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Research Article

Is Serum Tryptase a Dependable Biomarker for Diagnosing and Tracking Rheumatoid Arthritis?

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Abstract

Aim: Our aim in this study was to demonstrate that rheumatoid arthritis (RA) patients have an increase in serum tryptase concentrations and that this correlates with the level of disease activity.
Material and Method: The research involved 43 patients RA and 37 healthy participants as the control group. The average ages of the patients and the control group were 52.53±11.10 and 48.41±12.79 years, respectively. Sociodemographic information of all participants was recorded. Disease Activity Score 28 (DAS28), Health Assessment Questionnaire (HAQ) and Visual Analog Scale (VAS) scores were calculated after detailed examination to determine disease activity. Total serum tryptase concentrations were evaluated using enzyme-linked immunosorbent assay (ELISA).
Results: Serum tryptase levels were higher in the RA group compared to the healthy group and a statistically significant difference was found ($p<0.001$). A meaningful connection was detected between serum tryptase concentrations and DAS28, VAS and HAQ scores in RA patients ($p<0.05$). Erythrocyte sedimentation rate (ESR) and serum tryptase levels showed a notable and significant association ($p<0.05$). There was no statistically significant correlation between serum tryptase concentrations and C-reactive protein (CRP) ($p>0.05$).
Conclusion: The findings reveal that serum tryptase levels are upregulated in subjects with RA and demonstrate a correlation with disease activity. Serum tryptase may contribute to inflammation in RA.

Keywords: Biomarker, diagnosing, rheumatoid arthritis, serum tryptase

INTRODUCTION

Rheumatoid arthritis (RA) is a persistent intractable inflammatory entity of uncertain origin, typically accompanied by symmetrical polyarthritis. Along with the disease, various tissues and organs may be affected. In addition to the devastating damage it causes to joints, RA is connected to higher rates of morbidity and mortality, largely due to associated comorbidities and systemic effects. The inflammatory pathway in RA is stimulated by numerous cytokines, resulting in damage to the synovial joints and irreversible joint deterioration. Although RA is a common rheumatic disease, its prevalence has been reported as 0.5-1% (1-3).

Mast cells (MCs) originating in the bone marrow are particularly reliant on stem cell factors to sustain their survival. Although they are primarily responsible for allergic inflammation, they can also cause chronic inflammation through the secretion of various chemokines and cytokines (4). MCs exist in two forms: tryptase-positive MCs (MCT) and MCs positive for both tryptase and chymase (MCTC). MCTC cells are found in normal synovium, while MCT cells increase in rheumatic diseases and may play a role in inflammation. Tryptase, a tetrameric serine protease, is primarily synthesized by MCs and stored in their secretory granules. Upon activation of MCs, tryptase is released through degranulation, along with other stored mediators, into the extracellular environment. This release plays a pivotal role in various immunological responses, including inflammation, tissue remodeling and immune modulation (5,6).

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Serum tryptase is also involved in the etiopathogenesis of many diseases (7-9). The most important function of tryptase in these diseases is its pro-inflammatory effect. Elevated tryptase levels have been associated with allergic inflammation-related conditions such as allergic asthma and other mast cell-mediated diseases (10,11). Tryptase exerts its pro-inflammatory effects through various mechanisms. One such mechanism is the hypothesis of cytokine release and cell activation. In this case, tryptase stimulates endothelial cells to excrete pro-inflammatory cytokines, including interleukin-8 (IL-8) and interleukin-1 beta (IL-1β), which promote leukocyte recruitment and adhesion. Additionally, tryptase activates microglia and astrocytes in the central nervous system, leading to the release of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and reactive oxygen species via the protease-activated receptor 2 (PAR-2)-mitogen-activated protein kinase (MAPK)-NF-κB signaling pathway (12-14). Secondly, tryptase contributes to tissue remodeling and matrix degradation by activating matrix metalloproteinases and other proteolytic enzymes. This activity is particularly important in diseases like asthma, where tryptase-induced airway remodeling and hyperresponsiveness are observed (10,11). Third, tryptase enhances the production of neutrophil extracellular traps, a system by which neutrophils capture and destroy pathogens. This interaction further amplifies the inflammatory response. (15). Fourth, in conditions such as inflammatory bowel disease, tryptase activates fibroblasts through the PAR-2/Akt/mTOR signaling pathway, triggering fibrosis and leading to excessive extracellular matrix deposition (9). Finally, tryptase plays a role in cardiovascular diseases by stimulating endothelial cell activation, increasing platelet-activating factor production, and inducing neutrophil adhesion, which contributes to vascular inflammation and damage (16,17). In conclusion, tryptase appears to be a key mediator in various inflammatory processes. Its ability to trigger the TNF-α, IL-6, and IL-1β pathways, which are crucial in the pathogenesis of RA, may explain its significant role in this disease. Tryptase's role in these mechanisms positions it as a promising target for therapeutic interventions in inflammatory diseases.

This study sought to evaluate the link between serum tryptase levels and disease activity in RA, as well as to assess the potential of tryptase as a biomarker for inflammatory response. Given the limited data regarding the role of tryptase in RA pathogenesis, this study aims to make an important and novel contribution to the field.

MATERIAL AND METHOD

Participants

This cross-sectional, single-centre study was performed in the Physical Therapy and Rehabilitation Clinic of a Recep Tayyip Erdoğan University Training and Research Hospital with 43 RA patients diagnosed based on the 2010 American College of Rheumatology (ACR) diagnostic criteria and 37 healthy individuals as the control group. A detailed history was taken, and systemic and rheumatologic examinations were performed in all participants. Sociodemographic, clinical, and laboratory measurements were obtained from RA subjects for comparison with the control group. Subjects with a history of malignancy, those under 18 or over 75 years of age, those with advanced heart failure, advanced renal failure, acute infections, demyelinating diseases, idiopathic anaphylaxis, unexplained abdominal pain and/or cramping and/or syncope, other rheumatic diseases, psoriasis, atopic dermatitis, food allergies, drug allergies, venom allergies, allergic rhinitis, asthma or allergic rhinitis were ostracised from the study.

Consent for the research design was granted by the Clinical Research Ethics Committee of the Faculty of Medicine of a Recep Tayyip Erdoğan University (Ethics Committee approval date: 12.12.2014, decision no: 2014/167).

The sample size determination for this study was conducted using the G Power 3.1 software. With an alpha level of 0.5, an effect size of 0.66, and a target power of 80%, the analysis indicated that each group should consist of at least 36 participants (7).

Clinical Measurements

Disease Activity Score 28 (DAS28) is a widely used measure to determine disease activity in RA patients and reflects the person's current disease status. It considers swelling and tenderness in 28 joints, the erythrocyte sedimentation rate (ESR) value, and the patient's general health assessment or pain assessment. DAS28 scores below 2.6 were considered, indicating remission, 2.6 to just under 3.2 represented low disease activity, 3.2 to 5.1 indicated intermediate disease activity, and scores above 5.1 were categorized as high disease activity (18).

Visual Analog Scale (VAS) was used to estimate the violence of the disease. Patients were asked to mark a 10 cm line where one end represented the best period of the disease and the other the worst, with the current state marked in between. The distance from the zero point was measured in centimetres (0-10 cm) (19).

The Health Assessment Questionnaire (HAQ) contains 20 questions, organized into 8 domains: dressing, toileting, hygiene, rising, reaching, eating, gripping, walking, and other everyday activities. This questionnaire evaluates the last week. Each subsection was scored independently and a single HAQ score ranging from 0 to 3 was determined by averaging the scores of the 8 subsections (20).

Laboratory Analysis

Serum C-reactive protein (CRP) levels were quantified with an Abbott autoanalyzer (Architect C1600; Abbott, USA). Normal CRP values ≤0.5 mg/dL were considered. Serum specimens were preserved at -80°C until the day of analysis for measurement of total tryptase concentrations. Serum tryptase concentrations were assayed utilizing an enzyme-linked immunosorbent assay (ELISA) kit from Cloud-Clone Corp. (Houston, TX 77082, USA). The coefficients of variation (CV) for inter-assay and intra-assay precision were <12.0% and <10.0%, respectively, with a sensitivity of 14.1 pg/mL.

Statistical Analysis

IBM SPSS version 22 was used to analyze the research data. Mean, standard deviation, number, percentage and median (range) values of the research data were presented. Pearson Chi-Square, Yates Corrected Chi-Square and Fisher Exact Tests were used to examine categorical variables. The normality of data scatter, kurtosis and skewness values were statistically evaluated using the Kolmogorow Smirnow test. Student's t-test was used for comparisons between two independent groups in normally distributed data; Mann-Whitney U test was used for comparisons of non-normally distributed data, and Kruskal-Wallis test was used for comparisons of three independent groups. When meaningful comparisons were found between the three groups as a result of the Kruskal-Wallis test, Bonferroni correction was performed to determine the source of the differences. The relationships among variables were analyzed through Spearman's rank correlation method, and the level of statistical significance was defined as $p<0.05$.

RESULTS

80 individuals were analyzed. Of the participants, 43 (53.8%) were RA patients, while the remaining 37 (46.3%) were otherwise healthy subjects forming the healthy group. Sociodemographic data of the patient and control groups were analyzed and no significant discrepancy was observed between them (Table 1). Statistically significant differences were obtained regarding ESR, CRP and tryptase levels between RA patients and control group ($p<0.001$). ESR, CRP and tryptase levels were detected significantly higher in RA patients than in the control group (Table 2). In RA patients, tryptase levels showed a moderate, positive, and statistically significant correlation with VAS, DAS28, HAQ scores, and ESR values (correlation coefficients: $r=0.350$, $r=0.501$, $r=0.320$, $r=0.420$, respectively; $p<0.05$). However, there was no significant correlation between tryptase levels and disease duration or CRP levels ($p>0.05$) (Table 3). Significant disparities were detected between RA patients with different levels of disease activity in terms of VAS and HAQ scores as well as ESR, CRP and tryptase levels ($p<0.05$). Post-hoc binary comparisons suggested that significant variations in VAS and HAQ scores, as well as CRP and tryptase levels, resulted from groups of individuals with high disease activity. On the contrary, the significantly different ESR values were between patients with low and high disease activity. RA patients with high disease activity had significantly higher VAS and HAQ scores, CRP and tryptase levels compared to those who had low or moderate disease activity (Table 4). Statistical data on other laboratory investigations in the RA group are presented in Table 4. A statistically significant difference in tryptase levels was observed between Rheumatoid factor (RF)-negative and RF-positive RA patients ($p<0.05$). The level of tryptase was notably greater in RF-positive RA patients compared to those who were RF-negative. No significant difference was found between anti-cyclic citrullinated peptide (Anti-CCP) negative and positive RA patients ($p>0.05$) (Tables 5,6).

Table 1. Sociodemographic comparison between patient and control groups

	RA (n=43)	Control (n=37)	p
Age (years)	52.53±11.10	48.41±12.79	0.101
Gender			
Male	7 (16.3)	5 (13.5)	0.975
Female	36 (83.7)	32 (86.5)	
Educational level			
Illiterate	13 (30.2)	6 (16.2)	0.183
Primary school graduate	21 (48.8)	17 (45.9)	
Secondary/high school graduate	6 (14.0)	6 (16.2)	
College/university graduate	3 (7.0)	8 (21.7)	
Height (cm)	160.74±6.79	163.24±7.06	0.111
Body weight (kg)	76.21±14.04	73.81±13.05	0.434
BMI (kg/m²)	29.50±5.23	27.71±4.64	0.111

BMI: body mass index; continuous variables are presented as "mean ± standard deviation", and categorical variables as "number (column percentage)"

Table 2. Distribution of laboratory values between patient and control groups

	RA (n=43)		Control (n=37)		p
	$\overline{X}$±SD	Median (min-max)	$\overline{X}$±SD	Median (min-max)	
ESR (mm/h)	33.49±24.39	26 (6-103)	15.97±9.14	15 (2-37)	**<0.001**
CRP (mg/dL)	1.38±1.86	0,59 (0.09-7.35)	0.39±0.27	0.30 (0.09-1.31)	**<0.001**
Tryptase (pg/mL)	14.06±6.56	10.78 (6.13-35.01)	8.75±1.63	8.78 (5.01-13.48)	**<0.001**

$\overline{X}$: mean, SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. The association of serum tryptase levels with disease-related variables in RA patients

	Tryptase	
	r	p
VAS	0.350*	0.022
HAQ	0.320*	0.037
ESR	0.420**	0.005
CRP	0.278	0.071
DAS28	0.501**	0.001

*p<0.05, **p<0.01; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, VAS: Visual Analog Scale, HAQ: Health Assessment Questionnaire, DAS28: Disease Activity Score 28

Table 4. Distribution of clinical characteristics and laboratory values of RA patients according to disease activity

	Disease activity						p
	Low (n=10)		Moderate (n=15)		High (n=18)		
	$\overline{X}$±SD	Median (min-max)	$\overline{X}$±SD	Median (min-max)	$\overline{X}$±SD	Median (min-max)	
Disease duration (months)	85.20±53.80	72 (12-192)	107.60±88.25	84 (12-324)	89.33±91.41	48 (12-300)	0.518
VAS	2.60±1.08	2.5 (1-5)	4.00±1.60	4 (1-6)	6.28±2.24[ab]	6 (1-10)	**<0.001**
HAQ	0.58±0.56	0.37 (0-1.5)	0.87±0.36	0.87 (0.25-1.75)	1.62±0.66[ab]	1.81 (0.25-2.5)	**<0.001**
DMARD use							
Non-user [n (%)]	2 (20.0)		1 (6.7)		1 (5.6)		0.411
User [n (%)]	8 (80.0)		14 (93.3)		17 (94.4)		
Biological drug use							
Non-user [n (%)]	7 (70.0)		11 (73.3)		16 (88.9)		0.398
User [n (%)]	3 (30.0)		4 (26.7)		2 (11.1)		
RF							
Negative [n (%)]	8 (80.0)		5 (33.3)		6 (33.3)		0.034
Positive [n (%)]	2 (20.0)		10 (66.7)		12 (66.7)		
Anti-CCP							
Negative [n (%)]	5 (50.0)		5 (33.3)		5 (27.8)		0.491
Positive [n (%)]	5 (50.0)		15 (66.7)		13 (72.2)		
ESR (mm/h)	14.40±8.20	12 (6-29)	28.53±14.33	22 (15-65)	48.22±28.26[a]	39.5 (13-103)	**<0.001**
CRP (mg/dL)	0.54±0.39	9.68 (6.13-17.73)	0.55±0.32	0.41 (0.27-1.38)	2.54±2.42[ab]	1.49 (0.39-7.35)	**0.004**
Tryptase (pg/mL)	10.12±3.27	9.68 (6.13-17.73)	13.23±7.52	10.22 (8.01-35.01)	16.95±5.98[ab]	15.97 (8.01-29.77)	**0.003**

$\overline{X}$: mean, SD: standard deviation, %: percentage, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, VAS: Visual Analog Scale, HAQ: Health Assessment Questionnaire, DMARD: disease-modifying antirheumatic drug, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide antibody [a]Post-hoc pairwise comparison showed a significant difference with the "low" disease activity group (p<0.017); [b]Post-hoc pairwise comparison showed a significant difference with the "moderate" disease activity group (p<0.017); [c]Post-hoc pairwise comparison showed a significant difference with the "high" disease activity group (p<0.017)

Table 5. Tryptase levels in RA patients according to RF status

	RF negative (n=19)		RF positive (n=24)		p
	$\overline{X}$±SD	Median (min-max)	$\overline{X}$±SD	Median (min-max)	
Tryptase (pg/mL)	10.41±2.96	9.91 (6.13-17.73)	16.96±7.22	15.65 (8.66-35.01)	**0.001**

$\overline{X}$: mean, S: standard deviation, %: percentage, RF: rheumatoid factor

Table 6. Tryptase levels of RA patients according to anti-CCP status

	Anti-CCP negative (n=15)		Anti-CCP positive (n=28)		p
	$\overline{X}$±SD	Median (min-max)	$\overline{X}$±SD	Median (min-max)	
Tryptase (pg/mL)	11.97±6.71	10.49 (6.92-35.01)	15.18±6.32	14.12 (6.13-29.77)	0.070

$\overline{X}$: mean, S: standard deviation, %: percentage, Anti-CCP: anti-cyclic citrullinated peptide

DISCUSSION

Our research demonstrated that serum tryptase levels were markedly higher in RA patients than in the control group, with a notable relationship linking higher tryptase levels and greater disease activity. Tryptase levels exhibited a positive correlation with DAS28, VAS, HAQ scores, and ESR, whereas no significant link was identified with CRP levels. This evidence suggests on the possibility role of tryptase levels as a surrogate biomarker for the severity and progression of RA.

MCs are heterogeneous cells of bone marrow origin with multiple functions. They manage a wide range of functions in innate and gained immunity, including re-vascularization, inflammation, hypersensitivity reactions, vascular system regulation (21,22). MCs contain granules that store many substances. These granules contain proinflammatory structures, including proteoglycans and tryptase. When MCs are stimulated and activated, these granules are released into the environment, and hypersensitivity and inflammation develop (23). Recent studies demonstrating the presence of MCs in the synovium of RA patients and the classification of synovitis according to the density of these cells prove that MCs play an active role in the development of this disease and that the disease shows a heterogeneous structure. MCs secrete a number of chemokines in response to antigenic substances and subsequently cause inflammation, re-vascularization and edema formation in the regional tissue (24). In a study, it has been shown that synovial MCs are found at high rates in patients with RA and inflammation increases in direct proportion to the number of MCs and is associated with high disease activity (25). Kim et al.'s study revealed that MCs and tryptase levels were increased in the synovial tissues of RA patients, and this elevation promoted the differentiation of osteoclasts (26). According to a review by Rivellese et al., the presence of synovial MCs in untreated early RA patients was closely linked to heightened synovial and systemic inflammation, as well as increased disease activity. This connection highlights the significant role of MCs in driving RA pathology and points to their potential as a key focus for early therapeutic interventions (27). All these findings confirm that MCs and tryptase contribute to inflammation in RA.

Guo and colleagues' research revealed that serum tryptase levels were notably elevated in patients with both early and late-stage RA compared to healthy individuals. They investigated the presence of anti-tryptase antibodies in RA serum samples, considering that for a molecule to be recognized as an autoantigen involved in the etiopathogenesis of a disease, antibodies against these antigens must be present. They found that these antibodies were present in RA patients but not in patients with osteoarthritis or systemic lupus erythematosus. Again, when they examined synovial fluid samples of RA patients, they found the presence of tryptase and anti-tryptase antibodies. When compared with synovial fluids of osteoarthritis patients, they showed that these antibodies were absent. They also found a positive correlation between tryptase levels and DAS28, RF and anti-CCP in RA patients, but not with CRP and ESR (7). Similarly, in our study, serum tryptase concentration was found to be higher in RA patients compared to controls. In our study, we found a positive correlation between serum tryptase levels and DAS28, RF and ESR in RA patients. These findings support that tryptase may play an active and prominent role in disease activity and inflammation in RA. Research exploring the connection between anti-CCP and tryptase is scarce in the existing literature. Unlike the study by Guo et al., although no correlation was found between anti-CCP and tryptase in our study, tryptase levels were higher in the anti-CCP positive group. This may be due to the variability in the antigen responses of autoantibodies.

A study by Rossini et al. found no significant increment in serum tryptase concentrations in patients with early RA versus healthy controls. Additionally, a negative association has also been reported between CRP and serum tryptase levels in the same study. As a result, the authors suggested that tryptase may possess an anti-inflammatory role in RA (28). We enrolled only late RA patients in our study and similar to Guo's study; we detected the serum tryptase values were markedly elevated in RA patients relative to the control group. These conflicting results may arise from tryptase playing a more dominant role at different stages of inflammation or from the variability in antigen responses of autoantibodies. Factors such as patient selection, prolonged disease duration, comorbidities developing over the course of the disease, and the medications used could have influenced the outcomes.

In a study by Kim and colleagues investigating osteoclastogenesis in RA patients, they reported elevated serum tryptase levels, consistent with our study. However, no information regarding disease activity was provided in that study (26). In this article, we categorized disease activity into three groups—mild, moderate, and high—and demonstrated that tryptase levels increase as disease activity rises. To our knowledge, no other research in the literature has measured tryptase levels by classifying RA patients according to disease activity, making our research unique in this respect.

Another subject investigated in our study is the relationship between CRP and tryptase. CRP is a member of the pentraxin super family and its synthesis increases in inflammatory conditions. It is mainly regulated by IL-6 and IL-1β cytokines and synthesised from the liver. CRP is increased in many inflammatory events (29). When we analysed the relationship between CRP levels and serum tryptase, similar to the findings of Guo and colleagues, we did not observe a relationship between CRP and serum tryptase levels. Another study showed a negative correlation between serum trptase and CRP (7,28). This suggests that CRP and tryptase may be activated through different pathways and may be due to the temporal variation of the inflammatory response.

ESR is a test that measures the rate at which erythrocytes sediment. It is used in the diagnosis and monitoring of infectious processes, inflammatory conditions and a number of diseases. ESR is a low specificity test that is influenced by many factors. It may be incompatible with CRP in some diseases such as RA (30). In this study, we found a statistically meaningful distinction between ESR and tryptase concentrations, which differs from Guo and colleagues study (7). This discrepancy is presumably relevant to differences in disease activity and phenotypic heterogeneity in our RA group compared to Guo's study. Considering that ESR may objectively reflect the state of active inflammation, the correlation between ESR and tryptase levels suggests that serum tryptase could serve as an important indicator in assessing disease activity in RA.

The role of tryptase on inflammation in RA led the researcher to investigate the presence of tryptase in other inflammatory diseases. Paolino et al. investigated serum tryptase levels in patients with psoriasis and found that serum tryptase levels were in the normal range in psoriasis patients, but higher levels were found in patients with psoriatic arthritis (PsA) and scalp involvement. As a result, they argued that tryptase showed proinflammatory effect (31). In another study by Chimenti et al., it was reported that tryptase levels upregulated in patients with psoriasis and PsA and may contribute to joint damage as a result of stimulation of matrix metalloproteinases in these patients (32). In another study on sarcoidosis patients, serum tryptase concentrations were raised in sarcoidosis patients versus the control group. However, no distinction was observed between progressive and stable sarcoidosis groups (8). Considering these findings, it can be inferred that tryptase is a key factor in promoting systemic inflammation.

CONCLUSION

We believe that tryptase exerts pro-inflammatory effects. In our research, we detected a notable increase in tryptase levels as disease activity intensified. The positive association observed in the tryptase levels and ESR further supports this hypothesis. This correlation suggests the potential for targeting tryptase or its signaling pathways as a new therapeutic approach in RA. Additionally, the exact mechanisms by which tryptase contributes to RA pathogenesis remain unclear. Further investigation is necessary to clarify its contribution to disease mechanisms and its efficacy as a therapeutic target. Monitoring serum tryptase levels may also aid in classifying patients according to disease severity and tailoring treatment regimens accordingly. Patients with high tryptase levels may potentially benefit from more aggressive anti-inflammatory and immunomodulatory therapies.

Study Limitations

The main restriction of our study is that other cytokine levels implicated in the mechanism of disease pathogenesis, synovial fluid cytokine and tryptase levels, and histological sampling of the inflamed tissue were not analyzed. Additionally, the sample size was relatively small, and the study was cross-sectional, limiting the ability to establish causality between elevated tryptase levels and RA progression. Various treatment methods that could influence cytokine levels and the relationship between tryptase and other variables were used by patients.

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