A novel marker of systemic inflammation in psoriasis and related comorbidities: chitotriosidase

Abstract

Background/aim: Chitotriosidase (ChT) is an enzyme secreted by activated macrophages and neutrophils in response to proinflammatory signals. There is growing evidence indicating that ChT activity reflects the systemic inflammatory status. This study aimed to investigate whether serum ChT activity increased in patients with psoriasis and related comorbidities.

Materials and methods: This cross-sectional study included 53 (28 with associated comorbidities and 25 without comorbidities) patients with psoriasis and 52 healthy volunteers. All participants underwent laboratory investigations for serum ChT levels, complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum lipid levels.

Results: The patients with psoriasis showed significantly higher levels of ChT activity as compared to the healthy controls (23.5 ± 11.4 vs. 17.5 ± 10.4 μmol/mL/hour; $p = 0.015$). Additionally, the ChT activity was significantly higher in patients with comorbidities than in those without ($p = 0.042$).

Conclusion: Our data support the pathogenetic role of inflammatory processes induced by macrophage activation in patients with psoriasis and related comorbidities. We believe that high ChT activity in patients with psoriasis may serve as an early prediction of the possible related comorbidities.

Keywords: Chitotriosidase, comorbidity, macrophage, psoriasis

1. Introduction

Psoriasis is a relatively common chronic inflammatory cutaneous disease characterized by epidermal hyperproliferation. It is considered an immune-mediated inflammatory disorder in which the T lymphocytes, dendritic cells, and cytokines play crucial roles. Multisystem chronic inflammation in psoriasis can be associated with multiple comorbidities, including obesity, metabolic syndrome, and cardiovascular diseases [1-3]. Although the exact etiology remains unknown, there are various suggested risk factors for psoriasis. Genetic predisposition is a fundamental factor, and smoking, obesity, and alcohol use are well-known risk factors. Drugs and infections have also been described as triggering factors for psoriasis [1,4].

Chitotriosidase (ChT) is an enzyme secreted by activated macrophages and neutrophils in response to proinflammatory signals. Currently, it is used as a biochemical marker for the diagnosis and monitoring of lysosomal storage diseases [5-7]. Studies have reported high activities of ChT in a wide range of diseases such as atherosclerosis, malaria, bronchial asthma, sarcoidosis, non-alcoholic steatohepatitis, diabetes mellitus (DM), Alzheimer's disease, cancer, and thalassemia [8-12]. High ChT activity is reportedly associated with a high risk of cardiovascular events [13]. There is growing evidence indicating that ChT activity reflects the inflammatory status. Furthermore, it has been reported that ChT plays a vital role in the immune response against chitin-containing pathogens [14]. ChT is produced after at least 7 days of cell culture and increases with time; hence, it is considered a chronic inflammatory marker rather than an acute-phase reactant [15].

In this study, we aimed to investigate whether ChT could serve as a marker for the prediction of comorbidities in patients with psoriasis, which is a common chronic inflammatory skin disease.

2. Materials and methods

This cross-sectional study which was carried out between March and September 2020, included 53 patients with clinically and histopathologically confirmed psoriasis (28 with associated comorbidities and 25 without comorbidities) and 52 healthy volunteers. All procedures were in accordance with the principles of the Declaration of Helsinki, and the study was approved by the local clinical research ethics committee (approval date and number: 2020-02/16). Written informed consent was obtained from all participants.

Pregnant or breastfeeding females, patients under 18 years of age, those undergoing systemic treatment, and those with accompanying infections or malignancies were excluded. Patients who had received topical treatment or phototherapy within the last month or systemic treatment within the last 3 months were also excluded.

All participants underwent physical examination and laboratory investigations for serum ChT levels, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum lipid levels. Additionally, the Psoriasis Area and Severity Index (PASI) and disease duration were recorded for all the patients. PASI score $\leq$10 mild psoriasis, >10 determined as moderate to severe psoriasis [16].

Venous blood samples from all participants were obtained 5 mL in a tube without anticoagulant and 4 mL in K_2EDTA tube of the forearm in the morning after at least 8-10 hours of fasting. Blood collected in plain tubes was allowed to clot for 30 minutes and

then centrifuged at 2000 ×g for 10 minutes. Routine biochemical tests were immediately performed on some of the serum, and about 0.5 mL the remaining samples were stored at −80°C to measure the ChT levels. The CBC of the blood samples collected in K2EDTA tubes was evaluated using Sysmex XN1000 (Sysmex Corp.®, Kobe, Japan). Routine biochemistry and hormone tests were performed using Cobas c702 (Roche Diagnostics®, Japan) autoanalyzer system with standard laboratory methods.

The ChT activity was measured using the method proposed by Hollak et al. [5]. According to this method, after thawing frozen serum samples, each serum sample was incubated with a substrate containing 4-methylumbelliferyl-chitotrioside at 37°C for 2 hours. Fluorescence was detected by excitation at 360 nm and emission at 445 nm (Modulus microplate fluorometer, Turner Biosystems, Inc., California, USA). The ChT activity results were represented as μmol/mL/hour.

2.1. Statistical analysis

Statistical package for the Social Sciences software (version 21.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The conformity of the data to normal distribution was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Logarithmic conversion was performed for non-normally distributed variables. Normally distributed variables were presented as mean and standard deviation and non-normally distributed variables as median and interquartile range. Data were compared between the two groups using either student's t-test (normal distribution) or Mann-Whitney U-test (non-normal distribution). The chi-square test was used to compare the categorical data. Correlations were assessed using either the Pearson correlation test for normally distributed data or Spearman's P for non-normally distributed data. One-way analysis of

variance was used to compare the normally distributed variables between the groups, and the Kruskal-Wallis test was used to compare non-normally distributed variables. Post-hoc testing was performed using Tukey's test. Statistical significance was set at p-values <0.05.

3. Results

This study included 25 patients without comorbidities (11 males, 14 females), 28 patients with comorbidities (8 males, 20 females), and 52 healthy controls (15 males, 37 females). The demographic characteristics of the participants are summarized in Table 1.

In this study cohort, 16 patients had psoriatic arthritis (PsA), 10 had type II DM, 8 had hypertension (HT), and 4 had hypothyroidism. There were no statistically significant differences between patients with and without comorbidities in terms of the disease duration and PASI values (Table 1).

Patients without comorbidities showed significantly higher CRP levels as compared to the healthy controls ($p = 0.031$), but there were no statistically significant differences in the ChT activity, white blood cell (WBC) count, or ESR between control and patients without comorbidities (Table 2).

ChT activity, CRP, and ESR levels were significantly higher ($p = 0.001$, $p = 0.016$, and $p = 0.009$, respectively) in patients with comorbidities than in the healthy controls (Table 2).

All patients showed significant higher ChT activity as compared to the healthy controls (23.5 ± 11.4 vs. 17.5 ± 10.4 μmol/mL/hour; $p = 0.015$).

Moreover, the ChT activity was significantly higher in patients with comorbidities than in those without ($p = 0.042$) (Figure 1); however, there were no statistically significant differences in the WBC count, CRP, and ESR between the two groups (Table 2).

Spearman's correlation analysis revealed a positive correlation between the WBC count and PASI scores (rho = 0.426, p = 0.026) in patients with comorbidities. There was no correlation between inflammatory parameters and PASI scores in patients without comorbidities.

Based on the PASI scores, the patients were grouped as PASI >10 and PASI ≤10. The ChT activity was found to be significantly lower in patients without comorbidities with PASI >10 (p = 0.022). The other inflammation parameters showed no statistically significant differences (Table 3).

The WBC count was significantly lower in patients with PsA (p = 0.043) than in those without comorbidities. No inflammatory parameters showed statistically significant differences between the patients with and without comorbidities. The ChT activity and CRP levels were significantly higher in hypertensive patients (p = 0.025 and p = 0.035, respectively) than in patients without comorbidities (Table 4, Figure 2). No inflammatory parameters showed statistically significant differences in patients with hypothyroidism when compared with those without comorbidities (Table 4).

There was no statistically significant difference in the lipid levels between patients with and without comorbidities. Triglycerides, total cholesterol, and low-density lipoprotein (LDL) levels were significantly higher (p = 0.008, p = 0.001, and p = 0.004, respectively) in patients with comorbidities than in the healthy controls. However, there were no statistically significant differences in these parameters between patients without comorbidities and healthy controls. Notably, the high-density lipoprotein (HDL) levels were significantly lower in patients without comorbidities than in the healthy controls (p = 0.012) (Table 1).

4. Discussion

Recent studies on the pathogenesis of psoriasis have shown that the disease occurs because of complex relationships between T lymphocytes, dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes [1]. Macrophages are potent phagocytic cells capable of antigen presentation and secretion of a wide range of chemical mediators. They are thought to play a key role in psoriasis by releasing important inflammatory products, such as tumor necrosis factor (TNF)-α and interleukin (IL)-17 [17]. Along with genetic predisposition, chronic inflammation is responsible for occurrence of comorbidities, especially in severe forms of psoriasis [3,18].

ChT, a member of the mammalian chitinase family (GH18), hydrolyzes chitin in lysosomes. There is growing evidence that ChT can be used as a marker of inflammation. Although studies have shown high activities of ChT in a wide range of diseases, including cardiovascular diseases, DM, and cancer, there are no data regarding the role of ChT activity in patients with cutaneous disorders [5-12,19]. To the best of our knowledge, this is the first study to investigate the possible role of ChT activity in patients with psoriasis and related comorbidities. Our study results revealed a relationship between ChT activity and psoriasis, especially in patients with comorbidities. The ChT activity, CRP, and ESR levels were significantly higher in patients with comorbidities than in healthy controls. However, only ChT levels were significantly higher in patients with comorbidities than in those without comorbidities. Therefore, it can be speculated that ChT may be a marker for comorbid diseases, but more data are needed in a large group for evidence.

The PASI is a scoring system used to measure the severity and extent of psoriasis. To calculate the PASI score, a representative area of psoriasis is chosen for each body area

affected. The intensity of redness, thickness, and scaling of the lesion is evaluated as "none," "mild," "moderate," "severe," or "very severe." The three intensity scores are then added up for each of the four body areas to obtain the subtotals. Each subtotal is then multiplied by the body surface area represented by that region [16]. Our study revealed no correlation between the PASI scores and ChT activity. The majority of the cases included in our study were mild cases, and severe cases were in minority. This limitation could explain the absence of a statistical correlation between the PASI scores and ChT activity.

Dyslipidemia is not uncommon in psoriasis [20,21]. In our study, only HDL cholesterol was found to be lower in patients without comorbidities when compared with the healthy controls. The total cholesterol, triglyceride, and LDL cholesterol levels were higher in patients with comorbidities than in controls. There was no correlation between the lipid parameters and ChT activity. No lipid parameters showed statistically significant differences between patients with and without comorbidities.

In our study, 16 patients (30.1%) presented PsA. The prevalence of inflammatory arthritis has been reported to be 6-42% in patients with psoriasis [3]. The incidence of arthritis increases in proportion to the severity and duration of psoriasis. Early diagnosis of PsA can prevent joint damage and improve the quality of life [22]. In our study, ChT activity and other inflammatory parameters did not differ significantly in patients with psoriatic arthritis (Table 4).

Psoriasis is associated with an increased risk of DM and insulin resistance, independent of the traditional risk factors [3]. Inflammatory mediators secreted by macrophages, such as IL-6 and TNF-α, have been reported to cause insulin resistance in psoriasis [23]. Two different studies reported high ChT activity in patients with DM [9,24]. Similarly, in our

study, ChT activity was higher in patients with psoriasis and DM than in healthy controls, but there was no significant difference when compared with patients without comorbidities. This could be attributed to the low number of patients with DM (Table 4). Hypertension is another common comorbidity with psoriasis. Various proinflammatory cytokines released from macrophages, such as TNF-α and IL-1β, and increased reactive oxygen species have been suggested to play critical roles in the pathogenesis of hypertension [23,25]. In our study, ChT activity was found to be higher in patients with hypertension (30.9 ± 15.6 μmol/mL/hour) than in those with other comorbidities (Table 4). The higher activity of ChT in hypertension suggests that macrophages may play a greater role in the pathogenesis of hypertension. No study has investigated the relationship between hypertension and ChT activity in the relevant literature. However, the levels of YKL-40, an inflammatory protein in the same family as ChT, have been shown to be high in essential hypertension [26].

Early diagnosis and treatment of psoriasis-related comorbidities can improve the quality of life and reduce mortality. Currently, there are no specific laboratory tests for the prediction of psoriasis-related comorbidities. In our study, we found higher ChT activity levels in patients with comorbidities than in those without comorbidities and healthy controls. High ChT activity was particularly remarkable in patients with hypertension.

In conclusion, our data support the pathogenetic role of inflammatory processes induced by macrophage activation in patients with psoriasis and related comorbidities. We believe that the high ChT activity in psoriasis may serve as an early predictor of possible related comorbidities.

The main limitation of our study was the relatively low number of patients with high PASI scores. Another limitation of our study is that we could not look at the body mass

indexes of the participants. Therefore, we could not reliably evaluate the atherogenic lipid profile detected in patients. However, ChT appears to be a promising marker for predicting the comorbid complications of psoriasis. It is obvious that this marker needs to be evidenced with large sample series.

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Table 1. Demographic parameters, Psoriasis Area and Severity Index scores, and lipid levels of the participants

Parameters	**Controls (n = 52)**	**Patients without comorbidities (n = 25)**	**Patients with comorbidities (n = 28)**	**p-values**
Male/female (n)	15/37	11/14	8/20	0.437
Age (years)	42.8 ± 13.9	41.6± 15.5	52.3 ± 11.9*¥	**0.006**
Duration of psoriasis (years)	-	3 (1-18)	3 (1-8)	0.673
PASI	-	6.4 (5-10)	5 (4.1-10)	0.561
PASI ≤10 (n)/PASI >10 (n)		18/5	24/6	0.487
Triglycerides (mg/dL)	100 ± 50.2	136.3 ± 93.5	144.4 ± 71.1*	**0.012**
Total cholesterol (mg/dL)	160.7 ± 32.2	176.2 ± 40	198.2 ± 37.9*	**0.001**
HDL-cholesterol (mg/dL)	53.7 ± 12.8	45.7 ± 11.4*	49.4 ± 9.5	**0.016**
LDL-cholesterol (mg/dL)	89.5 ± 31	101 ± 36.7	124 ± 52.9*	**0.006**

The values are presented as mean±SD or median (25th and 75th percentiles)

* $p < 0.05$, compared to the controls (post-hoc Tukey test)

¥ $p < 0.05$, compared to patients without comorbidities (post-hoc Tukey test)

PASI, Psoriasis Area and Severity Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table 2. Inflammatory parameters of the participants

Inflammatory markers	**Controls (n = 52)**	**Patients without comorbidities (n = 25)**	**Patients with comorbidities (n=28)**	**p-value**
Chitotriosidase (µmol/mL/hour)	17.5 ± 10.4	20.1 ± 8.2	26.5 ± 13.1*¥	**0.003**
WBC (×10^9 cells/L)	7.6 ± 1.7	7.94 ± 1.89	7.49 ± 2.13	0.636
ESR (mm/hour)	6 (5-13)	8 (3-17)	14 (6-19)*	**0.032**
CRP (mg/L)	1.0 (0.4-1.9)	1.6 (0.9-3.2) *	3.0 (0.9-6.9)*	**0.018**

The values are presented as mean±SD or median (25th and 75th percentiles)

* $p < 0.05$, compared to the controls

¥ $p < 0.05$, compared to the patients without comorbidity

WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Table 3. Distribution of the inflammatory parameters by Psoriasis Area and Severity Index scores

Parameters	**Patients without comorbidities (n = 25)**			**Patients with comorbidities (n = 28)**		
PASI	≤10 (n = 19)	>10 (n = 6)	p-value	≤10 (n = 24)	>10 (n = 4)	p-value
Chitotriosidase (µmol/mL/hour)	19.26 ± 7.2	16.5 ± 2.78	**0.022**	27.5 ± 13.6	19.6 ± 7.0	0.392
WBC (×10^9 cells/L)	7.5 ± 1.6	8.4 ± 1.7	0.301	7.18 ± 2.0	9.2 ± 2.1	0.078
ESR (mm/hour)	1.6 (0.9-2.1)	2 (1.2-2.9)	0.341	2.3 (1.0-6.4)	3.9 (1.1-11.5)	0.792
CRP (mg/L)	6.5 (3-15)	13 (5.5-28)	0.720	14(5.5-20)	12.5(8-23)	0.599

The values are presented as mean±SD or median (25th and 75th percentiles)

PASI, Psoriasis Area and Severity Index; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Table 4. Distribution of the inflammatory parameters by the comorbidities

Inflammatory markers	**Patients without comorbidities (n = 25)**	**PsA (n = 16)**	**DM (n = 10)**	**HT (n = 8)**	**Hypothyroidism (n = 4)**
Chitotriosidase (µmol/mL/hour)	20.1 ± 8.2	21 ± 11.5 (p = 0.571)	25.3 ± 12.4 (p = 0.156)	30.9 ± 15.6 (**p = 0.025**)*	26.6 ± 10.4 (p = 0.154)
WBC (×10^9 cells/L)	7.94 ± 1.89	6.8 ± 1.3 (**p = 0.043**)*	7.9 ± 2.8 (p = 0.770)	9.4 ± 2.1 (p = 0.086)	7.5 ± 2.4 (p = 0.574)
ESR (mm/hour)	8 (3-15)	11 (7-20.5) (p = 0.112)	11 (7-17) (p = 0.180)	18.5 (11-24.5) (p = 0.055)	22.5 (13.5-27.5) (p = 0.051)
CRP (mg/L)	1.7 (1.0-3.5)	2.0 (0.9-6.4) (p = 0.772)	3.0 (1.4-6.4) (p = 0.167)	6.2 (2.5-9.2) (**p = 0. 035**)*	3.6 (1.2-7.7) (p = 0.590)

The values are presented as mean±SD or median (25th and 75th percentiles)

WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PsA, psoriatic arthritis; DM, diabetes mellitus; HT, hypertension

* $p < 0.05$, compared to the patients without comorbidities.

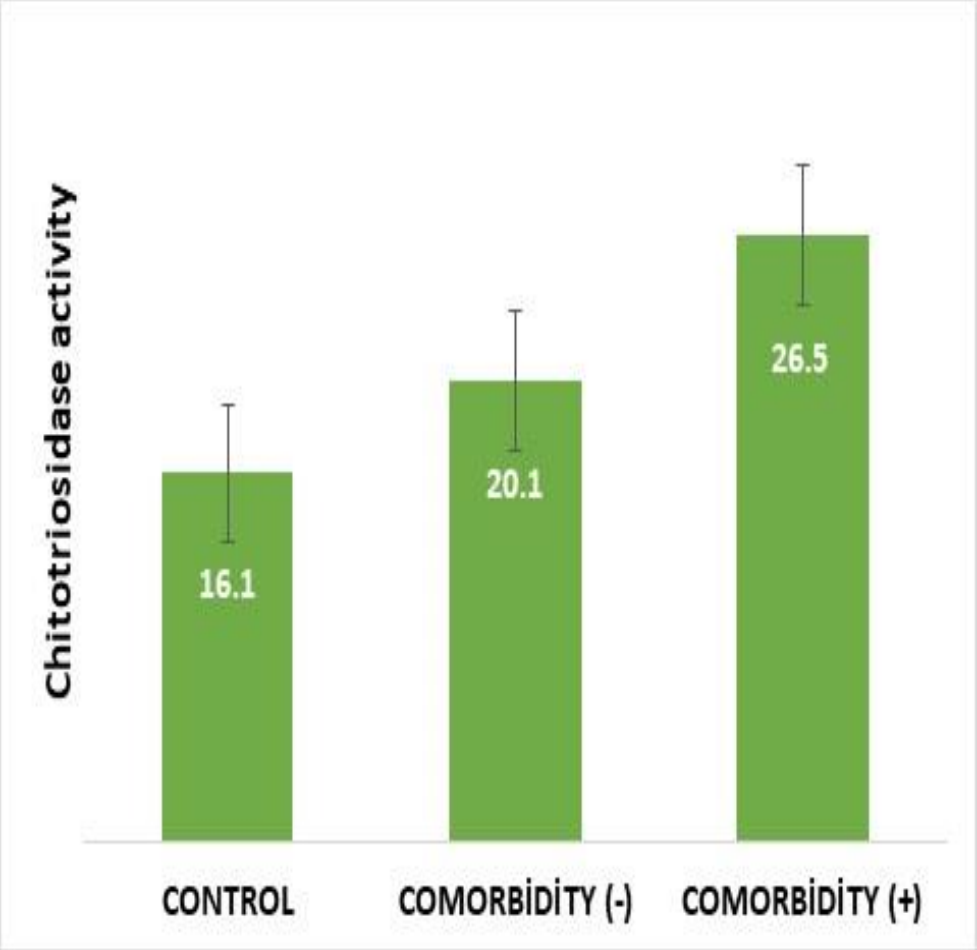

Figure 1. Mean values of the chitotriosidase activity in patients and controls

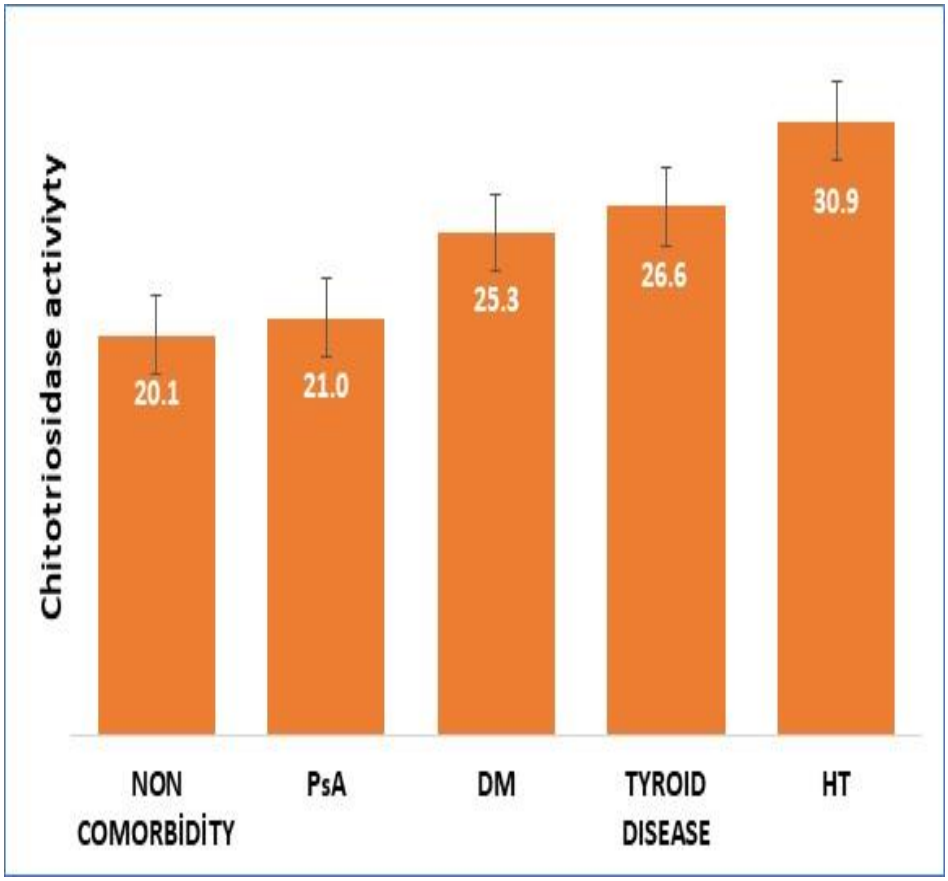

Figure 2. Mean values of the chitotriosidase activity for each comorbidity **(**PsA: Psoriatic arthritis, DM: Diabetes mellitus, HT: Hypertension)