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# The Role of Pentraxin 3 in the Assessment of Cardiovascular Risk and Disease Activity in Patients with Rheumatoid Arthritis and Spondyloarthritis

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**Background:** Pentraxin 3 (PTX3) is suggested to be both a marker of inflammation and cardiovascular (CV) risk.

**Aim:** The aim of this study was to identify and compare the role of PTX3 in assessment of disease activity and CV risk, in patients with chronic inflammatory diseases, rheumatoid arthritis (RA), and spondyloarthritis (SpA).

**Methods:** The study group consisted of 235 patients (109 RA, and 126 SpA). The following parameters were assessed: disease activity, traditional CV risk factors, carotid intima media thickness (cIMT), PTX3 plasma concentration.

**Results:** The median (IQR) PTX3 concentration was higher in RA than SpA patients [3.44 (2.56–4.79) vs 2.51 (1.72–3.62) ng/mL, p<0.001]. The mean (SD) cIMT value was higher in RA than SpA patients [0.85 (±0.21) vs 0.75 (±0.27) mm, p=0.02]. Atherosclerotic plaques were observed in similar number of patients with RA (31, 28.4%) and SpA (34, 27%) (NS). The PTX3 level was significantly higher in RA patients with moderate/high vs low disease activity, and in patients with presence vs no atherosclerotic plagues. In patients with RA correlations were found between PTX3 and disease activity parameters: C-reactive protein, erythrocyte sedimentation rate, tender joint count, disease activity score in 28 joints, white blood cell count (WBC). In multiple linear regression analysis, significantly positive association was confirmed for PTX3 and WBC. No significant relationships were found in patients with SpA.

**Conclusion:** The results of this study point to the dual role of PTX3 in patients with RA, as a biomarker of disease activity, and as a marker of CV complications risk.

**Keywords:** inflammation, disease activity, pentraxin 3, carotid intima media thickness, rheumatoid arthritis, spondyloarthritis

## Introduction

Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are the most common chronic joint and spinal inflammatory diseases in adults. Indeed, both RA and SpA are associated with increased cardiovascular (CV) morbidity and mortality, mainly related to premature atherosclerosis. The higher CV risk cannot be entirely explained by the higher prevalence of traditional CV risk factors, including obesity, diabetes, arterial hypertension, smoking, and dyslipidemia. It has been suggested that in patients with chronic inflammatory diseases the main cause of atherosclerosis is chronic inflammation and immune dysregulation resulting from persistent disease activity.[1–5]

Atherosclerosis is considered as a chronic inflammatory process of the arterial wall, which results in formation of atherosclerotic plaques.[6] There is a need to find a good biomarker to estimate CV risk in patients with chronic inflammatory diseases. Pentraxin 3 (PTX3) seems to be a marker of localized vascular damage and inflammation.[6,7]

PTX3 is a member of the pentraxin family. The two groups of pentraxins are distinguished, short- and long-chain pentraxins. Short-chain pentraxins include biomarkers useful in clinical practice, C-reactive protein (CRP), serum amyloid P (SAP), which are produced mainly by hepatocytes in response to pro-inflammatory cytokines, primarily interleukin 6 (IL-6) and are considered nonspecific markers of inflammation. Long-chain pentraxins include PTX3, and pentraxin 4, neuronal pentraxin 1, neuronal pentraxin 2. It has been reported that PTX3 plays and important role in infection, inflammation, and

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innate immunity as a component of the complement system, responsible for the clearance of apoptotic cells and regulation of self-antigen presentation.[6–8]

PTX3 is produced locally in the vessel wall, synthesized by cells involved directly in atherosclerosis including endothelial cells, smooth muscle cells, macrophages. PTX3 was observed in atherosclerotic plaques, and associated with myocyte damage in myocardial infarction, and unstable angina.[8] It has been suggested that PTX3 is a more sensitive biomarker of atherosclerotic plaque damage than high sensitive CRP (hsCRP), and could be a useful indicator of acute coronary syndrome (ACS), and predictor of mortality after ACS.[5,6] Moreover PTX3 is produced locally in inflamed tissue, by different cell types including fibroblasts, dendritic cells, adipocytes, synovial cells, chondrocytes. PTX3 production is induced by pro-inflammatory cytokines such as IL-1β, tumour necrosis factor alpha (TNF-α), and also IL-10.[5–8] It has been reported that anti-inflammatory cytokines (IL-4, IL-13) and other cytokines such as IL-6, IL-17, do not affect the production of PTX3.[8]

Higher PTX3 levels were reported in patients with autoimmune diseases (RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), multiple sclerosis) than in healthy controls.[7,9–11] In small vessel vasculitis, PTX3 level correlated with inflammatory activity. The results in patients with juvenile idiopathic arthritis and SLE were not consistent. In patients with RA concentration of PTX3 was correlated with disease activity and structural damage,[10] radiographic progression of joint damage,[9,11] inflammatory parameters,[11] or no correlation with disease activity[12] and severity[13] was found. In SpA no correlation was found between PTX3 and disease activity, and inflammatory markers.[14,15]

The aim of this study is to determine and compare the role of PTX3 in the assessment of the disease activity and CV risk in patients with RA and SpA.

# Materials and Methods

## Study Population

The study group consisted of 235 consecutive patients (109 with RA, 126 with SpA) treated in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland. Patients with RA fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.[16] Patients with SpA fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for SpA.[17] The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethical Committee of the Medical University of Lublin (approval number KE-0254/11/01/2023 dated 26 JAN 2023). The written informed consent was obtained from each patient, prior to the inclusion in this study.

## The Study Design

That was a cross-sectional study. The consecutive patients with RA and SpA, hospitalized in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland, were enrolled in the study, between February 2023 and June 2024.

The written informed consent was obtained from each patient, prior to the inclusion in this study.

The following procedures were performed consecutively in every patient: clinical interview, physical examination, blood samples collection, and ultrasound (US) examination of carotid intima media thickness (cIMT).

## Clinical and Laboratory Assessment

Clinical information was obtained through detailed interview, review of medical history, self-reported questionnaire, and physical examination, including examination of joints, as well as body weight and height. BMI was calculated as a ratio, body weight/height$^2$ (kg/m$^2$).[18]

In patients with RA the disease activity was assessed using disease activity score system (DAS28), calculated with tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and patient global assessment (PGA) in visual analogue scale (VAS).[19] The cut point for low disease activity was DAS28 value ≤ 3.2 and high disease activity > 5.1. The ability to perform daily activities was assessed using modified Health Assessment Questionnaire (M-HAQ), with range 0–3 (score 0 presenting no impairment of function).[20]

All blood samples were collected in the morning, after an overnight fast, and stored at −80° C in order to evaluate PTX3.

The following tests:ESR, CRP, creatinine, estimated glomerular filtration rate (eGFR), uric acid, glucose, lipid profile (total cholesterol, TC; high-density lipoproteins cholesterol (HDL-C); triglycerides (TG); low-density lipoproteins cholesterol (LDL-C) and complete blood cell count (CBC), were performed at the University Hospital central laboratory. The serum level of CRP was measured by immunoturbidimetric assay, and uric acid, and TC, HDL-C, LDL-C, TG by enzymatic method, using Beckman Coulter Analyzer AU5800. The CBC assessment was performed using Beckman Coulter DxH 900. The ALCOR Scientific iSED Analyzer was used for ESR assessment.

The normal ranges of laboratory tests are as follows: ESR <12 mm/hour (female), and <8 mm/hour (male); CRP <5 mg/l; creatinine 0.67–1.17 mg/dl; uric acid 2.6–6.0 mg/dl; glucose 70–99 mg/dl; TC <190 mg/dl, HDL-C >40 mg/dl, LDL-C <100 mg/dl, TG <150 mg/dl; hemoglobin 13.2–17.3 g/dl; white blood cell count (WBC) 4.5–10.5 $x10^9$/l; platelet count (PC) 150–400 $x10^9$/l. Atherogenic index (AI) was calculated as ratio TC/HDL-C (normal AI values: < 4.0 in women and <4.5 in men).[21]

## PTX3 Assessment

The plasma concentration of PTX3 was measured by enzyme-linked immunosorbent assay (ELISA), using the commercial kit, Human Pentraxin 3/TSG-14, Quantikine ELISA, R&D Systems. According to manufacturer's data, the median concentration of plasma PTX3 in healthy volunteers is 0.66 ng/mL (range non-detectable −1.36 ng/mL).

## Carotid Intima Media Thickness (cIMT) US Assessment

It has been shown that cIMT is a positive indicator of generalized atherosclerosis. All US procedures were performed by the same experienced specialist of radiology. The patient stayed in a supine position, in a quiet, temperature-controlled room. The cIMT measurement was performed using high-resolution B-mode US (Canon Aplio i800), bilaterally in three regions: common carotid artery (CCA), carotid bulb (BULB) and internal carotid artery (ICA). The average of the maximum IMT from all 6 carotid segments (defined as mean maximum cIMT) was used in all analyses. The value of cIMT 0.9 mm or greater is a marker of atherosclerosis.[22] The presence of carotid plaques is a marker of advanced atherosclerosis. Plaques were defined as a distinct protrusion greater than 1.5 mm into the vessel lumen.[23]

## Statistical Analysis

The results were tested for normality using the Kolmogorov–Smirnov's test. Continuous variables were presented using the mean ± standard deviation (SD) or median and interquartile range (IQR) if the data were parametric or nonparametric, respectively. Categorical data were presented as absolute numbers and percentages. The Student's *t*-test or nonparametric Mann–Whitney *U*-test were used in order to compare continuous variables in subgroups of patients. Correlation between the quantitative variables was assessed by Spearman's or Pearson's correlation test. The multiple linear regression test was performed introducing variables that showed statistically significant association with certain parameters. For all tests, p values < 0.05 were considered significant. All statistical analyses were performed using the StatSoft STATISTICA 12 application.

# Results

The study group consisted of 109 patients with RA and 126 patients with SpA (Table 1).

## Characteristics of Patients with RA

The group of RA patients consisted mainly of women (almost 80%). Disease duration ≥10 years was noted in more than 55% of patients. The vast majority of patients were seropositive (IgM rheumatoid factor, RF-IgM and/or anti-citrullinated peptide antibodies, anti-CCP). Extra-articular manifestations (rheumatoid nodules, sicca syndrome, interstitial lung disease, and vasculitis) in the course of the disease were observed in more than 50% of patients (Table 1).

Obesity or overweight was observed in almost 50% of RA patients. Current or former smoking was noted in more than 50% of cases. A family history of hypertension and cardiovascular disease (CVD) was reported in about 40%, while diabetes mellitus in almost 5% of patients.

**Table 1** Characteristics of Patients with RA and SpA

| Data | RA (n=109) | SpA (n=126) | *p* |
|---|---|---|---|
| Age, years | 54.0 (±11.8) | 42.7 (±12.5) | <0.001 |
| Gender, female/male (n,%) | 86 (78.9)/23 (21.1) | 51 (40.5)/75 (59.5) | <0.001 |
| Disease duration, years | 14 (7–20) | 8 (3–16) | 0.002 |
| Disease duration ≥10 years (n,%) | 63 (57.8) | 56 (44.4) | 0.04 |
| Positive RF-IgM (n,%) | 94 (86.2) | 11 (8.7) | <0.001 |
| Positive anti-CCP (n,%) | 96 (88.1) | 4 (3.2) | <0.001 |
| Positive HLA-B27 (n,%) | – | 82 (65.1) | – |
| Extra-articular manifestations (n,%) | 62 (56.9) | 39 (30.9) | <0.001 |
| BMI, kg/m$^2$ | 25.4 (±3.8) | 27.6 (±4.5) | <0.001 |
| Overweight/Obesity (BMI ≥25 kg/m$^2$) (n,%) | 54 (49.5) | 84 (66.7) | 0.008 |
| Current or former smoker (n,%) | 57 (52.3) | 53 (42.1) | NS |
| Arterial hypertension (n,%) | 44 (40.4) | 53 (42.1) | NS |
| Family history of cardiovascular diseases (n,%) | 45 (41.3) | 51 (40.5) | NS |
| Diabetes (n,%) | 7 (4.7) | 5 (3.9) | NS |
| Current conventional synthetic DMARD used (n,%)<br>MTX<br>Anti-malarial drug<br>Leflunomide<br>Other<br>NSAID | 107 (98.2)<br>98 (89.9)<br>35 (32.1)<br>14 (12.8)<br>16 (14.7)<br>– | 81 (64.3)<br>55 (43.7)<br>–<br>4 (3.2)<br>29 (23.0)<br>94 (74,6) | <0.001 |
| Current biological DMARD used (n,%)<br>Anti-TNFα<br>Other | 57 (52.3)<br>29 (26.6)<br>28 (25.7) | 48 (38.1)<br>47 (37.3)<br>1 (0.8) | 0.02 |
| Current low dose GC use (n,%) | 71 (65.1) | 25 (19.8) | <0.001 |

**Notes**: Values are displayed as mean±standard deviation (SD), median (IQR) or frequencies with corresponding percentages (%). Anti-CCP, anti-cyclic citrullinated protein antibodies; anti-TNFα, anti-tumor necrosis factor.

**Abbreviations**: BMI, body mass index; DMARD, diseases modifying anti-rheumatic drug; GC, glucocorticosteroid; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF-IgM, IgM rheumatoid factor; SpA, spondyloarthritis.

At the time of examination, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) were used in all but two patients, and included methotrexate (MTX) in 98 (89.9%) patients (dose 10–25 mg/week, in monotherapy or combination), leflunomide (LEF) 14 (12.8%), hydroxychloroquine (HCQ) or chloroquine (CQ) 35 (32.1%), other csDMARDs 16 (14.7%). Biological DMARDs (bDMARDs) were used in half of RA patients (57; 52.3%). Low-dose glucocorticoid (GC) therapy (prednisone ≤ 10 mg/day) was used in 71 (65.1%) patients (Table 1).

Low disease activity (DAS28 ≤ 3.2) at the time of examination was found in over 1/3 (40 patients) (Table 2).

The mean/median values of CBC, creatinine, eGFR, uric acid, and glucose remained within the normal reference ranges (Table 2).

## Characteristics of Patients with SpA

The axial SpA (axSpA) was found in 79 patients and peripheral SpA (pSpA) in 47 patients.

**Table 2** Clinical and Laboratory Parameters in RA and SpA Patients

| Data | RA (n=109) | SpA (n=126) | *p* |
|---|---|---|---|
| **Clinical parameters of disease activity** | | | |
| TJC | 3 (1–9) (out of 28) | 9 (4–13) (out of 68) | |
| SJC | 2 (0–6) (out of 28) | 3 (0–8) (out of 68) | |
| VAS back pain (mm) | – | 36.4 (±26.0) | |
| BASDAI | – | 4.7 (±2.2) | |
| ASDAS | – | 3.2 (±0.9) | |
| VAS back pain (mm) | – | 48.3 (±25.5) | |
| DAPSA | – | 25.2 (±14.2) | |
| Low Disease Activity:<br>RA (DAS28 ≤3.2) (n,%)<br>Axial SpA:<br>BASDAI ≤ 4 (n,%)<br>ASDAS < 1.3 (n,%)<br>Peripheral SpA<br>DAPSA ≤ 14 (n,%) | <br>40 (36.7)<br><br>–<br>–<br><br>– | <br>–<br><br>23 (18.3)<br>4 (3.2)<br><br>21 (16.7) | |
| Morning stiffness, minutes | 30 (10–60) | 60 (30–120) | |
| M-HAQ | 1.4 (±0.7) | 1.1 (±0.8) | 0.02 |
| **Laboratory results:** | | | |
| Hemoglobin, g/dl | 12.8 (±1.3) | 13.6 (±1.6) | <0.001 |
| WBC, $10^9$/l | 6.9 (±2.7) | 7.1 (±2.4) | NS |
| PC, $10^9$/l | 288.7 (±79.6) | 281.2 (±81.7) | NS |
| CRP, mg/l | 17.1 (2.1–19.8) | 17.8 (2.1–21.9) | NS |
| ESR, mm/h | 34.1 (13.5–49.5) | 26.1 (8–33) | 0.006 |
| Creatinine, mg/dl | 0.7 (0.6–0.8) | 0.8 (0.7–0.9) | <0.001 |
| eGFR, mL/min/1,73 $m^2$ | 89.8 (89.1–99.0) | 87.5 (88.2–90.0) | <0.001 |
| Uric acid, mg/dl | 4.6 (±1.2) | 5.4 (±1.3) | <0.001 |
| TC, mg/dl | 193 (±45.3) | 179.6 (±36.7)) | 0.01 |
| HDL-C, mg/dl | 57.6 (±17.0) | 48.5 (±13.1) | <0.001 |
| LDL-C, mg/dl | 111.7 (±36.0) | 110.1 (±28.2) | NS |
| TG, mg/dl | 113.2 (±52.6) | 114.5 (±61.7) | NS |
| TC/HDL-C | 3.3 (3.0–4.1) | 3.8 (±1.0) | 0.01 |
| Glucose, mg/dl | 88 (67–164) | 92 (88–97) | 0.002 |
| Pentraxin 3 (ng/mL) | 3.44 (2.56–4.79) | 2.51 (1.72–3.62) | <0.001 |

(*Continued*)

**Table 2** (Continued).

| Data | RA (n=109) | SpA (n=126) | *p* |
|---|---|---|---|
| cIMT (mm) | 0.85 (±0.21) | 0.75 (±0.27) | 0.02 |
| cIMT ≥ 0.9 mm (n,%) | 36 (33.0) | 30 (23.8) | NS |
| Patients with plaques (n,%) | 31 (28.4) | 34 (27.0) | NS |

**Notes**: Values are displayed as mean ± standard deviation (SD), median (IQR) or frequencies with corresponding percentages (%).
**Abbreviations**: CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; PC, platelet count; PGA, patient global assessment; M-HAQ–modified health assessment questionnaire; RA, rheumatoid arthritis; SJC, swollen joints count; TC, total cholesterol; TG, triglycerides; TJC, tender joint count; VAS, Visual Analogue Scale, WBC, white blood cell count.

The group of patients with SpA consisted mainly of men (almost 60%). Disease duration ≥10 years was noted in more than 40% of patients. A positive result for human leukocyte antigen B27 (HLA-B27) was observed in 65% of SpA patients, with 93% being anti-CCP negative and 91% RF-IgM negative. Extra-articular manifestations (anterior uveitis, inflammatory bowel disease, cardiac conduction abnormalities, valvular heart disease, osteoporosis) were observed in about 30% of SpA patients (Table 1).

Obesity or overweight was noted in 2/3 of SpA patients. Current of former smoking was reported in over 40% cases. Arterial hypertension and family history of CV disease (CVD) were noticed in about 40%, diabetes in almost 4% of patients.

At the time of evaluation, non-steroidal anti-inflammatory drugs (NSAIDs) were used in ¾ of patients, and csDMARDs in almost 65% (81 patients, primarily MTX in 55 patients). Therapy with bDMARDs was used in 48 patients (anti-TNFα in 47 patients). Low-dose GC (prednisone ≤10 mg/day) was used in 25 (almost 20%) of patients (Table 1).

Low disease activity according to BASDAI ≤ 4 was noted in 18%, and according to ASDAS < 1.3 in 3% of patients with axSpA (Table 2). In patients with pSpA, remission/low disease activity (DAPSA ≤14) was observed in about 17% patients (Table 2).

## Differences Between Patients with RA and SpA

Patients with RA as compared to those with SpA were characterized by: significantly older age, longer disease duration, lower BMI, as well as a higher number of those with disease duration ≥10 years and extra-articular manifestations, along with fewer cases with obesity or overweight (Table 1). The vast majority of RA patients were female, while SpA patients were predominantly male (Table 1).

RA patients, as compared to SpA patients, demonstrated higher ESR, lower hemoglobin concentrations, lower creatinine and uric acid concentrations, higher eGFR, lower glucose, higher TC and HDL-C concentrations, and lower AI value (Table 2).

No significant differences were found between the two groups in relation to CRP, LDL-C, TG concentrations, white blood cell count and platelet count (Table 2). There were no differences in relation to smoking history, family CVD, concomitant diseases (hypertension, diabetes) (Table 1).

## Comparison of cIMT Value in Patients with RA and SpA

The mean cIMT value was significantly higher in patients with RA when compared with SpA, respectively: 0.85 (±0.21) vs 0.75 (±0.27), p=0.02 (Table 2). The number of patients with US symptoms of atherosclerosis and with atherosclerotic plaques was comparable in the two groups of patients (Table 2).

The mean cIMT value was significantly lower in RA patients with low disease activity when compared with moderate/high disease activity, respectively 0.79 (±0.18) vs 0.88 (±0.22) mm, p=0.04 (Figure 1). No difference was found in patients with SpA.

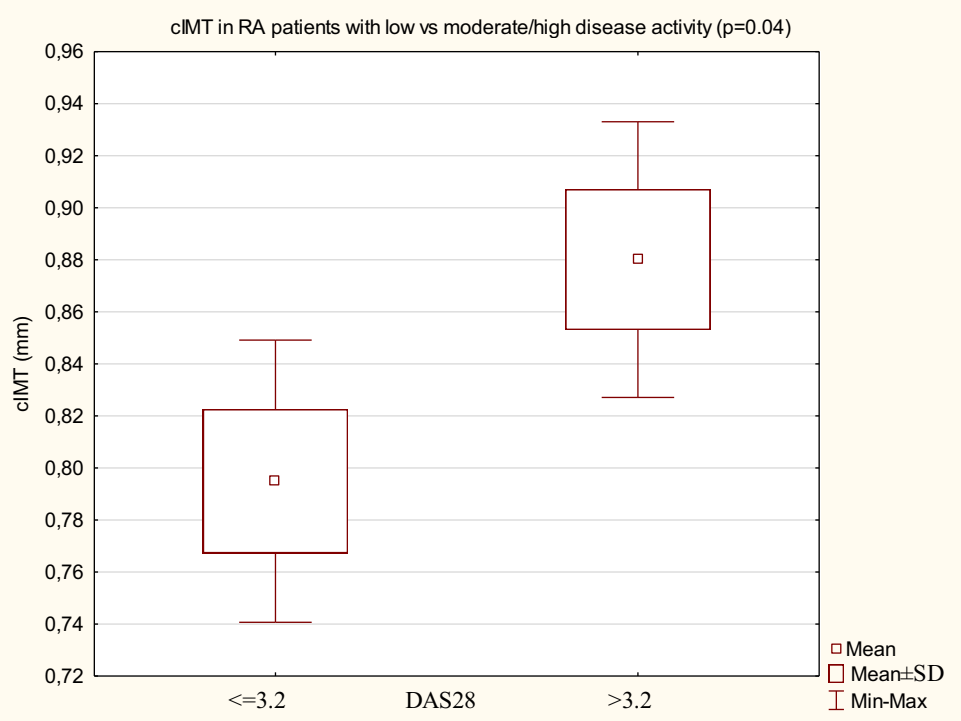


**Figure 1** Value of cIMT in RA patients with low vs moderate/high disease activity.

## Comparison of PTX3 Concentration in Patients with RA and SpA

Plasma concentration of PTX3 was higher in both patients groups (RA, SpA) in comparison with healthy volunteers, according to the manufacturer's data.

The median PTX3 concentration was significantly higher in patients with RA when compared with SpA, respectively: 3.44 (2.56–4.79) vs 2.51 (1.72–3.62), p<0.001 (Table 2).

The median PTX3 concentration was significantly higher in RA patients with moderate/high disease activity when compared with low disease activity, respectively 5.16 (2.68–6.07) vs 3.24 (2.37–4.0) ng/mL, p=0.04 (Figure 2). No difference was found in patients with SpA.

In RA patients, the median PTX3 level was significantly higher in those with atherosclerotic plaques when compared with no atherosclerotic plaques, respectively 4.24 (3.13–8.03) vs 3.24 (2.36–4.31) ng/mL, p=0.003 (Figure 3). No such correlation was found in SpA patients.

## Correlations of PTX3 in Patients with RA and SpA

In patients with RA, positive correlations were found between PTX3 and DAS28, TJC, CRP, ESR, and WBC (Table 3). There were no other correlations between PTX3 and disease activity parameters (SJC, PGA, M-HAQ), age, disease duration, and CV parameters (cIMT, BMI, lipid profile, glucose, uric acid, creatinine, eGFR).

In the multiple linear regression analysis, significantly positive association was confirmed for PTX3 with WBC (b = 0.36, p<0.001).

No significant correlation was found in patients with SpA, considering the entire group of SpA patients, as well as separately groups of patients with axSpA and pSpA.

## Correlations of cIMT in Patients with RA and SpA

In patients with RA, positive correlations were found between cIMT and age, disease duration, ESR, PGA, and AI (Table 4). There was no other correlation.

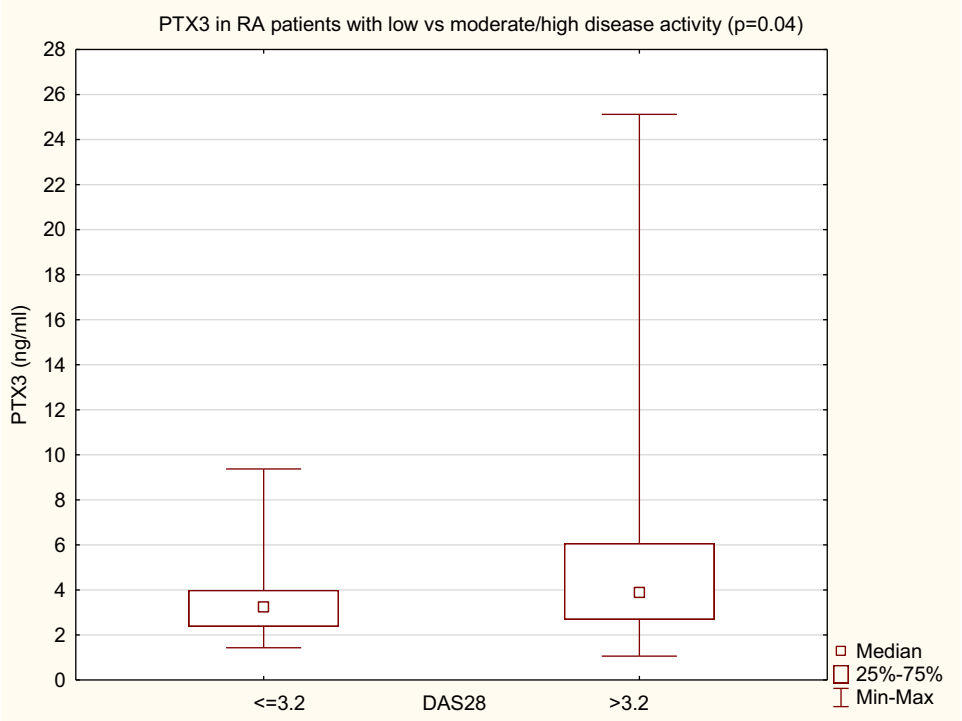


**Figure 2** PTX3 concentration in RA patients with low vs moderate/high disease activity.

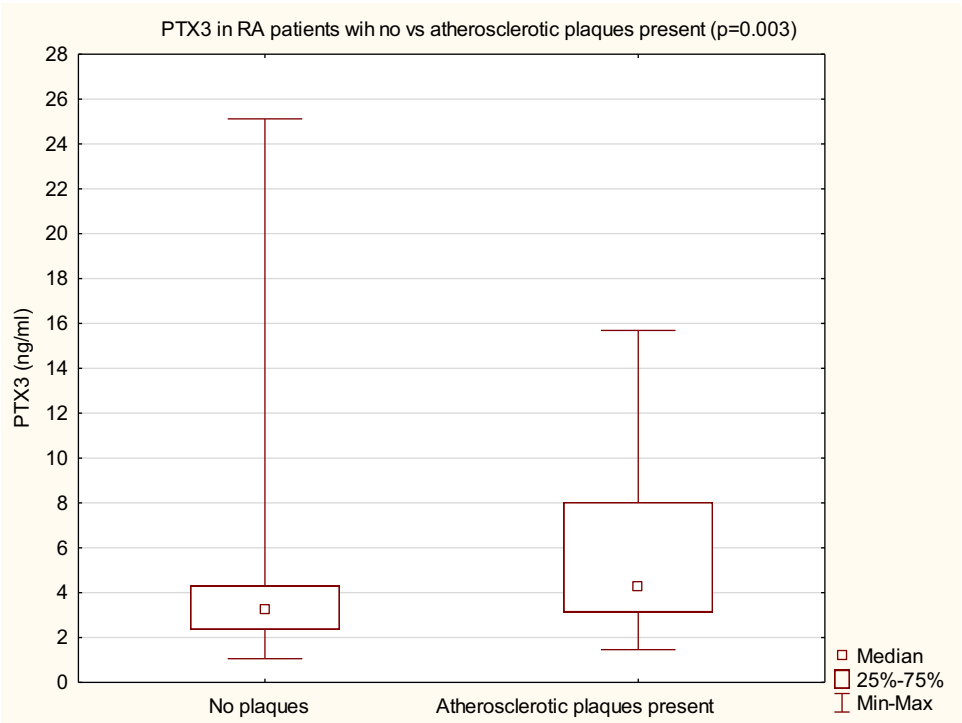


**Figure 3** PTX3 concentration in RA patients with no vs atherosclerotic plaques present.

**Table 3** Correlations Between PTX3 and Disease Activity Markers in Patients with RA

| Data | PTX3 | |
|---|---|---|
| | ***p* value** | **R** |
| **DAS28** | 0.02 | 0.22 |
| **TJC** | 0.04 | 0.02 |
| **CRP** | 0.39 | <0.001 |
| **ESR** | 0.22 | 0.02 |
| **WBC** | 0.37 | <0.001 |

**Abbreviations**: CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; TJC, tender joint count; WBC, white blood cell count.

**Table 4** Correlations Between cIMT and Data in Patients with RA

| Data | cIMT | |
|---|---|---|
| | ***p* value** | **R** |
| **Age** | 0.69 | <0.001 |
| **Disease duration** | 0.21 | 0.03 |
| **ESR** | 0.23 | 0.02 |
| **PGA** | 0.29 | 0.002 |
| **AI** | 0.24 | 0.01 |

**Abbreviations**: AI, atherogenic index (TC/HDL-C); ESR, erythrocyte sedimentation rate; PGA, patient global assessment in visual analogue scale.

In the multiple linear regression analysis, significantly positive associations were confirmed for cIMT with age ($b = 0.62$, $p<0.001$), and AI ($b = 0.16$, $p= 0.02$).

In patients with SpA, the only one positive correlation was found, between cIMT and age ($b = 0.66$, $p<0.001$) in the entire group of patients, as well as in axSpA and pSpA patients, respectively ($b = 0.38$, $p=0.02$) and ($b = 0.78$, $p<0.001$).

## Discussion

The present study found significantly higher median PTX3 concentrations in patients with RA as compared to SpA. PTX3 concentrations in both patient groups (RA, SpA) were higher than in those of healthy volunteers (assessment in healthy volunteers according to manufacturer's data).

PTX3 levels were significantly higher in RA patients with moderate/high disease activity as compared to those with low disease activity. Correlations between PTX3 and DAS28, TJC, ESR, CRP, WBC were noted, with a significantly positive relationship confirmed for PTX3 and WBC in multiple linear regression analysis. No such correlation was found in patients with SpA.

The cIMT value was significantly higher in RA patients with moderate/high disease activity compared to those with low disease activity. In RA patients, PTX3 level was significantly higher in those with atherosclerotic plaques. No such correlation was found in SpA patients. The results of the study indicate a dual role for PTX3 in RA patients, first as

a marker of disease activity and second as a marker of CV risk. The association between PTX3 and atherosclerotic plaques in RA patients may indicate the risk of plaques' vulnerability resulting in CV complications.

No such relationships occurred in patients with SpA, which could be based on a distinct pathogenesis of SpA and RA. Additionally, patients with RA were characterized by significantly higher age, disease duration, and more common extra-articular manifestations than patients with SpA.

In contrast, unfavorable metabolic parameters (higher BMI, uric acid, glucose, AI) were more common in SpA patients, possibly responsible for the comparable number of patients with increased cIMT and atherosclerotic plaques in both groups (RA and SpA).

To the best of our knowledge, a report is the first to present and compare the divergent correlations between PTX3 and US symptoms of atherosclerosis in patients with RA and SpA.

In accordance with the literature, PTX3 release may be a specific response to vascular damage. PTX3 expression increased with the progression of atherosclerotic lesions from fatty streaks to advanced atherosclerotic plaques. It has been suggested that PTX3 may have unique potential in monitoring acute changes in the atherosclerotic process as well as playing a causal role in atherosclerosis.[7] PTX3 is localized in atherosclerotic plaques and may promote lesion progression through an innate immune response, activating monocytes and endothelial cells, which can lead to thrombosis.[7] Higher levels of PTX3 have been reported in patients with more advanced atherosclerosis.[6] There was a significant correlation between plaque involvement and elevated PTX3 levels. In patients with ACS, PTX3 had a correlation with increased levels of T-troponin and creatinine kinase.[6]

The results of this study are consistent with those in the literature data. PTX3 was found to be highly expressed by synovial fibroblasts, however various other cells (infiltrating macrophages, endothelial cells, plasma cells, neutrophils) may be also a source of PTX3 upon inflammatory activation.[10] A significant positive correlation has been found between serum and synovial fluid concentrations of both PTX3 and CRP, suggesting that serum could be a true representation of synovial fluid PTX3 concentration in RA patients.[12]

According to the systemic meta-analysis and observational studies, serum/plasma levels of PTX3 were higher in autoimmune diseases (RA, ankylosing spondylitis (AS) SLE, SSc) than in normal controls.[8–11,13] Significant correlations were reported between PTX3 with ESR, CRP, radiographic damage according to Larsen Score, and no correlation between PTX3 with RF, anti-CCP, age, disease duration.[11] Positive correlations were found between serum and synovial fluid concentrations of PTX3 and CRP, and an association with RA severity.[12] The positive correlation was observed between PTX3 and disease activity at baseline, and the degree of structural damage at 12 month. Moreover, a high PTX3 level was detectable at month 6 after introduction of csDMARDs, regardless of treatment response.[10] In the 3-year prospective study in patients with RA, plasma PTX3 levels were associated with radiographic progression of joint damage, but PTX3 was not associated with an increase of cIMT.[9] Conversely, in other study no correlation between PTX3 and DAS28 or neutrophil/lymphocyte ratio (NLR) was reported.[13] The results of other study indicated that PTX3 levels in RA patients were similar to controls and did not correlate with inflammatory activity according to values of ESR, CRP, and DAS28. Serum PTX3 levels were higher in nonobese RA patients than in obese, and in non-obese, PTX3 correlated negatively with cIMT. The authors suggested that PTX3 might have a protective role in atherogenesis in non-obese RA patients.[24]

In patients with SpA, lower concentrations of plasma PTX3 were reported than in controls, and no correlation with disease activity indices (BASDAI, ASDAS), CRP, ESR. No differences of PTX3 levels were noted between patients with psoriatic arthritis (PsA) and AS.[14,15] Uveitis, presence of HLA-B27, smoking, age, and disease duration did not affect PTX3 levels.[14]

The lack of relationship between PTX3 and SpA activity might be associated with distinct pathogenesis of SpA. It was demonstrated, that IL-17 is the principal cytokine involved in AS, and levels of IL-17 are higher in patients with AS.[25] In PsA, IL-23 seems to play a role in initiating the development of the disease, and IL-17A primarily enhances the disease activity.[26] PTX3 is produced in response to pro-inflammatory cytokines, mainly IL-1, TNFα, and cytokines such as IL-6, IL-17, do not affect the production of PTX3.[8]

Our study has several potential limitations. First, it was a cross-sectional study without a control group. Second, the influence of concurrent treatment (DMARDs or glucocorticoids) could not be ruled out, as the study was conducted in a real-world patient population.

However, the study also possesses several strengths. First, the detailed characterization of patients, which encompassed all aspects of the pathology of RA and SpA. Second, the patients were not selectively chosen for the study; they are real-world patients. Third, this is the first report to present and compare divergent associations between PTX3 and US symptoms of atherosclerosis among patients with RA and SpA.

## Conclusions

In this study, PTX3 concentrations were significantly higher in RA patients compared to SpA patients. Among RA patients, PTX3 levels were elevated in those with moderate to high disease activity compared to those with low activity, as well as in patients with advanced atherosclerosis (characterized by atherosclerotic plaques). Notably, relationships were observed between PTX3 levels and markers of RA activity. However, no such relationships were identified in the SpA patient group.

The results of this study point to the dual role of PTX3 in RA patients, as a biomarker of disease activity and as a risk marker for CV complications.

## Data Sharing Statement

All data reported in this study are available upon request by contact with the corresponding author.

## Ethics Approval and Informed Consent

The study was approved by the Ethical Committee of the Medical University of Lublin and all procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient, following a detailed description of the aim of this study, prior to the inclusion in the study.

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## Author Contributions

The authors contributed significantly to the work reported, conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, critically reviewing the article; gave final approval of the version to be published, have agreed on the journal to which the article has been submitted.

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## Disclosure

The authors declare no conflict of interest in this work.

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