR	0·081	0·103	0·042	0·225	0·091	0·110	0·079	0·414
Systolic blood pressure (mmHg)	0·089	0·073	0·117	**0·001**	0·143	**0·012**	0·159	0·102
Diastolic blood pressure (mmHg)	0·017	0·733	0·062	0·073	0·025	0·666	0·168	0·083
Pulse pressure (mmHg)	0·111	**0·025**	0·126	**<0·001**	0·171	**0·003**	0·110	0·261
(log)CRP (mg/l)	0·041	0·413	–0·006	0·868	0·041	0·467	0·083	0·390
IDO	0·161	**0·010**	0·010	0·828	0·152	**0·035**	0·031	0·795
Carotid IMT (mm)	0·057	0·260	0·041	0·243	0·032	0·578	0·044	0·656
Carotid artery compliance (%/10 mmHg)	–0·051	0·339	–0·062	0·090	–0·085	0·155	0·038	0·707

Statistically significant correlations ($P < 0·05$) are shown in bold type. *Subjects excluded for CVD, MI, stroke, heart failure, insulin resistance, hyperlipidaemia or hypertension. BMI: body mass index; CAC: carotid artery compliance; CRP: C-reactive protein; PTX3: pentraxin 3; HDL: high-density lipoprotein; HOMA-IR: insulin resistance index; IDO: indoleamine 2,3-dioxygenase (IDO) enzyme; IMT: intima-media thickness; LDL: low-density lipoprotein.

to be LDL cholesterol and IDO in insulin-resistant subjects and pulse pressure in hypercholesterolaemic and hypertensive subjects, although these factors accounted for only 1·1–5·7% of the variation in the PTX3 levels. Interestingly, no statistically significant correlations for plasma PTX3 were observed in healthy subjects. Moreover, the PTX3 concentration did not correlate with indicators of subclinical atherosclerosis, IMT and CAC or with CRP and adiposity indicators in any of the subject groups.

The association of the PTX3 concentration with cardiometabolic risk factors has been documented previously. In subjects with metabolic syndrome, Zanetti *et al.* (2009) observed that plasma PTX3 correlated directly with triglyceride levels and inversely with HDL cholesterol levels [22], whereas Yamasaki and colleagues (2009) have reported inverse correlations between plasma PTX3 and triglyceride levels and between plasma PTX3 and BMI [23]. Negative findings on the relationships between the levels of all plasma lipids and PTX3 in rheumatic and non-rheumatic patients with CVD have also been presented [24,25]. Intriguingly, Alberti *et al.* (2009) detected expression of PTX3 in adipose tissue from obese and lean subjects and reported that the age- and sex-adjusted expression of PTX3 in visceral adipose tissue correlated with BMI, HDL, HDL/LDL ratio, triglycerides, CRP, fibrinogen and adiponectin [26]. They did not, however, find a correlation between the levels of adipose

Table 3. Independent determinants for plasma (log)pentraxin 3 (PTX3) in a stepwise linear regression model.

	Insulin-resistant subjects $n = 403$			Hypercholesterolaemic subjects $n = 845$			Hypertensive subjects $n = 311$		
Determinats	B	s.e.	*P*	B	s.e.	*P*	B	s.e.	*P*
LDL cholesterol	–0·054	0·019	0·005						
Pulse pressure				0·002	0·001	0·019	0·003	0·001	0·007
IDO	0·004	0·002	0·015						
	$R^2 = 0·057$			$R^2 = 0·011$			$R^2 = 0·025$		

The model included age, LDL cholesterol, total cholesterol, glucose, insulin, HOMA-IR, systolic blood pressure, diastolic blood pressure, pulse pressure and IDO as dependent variables. HOMA-IR: insulin resistance index; IDO: indoleamine 2,3-dioxygenase (IDO) enzyme; LDL: low-density lipoprotein; s.e.: standard error.

tissue-derived PTX3 expression and LDL cholesterol, glucose, insulin or blood pressure. In contrast, Bosutti *et al.* (2007) demonstrated that plasma LDL-cholesterol is associated with PTX3 mRNA levels in adipose tissue and white blood cells in non-diabetic pacemaker-implanted patients [27].

Results on the associations of PTX3 with CRP [4,7,25,28] and sex [6,7,23] also seem to be contradictory. With regard to age, however, there seems to be a consensus that advancing age is associated with higher PTX3 levels [7,23–25], a notion that was also verified in our study among insulin-resistant and hypercholesterolaemic subjects.

Even though the potential role of PTX3 in vascular biology and CVD has been studied intensively, the causalities between PTX3 levels and cardiovascular outcomes are still unclear. Similarly, the functional role of PTX3, if any, in atherogenesis has not been established. Nevertheless, PTX3 has been reported to be associated with cardiac events in heart failure patients [4,6] and in hospitalized AMI patients [2,3,7] and the PTX3 concentration has also been demonstrated to be associated with all-cause and cardiovascular mortality among ostensibly healthy subjects [25]. Additionally, recent mouse studies have proposed that PTX3 could have an atheroprotective role [11,12], potentially ascribed to its relationship with HDL cholesterol [29]. In keeping with the protective capability of PTX3, Deban and colleagues (2010) reported that, in both localized and systemic inflammatory conditions, PTX3 can act as a negative feedback mediator by dampening excessive neutrophil recruitment, thereby limiting inflammation [30]. Our novel observation that plasma PTX3 correlates directly with IDO activity in insulin-resistant and hypertensive subjects could similarly reflect the immunosuppressive function of PTX3 because IDO, a product of antigen-presenting cells, is a known immunoinflammatory down-regulator of type 1 T helper cell responses [31]. Currently, however, the relationship between elevated plasma PTX3 levels and acute cardiovascular events and PTX3's putative suppressive or protective role are unclear.

As a limitation of this study, it must be acknowledged that in our study the subject groups, especially the healthy subjects, were rather small, and the observed correlations between plasma PTX3 and cardiovascular risk factors were, although significant, somewhat weak. Consequently, it appears that in our population, PTX3 plasma levels were determined largely by factors other than the traditional CVD risk factors, as our regression models explained only a minor part of the variation in the PTX3 concentration. Additionally, the frequency of subjects with a diagnosed CVD in our study population was too low to carry out statistical analysis on plasma PTX3 levels among these subjects.

Analogously to the results of Zanetti *et al.* (2009) [22], we observed no correlation between cardiometabolic risk factors and plasma PTX3 in the group of healthy subjects, indicating that plasma PTX3 may not be a suitable risk indicator in healthy subjects. Similarly, the lack of correlation between plasma PTX3 and subclinical CVD indicators in all the subject groups in this study, as well as in a recent study by Miyaki *et al.* (2010), suggests that plasma PTX3 might not reflect early atherosclerotic changes. Nevertheless, a direct correlation between PTX3 levels and IMT was observed in elderly hypertensive patients by Yano *et al.* (2010) [32], whereas Yilmaz *et al.* (2009) demonstrated an independent association between PTX3 levels and endothelial dysfunction in diabetic renal disease patients [33]. Moreover, Jenny *et al.* (2009) have shown that plasma PTX3 correlates directly with the ankle-brachial blood pressure index, but not with IMT, in CVD-free individuals [25].

Taken together, the results of this study indicate that, although plasma PTX3 levels were not associated with subclinical atherosclerosis, they correlated with several cardiovascular risk factors in individuals at high risk of developing CVD. Further research is required to validate the use of plasma PTX3 as an auxiliary and/or adiposity- and CRP-independent risk marker in CVD-free individuals.

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Disclosure

The authors declare that there is no conflict of interest.

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