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

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Abstract

Background: 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 systemic inflammatory status. In this study, we aimed to investigate whether serum ChT activity is increased in patients with psoriasis and related comorbidities. Materials and Methods: This study included patients with psoriasis and healthy volunteers. All subjects underwent a laboratory investigation including serum ChT levels, complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum lipid levels. Results: 25 patients without comorbidity, 28 patients with comorbidity, and 52 healthy subjects were enrolled. The patients group showed statistically significant higher levels of ChT activity (23.5 ± 11.4 µmol / ml / h) compared to the healthy controls (17.5 ± 10.4/ µmol / ml / h) (p=0.015). ChT activity was also statistically significant higher in patients with comorbidity compared to patients without comorbidity (p = 0.042). Conclusions: Our data support the pathogenetic role of inflammatory processes induced by macrophage activation in psoriasis and related comorbidities. We believe that high ChT activity in patients with psoriasis may serve as a clue for the early prediction of possible related comorbidities.

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Ethical approval and informed consent All the procedures followed the Helsinki declaration and the study was approved by the local clinical research ethics committee (Approval date and number: 2020-02/16). Written Informed consent was also obtained from all the subjects.

Statement of Contribution

Bilal İlanbey, Ömer Faruk Elmas, Eser Yıldırım Sözmen, Ümran Günay : Literature searching, designing and writing the manuscript

Bilal İlanbey, Ömer Faruk Elmas, Eser Yıldırım Sözmen, Ümran Günay: Substantial contributions to conception and design, interpretation of data

Ömer Faruk Elmas, Abdullah Demirbaş : Editing, revising and final approval of the manuscript

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Materials and Methods: This study included patients with psoriasis and healthy volunteers. All subjects underwent a laboratory investigation including serum ChT levels, complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum lipid levels.

Results: 25 patients without comorbidity, 28 patients with comorbidity, and 52 healthy subjects were enrolled. The patients group showed statistically significant higher levels of ChT activity (23.5 ± 11.4 μmol / ml / h) compared to the healthy controls (17.5 ± 10.4/ μmol / ml / h) (p=0.015). ChT activity was also statistically significant higher in patients with comorbidity compared to patients without comorbidity (p = 0.042).

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

Keywords : Chitotriosidase, comorbidity, macrophage, psoriasis.

What's already known about this topic?

Chitotriosidase is an enzyme, secreted by activated macrophages and neutrophils, in response to proinflammatory signals. Studies have shown high activities of ChT in a wide range of diseases such as atherosclerosis, bronchial asthma, non-alcoholic steatohepatitis, diabetes mellitus.

What does this article add?

In this study, we aimed to investigate whether ChT may serve as a marker in the prediction of comorbidities in psoriasis which is one of the common chronic inflammatory skin diseases.

Introduction

Psoriasis is a relatively common chronic inflammatory cutaneous disease characterized by epidermal hyperproliferation. It is considered an immune-mediated inflammatory disorder in which 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 considered a fundamental contributor. Smoking, obesity, and alcohol use are well-identified 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 in the diagnosis and monitoring of lysosomal storage diseases [5-7]. Studies have shown high activities of ChT in a wide range of diseases such as atherosclerosis, malaria, bronchial asthma, sarcoidosis, non-alcoholic steatohepatitis, diabetes mellitus, Alzheimer's disease, cancer, and thalassemia [8-12]. Besides, high ChT activity has been reported to be associated with a higher risk of cardiovascular events[13]. There is growing evidence indicating that ChT activity reflects inflammatory status. It has been reported that ChT plays a vital role in the immune response to the chitin-containing pathogens [14]. ChT is produced after at least seven 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 may serve as a marker in the prediction of comorbidities in psoriasis which is one of the common chronic inflammatory skin diseases.

Materials and methods

This prospective case-control study included 53 patients with clinically and histopathologically confirmed psoriasis (28 with associated comorbidity and 25 without comorbidity) and 52 healthy volunteers. All the procedures followed the Helsinki declaration and the study was approved by the local clinical research ethics committee (Approval date and number: 2020-02/16). Written Informed consent was also obtained from all the subjects.

Pregnant or breastfeeding females, patients under 18 years old, those who were on systemic treatment, patients with accompanying infections or malignancies were excluded. Patients who have received topical treatment or phototherapy within the last month or systemic treatment within the last three months were also ruled out.

All subjects underwent a physical examination and laboratory investigations including serum ChT levels, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum lipid levels. The Psoriasis Area and Severity Index (PASI) and disease duration were also recorded for all patients.

Blood samples from all subjects were taken in the morning after at least 8-10 hours of fasting. Blood taken into plain tubes was allowed to clot for 30 minutes and then centrifuged at 2000g for 10 minutes. Routine biochemical tests were immediately performed from some of the serum formed, and some were stored at -80 ° C for measuring ChT levels. Complete blood count was studied on Sysmex XN1000 (Sysmex Corp. ®, Kobe, Japan) device from blood samples taken into K2EDTA tubes. Routine biochemistry and hormone tests

were studied in Cobas c702 (Roche Diagnostics®, Japan) autoanalyzer systems using standard laboratory methods.

ChT activity was measured by the method proposed by Hollak et al.[5]. According to this method, the patient's serum was incubated with a substrate containing 4- methylumbelliferyl-chitotrioside under 37 °C for 2 h. Fluorescence was detected as excitation 360 nm and emission 445 nm (Modulus microplate fluorometer, Turner Biosystems, Inc., California, USA). Results were given as μmol/ml/h.

Statistical analysis

SPSS software version 21.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The conformity of the data to normal distribution was examined with the Kolmogorov-Smirnov and Shapiro-Wilk's tests. The logarithmic conversion was performed for non-normally distributed variables. Normally distributed variables were presented as mean and standard deviation; otherwise, the median and interquartile range were presented. The comparison of data between the two groups was done by either student t-test (normal distribution) or Mann-Whitney U (not normal distribution) test. The chi-square test was performed to compare categorical data. Correlations were assessed using either Pearson correlation test for normally distributed data or Spearman's P when data were not normally distributed. One-way ANOVA was used to compare 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. Values of $p<0.05$ were deemed statistically significant.

Results

This study included 25 patients without comorbidity (11 males, 14 females) and 28 (8 males, 20 females) patients with comorbidity, and 52 (15 males, 37 female) age-gender matched healthy subjects. The demographic characteristics of the subjects are summarized in Table 1.

16 patients had psoriatic arthritis (PsA), 10 had type II diabetes mellitus (DM), 8 had hypertension (HT), and 4 had hypothyroidism. There was no statistically significant difference between patients with comorbidity and without comorbidity in terms of disease duration and PASI values (Table 1)

Patients without comorbidity showed statistically significant higher CRP levels compared to the healthy controls ($p = 0.031$). There was no statistically significant difference in terms of ChT activity, WBC count, and ESR between the two groups (Table 2).

ChT activity, CRP and ESR levels were statistically significant higher ($p = 0.001$, $p = 0.016$, $p = 0.009$, respectively) in patients with comorbidity compared to the healthy subjects (Table 2).

All patients showed statistically significant higher ChT activity (23.5 ± 11.4 μmol / ml / h) than those of healthy controls (17.5 ± 10.4 μmol / ml / h) ($p=0.015$).

ChT activity was also statistically significant higher in patients with comorbidity compared to patients without comorbidity ($p = 0.042$) (Fig. 1). There was no statistically significant difference in terms of WBC count, CRP, and ESR between the two groups (Table 2).

Spearman's correlation analysis showed a positive correlation between WBC counts and PASI scores ($rho = 0.426$, $p = 0.026$) in patients with comorbidity. There was no correlation between inflammatory parameters and PASI scores in patients without comorbidity.

When the patients grouped as PASI>10 and PASI [?]10; ChT activity was significantly lower in patients without comorbidity with a PASI score of more than 10 ($p=0.022$). The other inflammation parameters showed no statistically significant difference (Table 3).

WBC count was statistically significant lower in patients with PsA ($p = 0.043$) compared to patients without comorbidity. No inflammatory parameter showed statistically significant differences between patients with DM and patients without comorbidity. ChT activity and CRP levels were statistically significant higher in hypertensive patients ($p = 0.025$, $p = 0.035$, respectively) when compared to patients without comorbidity

(Table 4, Fig. 2). No inflammatory parameter showed statistically significant differences in patients with hypothyroidism compared to patients without comorbidity (Table 4).

There was no statistically significant difference between the patients with and without comorbidity in terms of the lipid levels. Triglyceride, total cholesterol, and LDL levels were statistically significant higher ($p = 0.008$, $p = 0.001$ and $p = 0.004$, respectively) in patients with comorbidity compared to healthy subjects. There was no statistically significant difference in triglyceride, total cholesterol, and LDL levels in patients without comorbidity compared to healthy subjects. However, HDL levels were statistically significant lower in patients without comorbidity compared to healthy subjects ($p = 0.012$) (Table 1).

Discussion

Recent studies on the pathogenesis of psoriasis have shown that the disease occurs as a result 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 TNFα and IL-17[16]. Along with genetic predisposition, chronic inflammation is responsible for comorbidities, especially in severe form psoriasis [3, 17].

ChT, a member of the mammalian chitinase family (GH18), hydrolyzes chitin in lysosomes. There is growing evidence that ChT can be a marker of inflammation. Although studies have shown high activities of ChT in a wide range of diseases including cardiovascular disease diabetes mellitus, and cancer, there is no data on the role of ChT activity in patients with cutaneous disorders [5-12, 18]. To the best of our knowledge, this is the first study investigating the possible role of ChT activity in patients with psoriasis and related comorbidities. Our study showed a relationship between ChT activity and psoriasis, especially in patients with accompanying comorbidity. ChT activity, CRP and ESR levels were statistically significant higher in patients with comorbidity compared to controls. However, only ChT levels were statistically significant higher in patients with comorbidity compared to patients without comorbidity. This outcome suggests that ChT may be a better marker in predicting the development of comorbid conditions compared to other parameters of systemic inflammation such as ESR and CRP.

Psoriasis Area and Severity Index (PASI) is a scoring system used to measure the severity and extent of psoriasis. To calculate a PASI score, a representative area of psoriasis is chosen for each body area. 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 added up for each of the four body areas to give subtotals. To calculate PASI score each subtotal is multiplied by the body surface area represented by that region [19]. 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 remained in the minority. This limitation may 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 low in patients without comorbidity compared to the healthy control group. In patients with comorbidity, total cholesterol, triglyceride, and LDL-cholesterol levels were higher compared to the controls. There was no correlation between lipid parameters and ChT activity. No lipid parameters showed statistically significant differences between patients with and without comorbidity. This indicates that the atherogenic lipid profile can occur in psoriasis patients regardless of the presence of comorbidity.

In our study, 16 (30.1%) patients had PsA. The frequency 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 quality of life[22]. In our study, ChT activity and other inflammatory parameters showed no statistically significant differences in patients with psoriatic arthritis (Table 4).

Psoriasis is associated with an increased risk of diabetes and insulin resistance, independent of 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 found high ChT activity in diabetic patients [9, 24]. In our study, the ChT activity was also higher in diabetic psoriasis patients compared to healthy subjects, but there was no significant difference compared to patients without comorbidity. The low number of patients with diabetes may explain this situation (Table 4).

Another common comorbidity in psoriasis is hypertension. 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 quite high in patients with hypertension compared to other comorbidities (30.9 ± 15.6) (Table 4). The higher activity of ChT in hypertension suggests that macrophages may have a greater role in the pathogenesis of hypertension. Apparently, there is no study investigating 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, has 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 is no specific laboratory test for the prediction of psoriasis-related comorbidities. In our study, we found a high activity of ChT in patients with comorbidity compared to patients without comorbidity and healthy individuals. The high ChT activity was especially remarkable in patients with hypertension.

To conclude, our data support the pathogenetic role of inflammatory processes induced by macrophage activation in psoriasis and related comorbidities. We believe that high ChT activity in patients with psoriasis may serve as a clue for the early prediction of possible related comorbidities.

The main limitation of our study was relatively small number size of the patients having high PASI scores. However, ChT seems as a promising marker to predict comorbid complications of psoriasis. It is obvious that this clue needs to be evidenced with large sample series.

Data availability: The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

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Table Legends

Table 1. Demographic parameters, psoriasis area and severity index scores and lipid levels of the subjects.

Table 2. Inflammatory parameters of the subjects.

Table 3. Distribution of the inflammatory parameters by psoriasis area and severity index values.

Table 4. Distribution of the inflammatory parameters by the comorbidites.

Figure Legends

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

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

Table 1. Demographic parameters, psoriasis area and severity index scores and lipid levels of the subjects.

Parameters	**Controls (n=52)**	**Patients without comorbidity (n=25)**	**Patients with co**
Male/female (n)	15/37	11/14	8/20
Age (year)	42.8 ± 13.9	41.6± 15.5	52.3 ± 11.9*¥
Duration of psoriasis (year)	-	3 (1-18)	3 (1-8)
PASI	-	6.4 (5-10)	5 (4.1-10)
PASI [?]10 (n) / PASI>10 (n)		18/5	24/6
Triglyceride (mg/dL)	100 ± 50.2	136.3 ± 93.5	144.4 ± 71.1*
Total cholesterol (mg/dL)	160.7 ± 32.2	176.2 ± 40	198.2 ± 37.9*
HDL-cholesterol (mg/dL)	53.7 ± 12.8	45.7 ± 11.4*	49.4 ± 9.5
LDL-cholesterol (mg/dL)	89.5 ± 31	101 ± 36.7	124 ± 52.9*

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

¥ p<0.05 compared to the patients without comorbidity (post-hoc Tukey)

PASI: Psoriasis area and severity index, HDL: High density lipoprotein, LDL: Low density lipoprotein.

Table 2. Inflammatory parameters of the subjects.

Inflammatory markers	**Controls (N=52)**	**Patients without comorbidity (n=25)**	**Patients with co**
ἠιτοτριοσιδασε (μμολ/μλ/η)	17.5 ± 10.4	20.1 ± 8.2	26.5 ± 13.1*¥
WBC (x10^{9}cells/L)	7.6 ± 1.7	7.94 ± 1.89	7.49 ± 2.13
ESR (mm/h)	6 (5-13)	8 (3-17)	14 (6-19) *
CRP (mg/L)	1.0 (0.4-1.9)	1.6 (0.9-3.2) *	3.0 (0.9-6.9) *

*Compared to the controls p<0.05 (post-hoc Tukey)

¥ Compared to the patients without comorbidity p<0.05 (post-hoc Tukey)

WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. Distribution of the inflammatory parameters by psoriasis area and severity index values.

Parameters	**Patients without comorbidity (n=25)**	**Patients without comorbidity (n=2**
PASI	[?]10 (n=19)	>10 (n=6)
ἠιτοτριοσιδασε (μμολ/μλ/η)	19.26 ± 7.2	16.5 ± 2.78
WBC (x10^{9}cells/L)	7.5 ± 1.6	8.4 ± 1.7
ESR (mm/h)	1.6 (0.9-2.1)	2 (1.2-2.9)
CRP (mg/L)	6.5 (3-15)	13 (5.5-28)

PASI: Psoriasis area and severity index, WBC: White blood cells, ESR: Erythrocyte sedimantation rate, CRP: C-reactive protein

Table 4. Distribution of the inflammatory parameters by the comorbidites.

Inflammatory markers	Patients without comorbidity (n=25)	PsA (n=16)	DM (n=10)
ἢιτοτριοσιδασε (μμολ/μλ/η)	20.1 ± 8.2	21 ± 11.5 (p=0.571)	25.3 ± 12.4 (p=
WBC (x10^{9}cells/L)	7.94 ± 1.89	6.8 ± 1.3 (**p=0.043**)	7.9 ± 2.8 (p=0
ESR (mm/h)	8 (3-15)	11 (7-20.5) (p=0.112)	11 (7-17) (p=0.
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=

WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PsA: Psoriatic arthritis, DM: Diabetes mellitus, HT: Hypertension.