

# Serum chitotriosidase and neopterin levels in patients with ankylosing spondylitis

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## Abstract

**Background:** The aim of this study was to assess the serum chitotriosidase (ChT) and neopterin levels in patients with ankylosing spondylitis (AS) and to evaluate whether serum ChT and neopterin levels are related to disease activity.

**Methods:** A total of 86 patients with AS were included in the study. Patients were divided into two groups based on Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores: The active AS patients group included 40 patients who had a BASDAI score  $\geq 4$ . The inactive AS patients group included 46 patients who had a BASDAI score  $< 4$ . We compared the serum level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ChT and neopterin between the two groups.

**Results:** Active AS patients had significantly higher ESR, CRP, serum ChT and neopterin levels compared with the inactive AS patients group ( $p < 0.05$ ). Positive correlations were found between serum ChT levels and ESR ( $r = 0.87$ ,  $p = 0.005$ ), and CRP levels ( $r = 0.86$ ,  $p = 0.006$ ). Also, there was a positive significant correlation between serum ChT levels and BASDAI scores ( $r = 0.67$ ,  $p = 0.03$ ). No correlation was found between serum neopterin levels and the BASDAI scores, ESR, and CRP levels ( $p > 0.05$ ). Higher disease activity (BASDAI score  $\geq 4$ ) was found to be associated with ChT ( $p = 0.012$ ) in the multiple logistic regression analysis.

**Conclusion:** The present study emphasized that serum ChT levels can be useful in the determination of the disease activity of AS patients.

**Keywords:** ankylosing spondylitis, chitotriosidase, disease activity, neopterin

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## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the spine and sacroiliac joints, and macrophages play a major role in the inflammation.<sup>1</sup> Human chitotriosidase (ChT) is a member of the chitinase family and has the capability to hydrolyze chitin.<sup>2</sup> Macrophages are able to produce large amounts of ChT when activated.<sup>3,4</sup> Neopterin is a low-molecular weight compound derived from guanosine triphosphate. Human monocytes and macrophages constitute the most important source of neopterin stimulated by interferon- $\gamma$ .<sup>5</sup> Therefore, the serum levels of neopterin and ChT have been considered as a marker of macrophage activation.

Increased levels of ChT have been observed in patients with Alzheimer's disease, multiple sclerosis, thalassemia and atherosclerosis all of which comprise lysosomal storage diseases and macrophage activation.<sup>4,6–8</sup> Increased serum ChT levels were also observed in patients with sarcoidosis<sup>9</sup> and juvenile idiopathic arthritis.<sup>10</sup> The result of these studies has showed that serum ChT can be used in monitoring disease activity, in following treatment efficacy and in investigating disease prognosis. Neopterin has been also observed as a biochemical marker of immune system activation in some diseases such as polycystic ovary syndrome,<sup>11</sup> rheumatoid arthritis,<sup>12</sup> autoimmune diseases such as insulin-dependent diabetes mellitus, systemic lupus erythematosus,

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multiple sclerosis, coeliac disease,<sup>13,14</sup> Crohn's disease and ulcerative colitis.<sup>15</sup>

To the best of our knowledge, no study has yet been performed for investigating the serum neopterin and ChT levels in patients with AS. The aim of this study was to assess the serum ChT and neopterin levels in patients with AS and to evaluate whether serum ChT and neopterin levels are related to disease activity.

## Materials and methods

### Study design and patients

This prospective designed study was conducted with 86 patients fulfilling the modified New York criteria<sup>16</sup> for AS. The patients were recruited from the physical medicine and rehabilitation outpatient clinic. The same researcher examined the patients and carried out the measurements of disease activity. Disease activity was measured with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).<sup>17</sup> The BASDAI consists of six questions pertaining to the five major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness. Patients were asked to answer each item using a 0–10 cm visual analogue scale, on which the patients could indicate their assessment along a 10 cm line ranging from 0 ('no complaint at all') to 10 ('the most severe complaint'). The possible BASDAI score is ranged from 0 to 10. Scores of 4 or greater suggest active disease (uncontrolled, disease activity) while scores less than 4 suggest inactive disease (controlled, disease activity). We also recorded patients' age, sex, duration of disease and drugs used by the patients such as disease-modifying anti-rheumatic drugs (DMARDs), anti-tumor necrosis factor (TNF) drugs and nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients were divided into two groups based on BASDAI scores. The active AS patients group included 40 patients who had BASDAI score  $\geq 4$ . The inactive AS patients group included 46 patients who had BASDAI score  $< 4$ . We compared the serum level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ChT and neopterin between the two groups. Patients were excluded if they had acute or chronic infection disease, other chronic inflammatory rheumatic disease, lysosomal storage diseases or metabolic diseases. The study protocol was

approved by the Hospital Ethical Committee and each patient provided written informed consent.

### Blood sampling and analysis

Blood samples of all the participants were collected to determine the serum level of acute-phase reactants, ESR or CRP, and serum neopterin and ChT levels. Plasma samples of the neopterin and ChT were stored at  $-80^{\circ}\text{C}$  for the analysis. Serum ChT activity determination was performed as described by Hollak and colleagues<sup>2</sup> with minor modifications. Serum ChT activity was measured using a Microfluor fluorimeter (Bio-Tek Instruments, Neufahrn, Germany; excitation, 355 nm; emission, 460 nm). Serum ChT activities were expressed as nanomoles of substrate hydrolyzed per milliliter per hour (nmol/ml/h). The normal levels for ChT was 6.2–27.0 nmol/ml/h. Serum neopterin concentration was measured with a high-performance liquid chromatography device (Agilent Technologies 1200 Series System, Santa Clara, CA, USA) using a fluorometry detector, as previously defined by Fuchs and colleagues.<sup>18</sup> The calculated overall intra-assay and inter-assay coefficient of variation (CV) was 1.2% and 2.6% respectively. The normal levels for neopterin was 3.5–15.0 nmol/l. Serum ChT activities and serum neopterin concentration were measured by the same clinicians of the Department of Biochemistry. CRP levels were measured by the immunoturbidimetric method (Schiapparelli Biosystems, The Netherlands) and levels lower than 3.23 mg/l were accepted to be negative. The Westergreen method was used to measure ESR in which the range between 1 and 20 mm/h was accepted as normal.

### Statistical analysis

The sample size of 86 patients was based upon a sample size calculation, with an anticipated mean difference of 14 and a standard deviation of 8 in ChT level, and with an anticipated mean difference of 10 and a standard deviation of 6 in neopterin level, between the two groups, allowing for a  $p$  value of 0.05 and a power of 0.95.

Statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL). Categorical variables are presented as a proportion and percentage. Continuous variables are presented as mean  $\pm$  standard deviation. Patients' sex and medications were compared using the Pearson Chi-square test between the two groups. The comparisons between the two groups were performed using a

**Table 1.** Comparison of clinical and biochemical parameters between the two groups.

Characteristics	Active disease group (n = 40)	Inactive disease group (n = 46)	p
Age (mean ± SD); year	37.4 ± 15.2	41.7 ± 15.0	0.11 <sup>a</sup>
Sex		26/20	0.54 <sup>b</sup>
Male	20 (50%)	26 (56.5%)	
Female	20 (50%)	20 (43.4%)	
Medication; number of patients			
DMARD plus NSAID	20 (50%)	20 (43.4%)	0.23 <sup>b</sup>
NSAID alone	7 (17.5%)	9 (19.5%)	0.67 <sup>b</sup>
DMARD alone	5 (12.5%)	7 (15.2%)	0.78 <sup>b</sup>
Anti-TNF alone	8 (20%)	10 (21.7%)	0.93 <sup>b</sup>
Duration of disease (mean ± SD); month	51.57 ± 33.43	46.21 ± 42.66	0.59 <sup>a</sup>
ESR (mean ± SD); mm/h	28.98 ± 23.00	8.14 ± 3.80	<b>0.001<sup>a</sup></b>
CRP (mean ± SD); mg/l	15.16 ± 14.44	6.45 ± 5.94	<b>0.03<sup>a</sup></b>
ChT (mean ± SD); nmol/ml/h	49.14 ± 31.40	26.50 ± 8.69	<b>0.01<sup>a</sup></b>
Neopterin (mean ± SD); nmol/l	37.25 ± 25.36	20.71 ± 10.85	<b>0.02<sup>a</sup></b>
<sup>a</sup> As determined by the Mann–Whitney U test. <sup>b</sup> As determined by the Pearson Chi-square test. Bold values indicate a p value <0.05. ChT: chitotriosidase; CRP: C-reactive protein, DMARD, disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TNF, tumor necrosis factor.			

nonparametric test (Mann–Whitney U test). A Spearman rank correlation was used to examine the relationship between the parameters. Multiple logistic regression analysis was performed to identify the influence of multiple variables (age, sex, duration of disease, and ChT) on a dependent variable (presence of active disease, BASDAI score  $\geq 4$ ). We used receiver operating characteristic (ROC) plot analysis to evaluate and compare the performance of ESR, CRP and serum ChT in assessing disease activity. ROC analysis is a non-parametric method used to quantify the accuracy of the prediction. The level of statistical significance was set at  $p < 0.05$ .

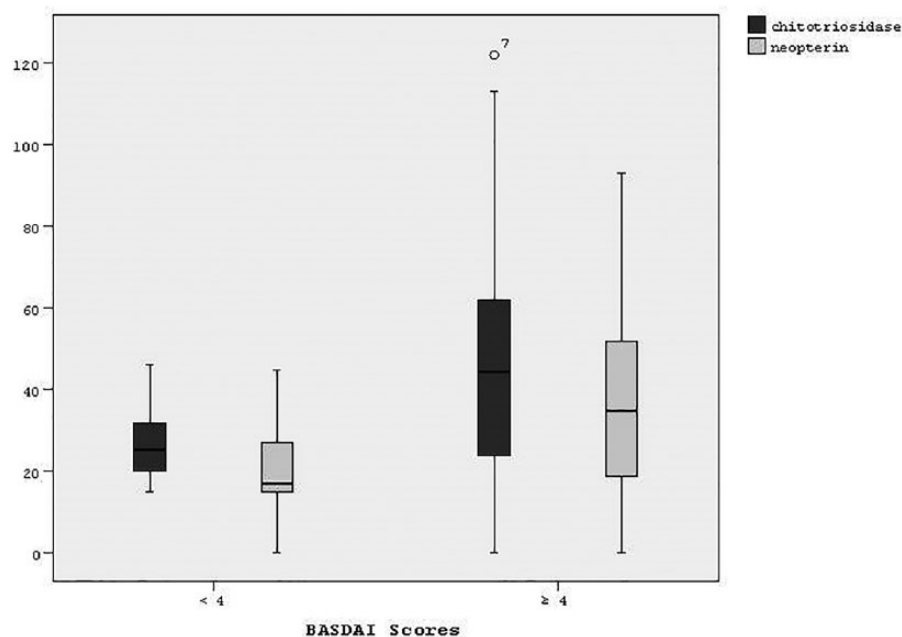
## Results

The distribution of clinical and biochemical parameters of the groups are shown in Table 1. There were no significant differences between the two groups in terms of age, sex, use of drug and duration

of disease. The patients in the active disease group had significantly higher ESR, CRP, serum ChT and neopterin levels compared with patients in the inactive AS group ( $p < 0.05$ ). The distribution of serum ChT and neopterin levels according to BASDAI scores are shown in Figure 1.

When we investigated the serum level of ESR, CRP, neopterin and ChT among the patients in the active disease group, we found that 33% of the patients had a normal ESR level, 21% of the patients had a normal CRP level, 65% of the patients had a normal neopterin level, and 28% of the patients had a normal ChT level.

Positive correlations were found between serum ChT levels and ESR ( $r = 0.87$ ,  $p = 0.005$ ), and CRP levels ( $r = 0.86$ ,  $p = 0.006$ ). Also, there was positive significant correlation between serum ChT levels and BASDAI scores ( $r = 0.67$ ,  $p = 0.03$ ). No correlation was found between serum



**Figure 1.** The distribution of serum ChT and neopterin levels according to BASDAI scores. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ChT, chitotriosidase.

**Table 2.** Correlation analysis of serum ChT and neopterin levels with other parameters.

Variables	Correlation with ChT		Correlation with neopterin	
	<i>r</i>	<i>p</i> <sup>a</sup>	<i>r</i>	<i>p</i> <sup>a</sup>
ESR	0.87	<b>0.005</b>	0.36	0.18
CRP	0.86	<b>0.006</b>	0.54	0.23
BASDAI scores	0.67	<b>0.03</b>	0.25	0.42

<sup>a</sup>Spearman correlation test was used. Bold values indicate a *p* value <0.05. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ChT: chitotriosidase; CRP, C-reactive protein; ESR: erythrocyte sedimentation rate;

neopterin levels and the BASDAI scores, ESR, and CRP levels (*p* > 0.05). The results of correlation analyses were shown in Table 2.

Higher disease activity (BASDAI score ≥4) was found associated with age (*p* = 0.043), ESR (*p* = 0.018) and ChT (*p* = 0.047) in the multiple logistic regression analysis (Table 3).

We also used ROC analysis to evaluate the degree of usefulness of ESR, CRP, and serum ChT for assessing disease activity. ESR, CRP, and serum

ChT showed the best and significant area under the curve (AUC), when distinguishing the AS patients with higher score of BASDAI (AUC values were 0.815, 0.722, and 0.713, respectively, all *p* < 0.05; Figure 2).

### Discussion

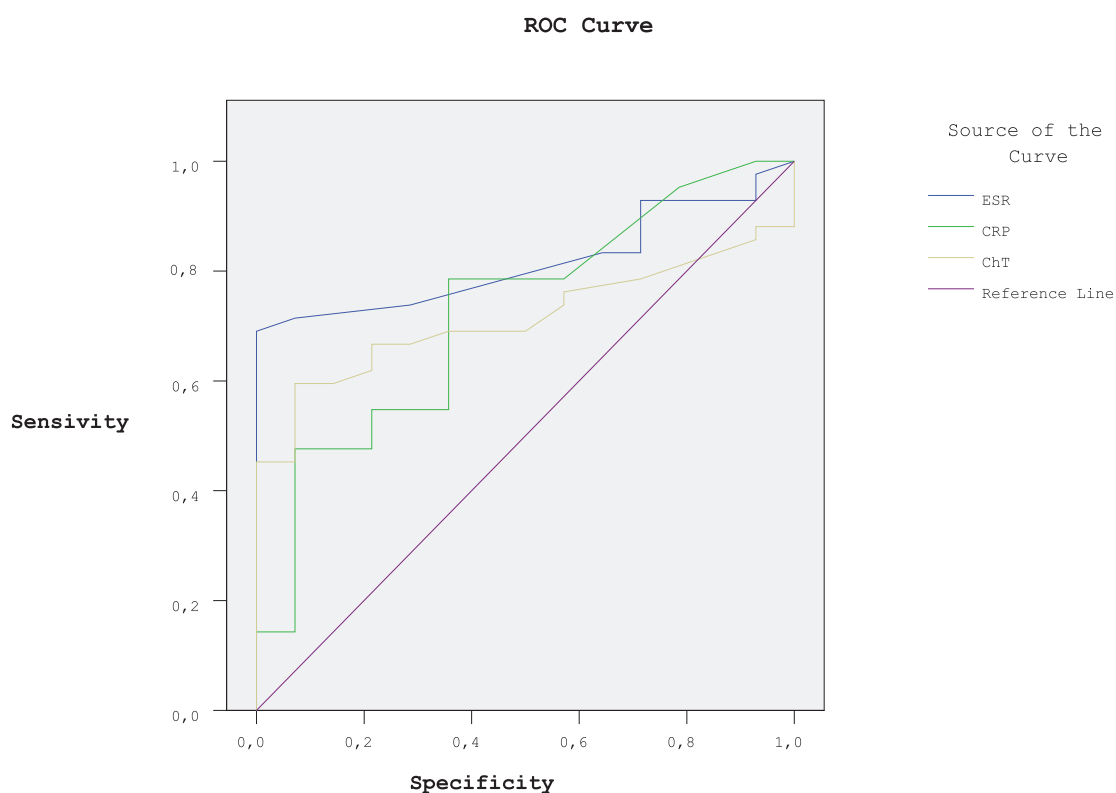
Our results revealed that serum ChT and neopterin levels were significantly higher in patients with active AS. Moreover, the significant correlation of ChT activity with clinical disease activity and acute-phase response parameters could be interpreted that serum ChT might be a significant predictor for disease activity in AS patients. However, neopterin did neither correlate with clinical disease activity nor with acute-phase response parameters in patients with AS. Higher disease activity was associated with ChT.

ChT has been considered as a marker of macrophage activation, and ChT secretion in chronic inflammatory diseases is a popular scientific subject, which is still not fully understood and to our knowledge, this is the first study showing a relation with ChT levels in patients with AS. Patients with active AS showed significantly higher levels of ChT when compared with patients with inactive AS. ChT is selectively expressed in chronically activated tissue macrophages and

**Table 3.** Multiple logistic regression analysis for disease activity in patients with ankylosing spondylitis ( $n = 86$ ).

Variables	Presence of active disease (BASDAI $\geq 4$ )		
	Standardized $\beta$ coefficient	$t$	$p$
Age	-0.56	0.946	0.056
Sex	-0.746	0.474	0.383
Duration of disease	-0.008	1.008	0.428
ChT	0.052	1.054	<b>0.012</b>

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ChT: chitotriosidase.  
Bold values indicate a  $p$  value  $<0.05$ .

**Figure 2.** ROC curves analysis: comparison of ESR, CRP and serum ChT in demonstrating of active AS patients. [BASDAI  $\geq 4$  as being positive for high disease activity ; area under the curve (AUC) ( $p$  value) are 0.815 ( $<0.05$ ), 0.722 ( $<0.05$ ), and 0.713 ( $<0.05$ ), respectively.] Null hypothesis: true area = 0.5.

AS, ankylosing spondylitis; AUC, area under the curve; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ChT, chitotriosidase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ROC, receiver operating characteristic.

reflects chronic inflammation rather than acute inflammation.<sup>4</sup> In the present study, ChT showed a positive significant correlation with clinical disease activity and acute-phase response parameters. Thus, serum ChT levels can be helpful not only in estimating the long-term course of AS disease, but also in predicting short-term disease activity levels. A previous study of ChT in

juvenile idiopathic arthritis (JIA) was performed to define the relationship between serum ChT level and disease activity.<sup>10</sup> This found that there was no correlation between serum ChT, and the clinical disease activity and inflammation markers in patients with JIA. The difference may be due to the age range in this study, as it was juvenile patients.

Neopterin is produced mainly in macrophages and T helper (Th1) lymphocytes derived from interferon gamma (IFN- $\gamma$ ).<sup>19</sup> Neopterin concentrations are increased in the body fluids of patients with an activated cellular immune response, such as polycystic ovary syndrome,<sup>11</sup> rheumatoid arthritis,<sup>12</sup> autoimmune diseases,<sup>13,14</sup> Crohn's disease and ulcerative colitis.<sup>15</sup> Previous studies of neopterin in rheumatoid arthritis have been performed to define the relationship between neopterin and disease activity. Generally, they found that neopterin correlated with disease activity in patients with rheumatoid arthritis.<sup>20–22</sup> In contrast with the previous studies, our study showed that there was no significant correlation between serum neopterin, and the clinical disease activity and acute-phase response parameters in patients with AS. The difference in the results may be attributed to the pathogenesis of various diseases.

Arshadi and colleagues<sup>23</sup> detected significantly higher levels of neopterin in patients with rheumatoid arthritis compared with healthy controls, and found that there was a higher neopterin level in male patients with rheumatoid arthritis than female patients, and a significant correlation of plasma levels of neopterin with age in both the rheumatoid arthritis and control groups. Previous studies have showed an increase in neopterin levels with increasing age.<sup>24,25</sup> However, contrary to the previous results, we did not find any significant association between age, medication and duration of disease, and serum level of ChT and neopterin.

The measurement of the levels of the acute-phase reactants appears to have limited value in determining disease activity.<sup>26</sup> Only 50–70% of patients with active AS will have an increased level of CRP and ESR.<sup>27</sup> Similar to these results, in our study we found that 67% of the patients with active AS had an increased level of ESR, and 79% of the patients with active AS had an increased level of CRP. Yildirim and colleagues showed a significant relationship of BASDAI with only CRP but not with other acute-phase reactants such as ESR, haptoglobin (Hp), beta-2-microglobulin.<sup>28</sup> In the present study, we grouped patients as inactive and active according to BASDAI scores <4 or  $\geq$ 4 and showed that the acute-phase response markers were significantly higher in patients with active AS. We also showed a positive significant correlation between serum ChT and BASDAI scores.

The present study has several limitations. First, the effects of the type of therapy on serum neopterin and ChT levels were not followed, so their use as a marker for therapy efficacy could not be evaluated. Second, there was a lack of repeated measures in the follow-up period. Third, a potent association with B27 is axial inflammation in the bone, cartilage, and entheses. The role of B27 is in an immune response that initiates or perpetuates this inflammation. HLA-B27 was not considered in this study. Fourth, assessment of the disease activity was only based on BASDAI scores. The Ankylosing Spondylitis Disease Activity Score in addition to BASDAI might have been used to strengthen the results of the present study. Finally, this study was cross-sectional and did not have a healthy control group.

### Conclusion

The present study emphasized that serum ChT levels can be useful in the determination of disease activity in patients with AS. Further studies are needed to assess the relationship between serum neopterin levels and AS activity.

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### Conflict of interest statement

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