Original paper

An evaluation of thiol/disulphide homeostasis in patients with psoriasis

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Abstract

Introduction: The role of oxidative stress in the pathogenesis of psoriasis has been investigated in previous studies with conflicting results. On the other hand, well-established treatments currently used in psoriasis exert their effects via a boost of oxidative stress. Recently, a strong positive association between psoriasis, metabolic syndrome and dyslipidemia has also been described showing the complex nature of the disease.
Aim: To examine thiol/disulphide homeostasis, a newly developed homeostasis assay in psoriasis and evaluate the possible association between thiol/disulphide homeostasis and dyslipidemia in psoriasis.
Material and methods: The study population included 92 psoriasis patients and 71 healthy subjects. Serum native thiol, total thiol and disulphide levels were investigated in patients with psoriasis and in healthy subjects. In addition, lipid profile (serum total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) levels were investigated in both groups. The association between thiol-disulphide parameters and dyslipidemia was also evaluated.
Results: Serum total cholesterol and triglyceride levels were found to be higher in patients with psoriasis than in the healthy group. Lower plasma disulphide and higher native thiol levels were found in patients with psoriasis indicating an antioxidant status.
Conclusions: To our knowledge, this is the first study showing the shift of dynamic thiol/disulphide homeostasis towards the thiol form in psoriasis which indicate higher antioxidant status.

Key words: psoriasis, thiol/disulphide homeostasis, dyslipidemia.

Introduction

Psoriasis is a common chronic, immune-mediated, hyperproliferative skin disease [1]. A complex interaction of a number of biochemical and immunological mechanisms has been implicated in the pathogenesis of psoriasis [1–4]. Psoriasis has also been associated with dyslipidemia and metabolic syndrome suggesting the inflammatory process in psoriasis [5–8]. In addition, several studies have been conducted on the role of oxidative stress in the pathogenesis of psoriasis, although some of them yielded conflicting results [9–15]. There are data detecting either oxidant status or antioxidant status in the serum and/or lesional skin of psoriasis patients in various reports [3, 9–14].

Aim

In this study, we aimed to investigate thiol/disulphide homeostasis in psoriasis, by a newly developed reliable assay, and also the association between thiol-disulphide homeostasis and dyslipidemia.

Material and methods

The study population included a total of 92 cases with psoriasis who had not received any topical and/or systemic treatment for the preceding 3 months, and 71 healthy age- and sex-matched volunteers.

The patients with a known history of diabetes mellitus, cardiovascular, cerebrovascular diseases and/or who had

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a smoking habit, alcohol consumption, who were taking medications including antilipidemics, vitamins or analgesic drugs were excluded from both patient and control groups. The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local Ethical Committee of Ankara Numune Education and Research Hospital.

Systemic and dermatological examinations were performed in each patient and psoriasis area, and the severity index (PASI) was calculated.

Serum total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol levels (LDL-C), native thiol, and total thiol levels were measured and disulphide levels, disulphide/total thiol ratio and native thiol/total thiol ratio were calculated in both groups.

A correlation analysis was performed to assess not only the relation between serum lipid and thiol/disulphide levels but also the association between psoriasis severity and serum thiol/disulphide levels.

Collection and analysis of blood samples

Venous blood samples were obtained from all participants in the morning between 8:00 and 10:00 A.M. after 12 h of fasting. To separate serum from cells, collected blood samples were centrifuged at 1500 rpm for 10 min. Serum total cholesterol, triglyceride, HDL-C and LDL-C levels were determined using an automated clinical chemistry analyzer (Beckman Coulter Inc., Brea, CA, USA) with original Beckman Coulter reagents. Remaining serum samples were stored at –80°C until all samples were collected.

Native thiol and total thiol were measured by using a new and fully automatic system, disulphide and ratios of disulphide/native thiol, disulphide/total thiol and native thiol/total thiol were calculated (Erel Neselioglu) [16].

Statistical analysis

Statistical analyses were performed using the PASW Statistics 18 software. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Comparisons of variables with a normal distribution were made using the student *t*-test, and values were provided as mean ± standard deviation (SD). For parameters with an abnormal distribution, the Mann-Whitney *U* test was used for comparisons, and values were given as median (minimum-maximum). A *p*-value of less than 0.05 was considered indicative of statistical significance.

Results

Ninety-two patients (48 males and 44 females) with psoriasis and 71 healthy controls (30 males and 41 females) were included in the study. The mean age was 42.23 ±13.34 years in the patient group and 38.66 ±12.21 years in the control group ($p = 0.081$).

The duration of psoriasis was between 3 months and 45 years. The median duration was 114 months. Psoriasis area and severity index (PASI) scores ranged between 2 and 39 (9.81 ±7.25).

Serum total cholesterol and triglyceride levels were significantly higher in the psoriasis group compared to the control group ($p = 0.037$ and $p = 0.007$, respectively; $p < 0.05$). Although, serum LDL-C levels were found to be higher and serum HDL-C levels were found to be lower in the psoriasis group, there was no significant difference between two groups ($p = 0.448$, $p = 0.294$, respectively) (Table 1).

When oxidative stress parameters were investigated; patients with psoriasis had lower levels of serum disulphide (18.38 ±4.86 µmol/l; $p < 0.001$), whereas higher native thiol and total thiol levels (481 ±47 µmol/l vs. 513 ±69 µmol/l) were detected. Disulphide levels were significantly lower in the patient group than the control group ($p < 0.001$), while no statistical difference was detected between patient and control groups in terms of native thiol and total thiol levels. In patients with psoriasis, the disulphide/total thiol ratio (%) (3.6 ±1.0 vs. 4.5 ±1.6; $p = 0.001$) was lower than the control group (Table 2).

There was no correlation either between duration of psoriasis and serum native thiol-disulphide, or between PASI scores and serum native thiol/disulphide or between serum lipid and native thiol-disulphide levels.

Discussion

Psoriasis is a chronic inflammatory dermatosis characterized by proliferation and abnormal differentiation of keratinocytes associated with infiltration of T cells in the epidermis and dermis [1, 2].

Nowadays, psoriasis is accepted as a complex disease not only affecting the skin but also having a systemic involvement with multiple comorbidities such as metabolic syndrome and its components; obesity, dyslipidemia, hypertension and insulin resistance and further associated diseases such as cardiovascular diseases and stroke [5–8]. Both psoriasis and the metabolic syndrome constitute

Table 1. Evaluation of serum lipid levels in psoriasis and patient groups

Parameter	Patient group Mean ± SD ($n = 92$)	Control group Mean ± SD ($n = 71$)	*P*-value
Total cholesterol	207 ±48	192 ±44	0.037
Triglycerides	153 ±79	123 ±61	0.007
HDL-C	46.14 ±10.82	47.28 ±8.31	0.448
LDL-C	130 ±39	124 ±34	0.294

HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol. Normal values: total cholesterol (N < 200 mg/dl), triglyceride (N < 200 mg/dl), HDL-C (N: 45–65 mg/dl), LDL-C (N < 100 mg/dl).

Table 2. Serum thiol and disulphide levels in psoriasis and patient groups

Variable	Patient group	Control group	*P*-value
Native thiol	481 ±47	469 ±49	0.101
Total thiol	513 ±69	513 ±54	0.984
Disulphide	18.38 ±4.86	22.32 ±5.30	< 0.001
SS/SH	3.82 ±0.98	4.79 ±1.05	0.497
SS/total SH	3.53 ±0.84	4.35 ±0.85	< 0.001
SH/total SH	93 ±1.68	91 ±1.79	< 0.001

SS – disulphide (µmol/l), SH – native thiol (µmol/l), total SH – total thiol (µmol/l), SS/SH – ratio of disulphide/native thiol (%), SS/total SH – ratio of disulphide/total thiol (%), SH/total SH – ratio of native thiol/total thiol (%).

a proinflammatory state and psoriasis shares many pathogenic features with the development of atherosclerotic plaques [5, 8, 17].

Oxidative stress has been one of the questioned factors in the pathogenesis of psoriasis in several studies, but its exact role is still unclear [10–14, 18–21]. Since it is still controversial whether the alterations in oxidative stress parameters in psoriasis are the primary or secondary event or if it is possibly affected by the duration or severity of the disease. While some of the reported studies indicate a correlation between oxidative stress parameters and disease severity [10, 11, 18, 20], a few data advocated otherwise or reported no correlation [13, 18, 19, 21].

On the other hand, there is clear evidence that currently used effective treatments in psoriasis such as phototherapy, fumaric acid esters and methotrexate induce oxidative responses [22–27].

Recently, Erel and Neselioglu [16] developed a novel and automated assay determining thiol/disulphide homeostasis status, which has a critical role in antioxidant protection, detoxification, signal transduction, management of enzyme activity, and apoptosis in the human body [28, 29].

There is a growing body of evidence pointing that an abnormal thiol/disulphide homeostasis is involved in the pathogenesis of a variety of disorders including diabetes, cardiovascular disease and malignancies [16, 30–34].

Erel and Neselioglu suggested that in degenerative diseases such as diabetes, obesity and pneumonia, disulphide levels have a tendency to increase while native thiol and total thiol levels decrease [16]. They reported higher levels of native thiol and total thiol and lower levels of disulphide levels in proliferative diseases [16].

Previous studies researched thiol/disulphide homeostasis in diabetes and metabolic diseases [16, 30–32]. Until now, there has been no study researching thiol/disulphide homeostasis in psoriasis. In this study, we aimed to investigate this newly developed method in psoriasis.

Our study results revealed higher levels of native thiol, total thiol and lower levels of disulphide levels indicating a shift to high thiol levels that are expected to be seen in proliferative diseases confirming the results of Erel and Neselioglu [16]. In addition, dyslipidemia was found in the patient group confirming the association between psoriasis and dyslipidemia.

Our results were in accordance with some of the studies in which higher antioxidative status was found in psoriatic patients [12, 14, 35, 36]. As reported previously in the literature, Therond *et al.* found elevated antioxidant enzyme activities in fibroblasts and erythrocytes of psoriatic patients [14] and Severin *et al.* detected several single antioxidative components to be elevated while total antioxidative activity to be at normal levels in sera of psoriatic patients [12]. In another study, thiol/protein ratios of extracts from stripped corneocytes were analyzed, and no significant differences were observed between healthy controls, psoriatic uninvolved skin, and psoriatic lesions [35]. In a study by Magnus, increased thiol levels of psoriatic scales were observed and this high content of thiol has been interpreted as the result of failure of oxidation due to the increased rate of keratinization [36].

In spite of the data that suggest increased oxidative stress in the course of psoriasis [10, 11, 13, 34], there is another fact that several well established treatments currently used for the therapy of psoriasis rely on a boost of the oxidative stress [22–27]. Phototherapy (Psoralen-UVA (PUVA) combined therapy and/or UVB), a commonly used treatment in psoriasis, leads to massive generation of singlet oxygen in the skin [22–24]. Psoralens, another widely used treatment in psoriasis, also produces lesional singlet oxygen and superoxide radicals [27]. Again, fumaric acid esters (FAE), used for the systemic therapy of psoriasis with high clinical efficacy, were found to cause elevation of superoxide anion production [25, 26].

Considering various results of the studies investigating the role of oxidative stress in psoriasis and the effects of widely used treatments such as phototherapy, fumaric acid esters, topical anthralin in psoriasis through the activation of oxidant status; we believe that oxidant/antioxidant status in psoriasis is a dynamic balance which may give a clue to explain the change in thiol/disulphide homeostasis towards thiol imbalance in our study.

Our study is of importance to research on the thiol/disulphide homeostasis in psoriasis. To the best of our knowledge, this is the first study that investigates thiol/disulphide homeostasis in psoriasis and the association between thiol/disulphide homeostasis and dyslipidemia.

On the other hand, our study has a few limitations such as a relatively small sample size of patients who were admitted to a single center, the variations in the duration of the psoriasis among the participants and the absence of long-term follow-up of the patients as various factors may affect thiol/disulphide homeostasis.

As a result of our study, we believe that thiol/disulphide homeostasis may be a useful tool in following a patient with psoriasis to predict which patients are at greatest

risk of metabolic syndrome or cardiovascular events or in choosing the effective treatment for the patients. Further studies with larger samples need to be carried out in order to clarify the exact role of thiol/disulphide homeostasis in the pathogenesis of psoriasis by focusing on cellular biology of oxidation, anti-oxidant defense mechanisms against oxidative stress, and the genetic details of this complex phenomenon. The future perspective of this subject will lead to new developments in choosing the treatment, and follow-up of psoriasis.

Conflict of interest

The authors declare no conflict of interest.

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