

Research of Thiol-Disulphide Balance in Patients with Pityriasis Rosea

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Abstract

Background: Pityriasis Rosea (PR) is a self-limiting papulosquamous dermatosis, of which etiopathogenesis has not been completely enlightened yet. Discovering the role of oxidative stress on many diseases, draws the attention towards that direction lately. Therefore, the factors of oxidative stress are studied in various skin diseases' etiopathogenesis. While, thiols are sulfur group bearing antioxidant compounds, the thiol-disulphide balance has a great importance in oxidative stress formation and its prevention. This balance is disturbed in various diseases, in degenerative diseases it increases on the other hand in proliferative diseases it decreases. However the effects on skin diseases including PR are not known yet

Objectives: The main objective of this study is to search the thiol-disulphide balance in patients with PR.

Methods: Within the context of this study 52 PR patients and 47 healthy control groups have been examined. Native thiol, disulfide and total thiol levels are evaluated by the help of the new and automated spectrophotometric methods. Disulphide/total thiol, disulphide/native thiol and native thiol/total thiol ratios are calculated.

Results: According to the results there aren't any statistical differences between PR group and control group in regard to native thiol, disulphide, total thiol levels. To conclude, it is realized that in PR thiol-disulphide balance is protected and it is not affected.

Keywords: Pityriasis rosea, Oxidative stress, Thiol-disulphide balance, Skin diseases

INTRODUCTION

Pityriasis rosea (PR) which is more commonly observed between the ages of 10 and 35, is an acute onset skin disease. It was firstly identified in 1860 by Gilbert. In some studies it was stated that both genders are affected at the same level, whereas in some studies it is determined that PR is mostly observed in women. Following the formation of precursor plaque, PR emerges with oval, erythematous, squamous lesions which are parallel to the skin lines on the trunk and extremities. They are asymptomatic and heal spontaneously [1-4]. Lesions generally last within 6-8 weeks, but sometimes can extend up to 4-5 months [4,5]. It rarely repeats itself [6].

PR has been classified according to clinical features and course of the disease. Classification is helpful in identifying the atypical forms of PR, including the persistent and the relapsing form [7].

Although its etiology is not completely known, factors such as infectious agents, atopic background, autoimmunity, drugs have been proposed but not fully enlightened [3,4,8].

Condition in which the balance between body's antioxidant defense system and free radicals shifts in favor of the oxidants is called oxidative stress (OS) [9-11]. Besides the balance between oxidants and antioxidants, reactive oxygen species (ROS) and reactive nitrogen species (RNS) that are harmful to the organism and come out by metabolic activities are controlled continuously by the defense systems having an antioxidant role [10,11-16,18]. Especially proteins are very sensitive to oxidation. The oxidant substances cause decarboxylation in proteins, hydrolysis of

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peptide bonds, formation of disulphide cruciate ligaments [19,20].

Sulphydryl group bearing thiols are the most and the fastest affected proteins. The plasma thiols are strong antioxidants which annihilate physiologically the free radicals [21]. The serum values of protein thiols are indicators of antioxidant status in the body [22].

The plasma thiols are composed mostly of albumin and a lesser amount of cysteine and glutathione [21]. In order to protect cellular redox homeostasis, thiols and disulphides are in balance. The cysteine groups of thiols present in the medium are oxidized with ROS and reversible disulphide bounds are formed between thiols with low molecular weight and protein thiols. By this way, free radicals are eliminated and OS is avoided. These can be reduced again to thiol groups depends on condition. This is defined as dynamic thiol disulphide homeostasis [21,23-27]. It has been suggested that ROSs may also play a role in the pathogenesis of various inflammatory allergic skin diseases and conflicting information has been reported [28-33]. As far as is known, OS and thiol-disulphide homeostasis have never been investigated in PR patients.

In this research, with the help of a new and automated method developed by Erel and Neşelioğlu, by comparing with healthy control group it was aimed to evaluate thiol / disulphide homeostasis in PR patients [23].

MATERIAL & METHODS

This single-centered prospective case-control study was conducted between January and August 2015. 52 patients who don't smoke, don't have any additional diseases, who received clinically and/or histopathologically the PR diagnose and 47 healthy control groups are examined in this study. The control groups are selected from the patients who are coming to the hospital for general control purposes, healthy, nonsmoker and also having no other disease. From the patients who were diagnosed with PR, the ones who were pregnant, under 18 years old, having food or medication allergies, having infectious diseases, having systemic or neoplastic diseases such as heart, liver, renal disorders, having diabetes, smoking patients, or patients who use medications for any reasons were not involved.

Permission was obtained from the ethics committee before the study and then the study was conducted in accordance with good clinical practices and the Helsinki declaration. Before being included in the study, written informed consents were taken from all the participants. The age, gender, disease duration, stress history, inflammatory disease history and recurrence history of the participants were investigated.

Venous blood samples were kept under -80 degrees in the deep freeze. Blood samples were centrifuged at 1500 revolutions per minute for 10 minutes and thiol/disulphide homeostasis tests were measured by newly developed automatic spectrophotometric method [23]. By reducing the disulphided bonds with sodium borohydride, free functional thiol groups were released. Reduction of unused reduced sodium borohydride 5,5'-dithiobis-2(2nitrobenzoic) (DNTB) was inhibited by formaldehyde. Total thiol groups, formed by reduced and native thiol groups, were identified after reaction with DTNB. Dynamic disulphide amount was found by dividing the difference of the total thiol and native thiol by two. Disulphide/native thiol (Index 1), Disulphide/total thiol (Index 2), and native thiol/total thiol (Index 3) rates were calculated.

The suitability to the normal distribution of the continuous variables such as age, total protein, and total thiol in the study was examined by Shapiro Wilk test. The variables which are suitable to normal distribution were expressed by average $\pm$ standard deviation ($\text{avr} \pm s$), variables which do not show normal distribution were expressed by median (IQR: interquartile range) and categorical variables such as gender were expressed by numbers (%).

Depending on the distribution of the variables and whether the groups are balanced, t test or Mann Whitney U test was used for independent groups. When relations between variables and thiol values were examined, Pearson r coefficient and spearman rho coefficient were calculated depending on the distribution of variables. Statistical significance level was accepted as $p < 0.05$.

For statistical analysis and calculations IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) Program was used.

RESULTS

The average age of 52 PR patients and 47 healthy controls participating the study, were calculated as 34.08 ± 10.28 years and 36.66 ± 11.29 years respectively and the age of the two groups was identified to be similar ($t = -1.192$, $p = 0.236$, **Table 1**). In the study, 53.8% ($n = 28$) of the patient group and 59.6% ($n = 28$) of the control group were female. There was no statistically significant difference found in terms of gender distribution in the patient and control groups. ($\chi^2 = 0.138$, $p = 0.711$).

The complaint of the 77.7% of the patients ($n = 30$) was present for 15 days. It was determined that in 8 patients (15.4%) inflammatory disease history and in 35 patients (67.3%) stress history was present (**Table 2**).

Table 1. Demographic characteristics of patients

	Patient Group (n=52)	Control Grubu (n=47)	Test Statistics	p
Age[avr±s]	34.08±10.28	36.66±11.29	t=-1.192	0.236
Gender[n (%)]				
Male	24 (46.2)	19 (40.4)	$\chi^2=0.138$	0.711*
Female	28 (53.8)	28 (59.6)		
*Yates Correction test results				

Table 2. Features related to the disease

Illness Duration	n (%)
0-15 days	30 (77.7)
16-30 days	17 (32.7)
31-45 days	1 (1.9)
+45 days	4 (7.7)
Inflammatory disease	8 (15.4)
Stress	35 (67.3)

The median total protein value was obtained as 7.31 (IQR=0.54) for the patients and 7.47 (IQR=0.78) for the control groups (**Table 3**). The total protein values of the patients were determined to be meaningfully lower than control groups ($Z=2.077$, $p=0.038$).

Index 1, 2 and 3 were calculated respectively as disulphide/native thiol, disulphide/total thiol and native/total thiol.

In respect to albumin, native thiol, disulphide, total thiol, index 1, index 2 and index 3, it was determined that patient and control groups were similar ($p>0.05$).

Table 3. Total protein, albumin, thiol, disulphide and index values for the patient and control groups

	Patient Group Avr±S Median (IQR)	Control Group Avr±S Median (IQR)	Test Statistics	p
Total Protein(gr/L)	7.31 (0.54)	7.47 (0.78)	$Z=2.077$	0.038
Albumin(gr/L)	4.77 (0.43)	4.72 (0.43)	$Z=0.022$	0.983
Native Thiol(μmol/L)	456.63 (46.35)	451.68 (45.50)	$Z=0.521$	0.603
Disulphid(μmol/L)	18.50±5.75	19.41±7.23	$t=-0.684$	0.496
Total Thiol(μmol/L)	490.48±50.08	490.46±45.68	$t=0.002$	0.998
Index 1	0.04 (0.02)	0.04 (0.03)	$Z=0.551$	0.582
Index 2	0.04 (0.02)	0.04 (0.02)	$Z=0.330$	0.741
Index 3	0.93 (0.03)	0.91 (0.04)	$Z=1.210$	0.226

The results of the comparison in terms of thiol values of 24 male patients and 28 female patients are given at **Table 4**. The median native thiol values were calculated as 457.40 (IQR=50.38) for females and 483.15 (IQR=66.93) for males. It was observed that the male native thiol values are higher than that of females ($Z=2.294$, $p=0.022$). Similarly, it was determined that the total thiol values were meaningfully higher in males when compared with females. It was determined that there was no statistically significant

difference in disulphide, index 1, index 2 and index 3 in respect to gender ($p>0.05$).

The native thiol median of 35 patients with stress history and 17 patients without stress history were respectively identified as 472.90 (IQR=60.10) and 439.00 (IQR=65.55) (**Table 5**). It was identified that native thiol values in patients having stress history was higher when compared with patients who did not have stress history ($Z=2.146$,

p=0.032). In respect to other thiol values, in patient groups statistically meaningful difference was not detected (p.0.05).

Table 4. Distribution of thiol values respect to gender in the patient group

	Female (n=28)	Male (n=24)	Test	p
	Avr±S	Avr±S	Statistics	
	Median (IQR)	Median (IQR)		
Native Thiol(μmol/L)	457.40 (50.38)	483.90 (66.93)	Z=2.94	0.022
Disulphide(μmol/L)	17.34±3.50	19.84±7.45	t=-1.504	0.142
Total Thiol(μmol/L)	485.80 (67.48)	521.55 (71.60)	Z=2625	0.009
Index 1	0.04 (0.01)	0.05 (0.02)	Z=0.725	0.468
Index 2	0.04 (0.01)	0.04 (0.02)	Z=0.670	0.503
Index 3	0.93 (0.02)	0.92 (0.04)	Z=0.532	0.595

When thiol values were considered according to the presence of inflammatory disease history in patients, there was no difference in terms of thiol disulphide parameters between those with inflammatory disease history and those without inflammatory disease history (p.0.05).

When the relation between age and thiol values were evaluated; a negative relation between age and native and

total thiol was observed (respectively Spearman rho=-0.429, rho=-0.392, p<0.001).

Between the disease duration and only index 2, a negative, moderate degree, meaningful relation was determined (Poliserialrho=-0.436, p<0.05).

The positive and moderate degree relation was observed in between total protein and total thiol, albumin and native thiol and also albumin and total thiol.

Table 5. Relations between age, disease duration, total protein, albumin and thiol values

	Age	Disease Duration	Total Protein	Albumin
Native Thiol(μmol/L)	-0.429 ^{3,*}	-0.260	0.332 ^{3,*}	0.650 ^{3,*}
Disulphide(μmol/L)	-0.046 [*]	0.240	0.264 ^{2,*}	0.267 ^{2,*}
Total Thiol(μmol/L)	-0.392 ^{3,*}	0.053	0.415 ^{3,*}	0.633 ^{3,*}
Index 1	0.093 [*]	0.097	-0.099 [*]	0.026 [*]
Index 2	0.008 [*]	-0.436 ¹	-0.105 [*]	0.041 [*]
Index 3	-0.078 [*]	0.170	-0.177 [*]	-0.107 [*]
¹ p<0.05; ² p<0.01; ³ p<0.001				
*Spearmanrho coefficient, others Poliserialrho coefficient.				

DISCUSSION

Thiols are antioxidants which protect redox homeostasis and it is essential for cell life. Formations of reversal disulphide bonds by oxidation of thiols from these proteins and protection of the structure of proteins by these bonds are important. [16,17,32]. The deterioration of the structure and function of enzymes bound to thiols, causes to change the thiol/disulphide ratio in the cell. This ratio indicates that the plasma thiol concentration decreases and free radical production increase [23].

Mechanism of oxidative stress in PR has not been fully enlightened and the study on this subject is not yet available. For this reason, the effect of OS on the etiopathogenesis of PR was investigated in this study.

Pre-illness fever, lack of appetite, prodromal symptoms, frequent occurrence in crowded environments, frequent repetition in certain seasons such as spring and winter, usually being non repetitive, the type of skin eruptions supports that PR could be infectious [1,4]. Like Drago et al. have found high levels of HHV6,7 in peripheric blood and tissues, Watanabe et al. have found high levels of HHV 6,7 in skin, saliva and blood by PCR method and they have argued that PR is associated with these active viruses [34,35]. It has been suggested that PR is not a primary infection and formed as the result of cutaneous infiltration of infected lymphocytes during systemic viral replication [8]. In other words, it is believed that there may be delayed hypersensitivity to an infectious agent [36]. As the infectious agent, although bacteria, influenza, cytomegalo virus (CMV), Epstein bar virus (EBV) and herpes viruses were accused, the recent studies have concentrated on human herpes virus (HHV) 6 and 7. [8,35,37]. Chuh et al. could not find evidence of HHV 6-7 infection in the peripheral blood of PR patients by PCR in situ hybridization method [38]. Infectious agents and immune system's cells making phagocytosis such as neutrophil, eosinophil, monocyte and macrophage, consume oxygen very rapidly and cause oxidative stress [15]. Radicals are the primary toxic substance produced in viral diseases. Beside, radicals may explain both the mechanism of organs and tissues damage where viruses replicate and the interaction between viral infections and immune system. Since the virus replicates in living cells, such metabolites serve as a host defense mechanism, as well as affect the multiplication of the virus [15,39]. Oxidative stress in humans has been proven to be present in immunodeficiency infection and viral diseases such as herpes 1 infections, measles, influenza, hepatitis [40-42].

There are multi studies related to dynamic thiol/disulphide homeostasis associated with skin diseases [43-46]. While in this study the thiol disulphide balance in PR patients is investigated. When native thiol, total thiol and disulphide values and disulphide/ total thiol, disulphide/ native thiol and native thiol / total thiol ratios of patients were compared

with the control group, it was determined that the native thiol, total thiol and disulphide values of PR did not change statistically. Although the thiol-disulphide balance statistically was not disturbed, the native thiol was increased in the patients while it was found to be decreased in the control group. In addition to that, disulphide values were decreased in patients and increased in controls. Moreover, the thiol disulphide balance shifted to the side of the thiol. Similar results can be seen in non-oxidative stress conditions. But the important thing is the change in the ratios representing the whole balance. And this may be related to the immune response of the thiol in inflammation [9,47]. At this point it can be said that thiols get affected from OS however it increases in order to protect the balance.

In this study, males' native thiol and total thiol values were observed significantly higher when compared with women's values. This suggests that males get affected from OS faster than women.

In patients with PR, the prodromal period can be observed. In the study, there was an inflammatory disease in 15% (n=8) of patients' medical history. However, thiol parameters are shown similarities with controls. This may indicate that during prodromal period, which means at the beginning, thiols are not affected.

In PR, it is assumed that cellular immunity plays an important role in the pathogenesis. In patients with PR, in lesions' immune histopathological examinations, similarly to skin diseases such as psoriasis, atopic dermatitis, T cell dominance is observed [48,36]. At stratum corneum, Langerhans cells and active CD4T cells presence is observed. From these cells, especially interleukin 17 like cytokines, chemokines, antimicrobial peptides are released [36]. This shows the active immunologic response. Briefly, in PR with viral triggering inflammation, immunological activation, ROS increase and eventually OS might be seen [5,9,29,47]. In this study, patients' immune response stepped in, so this might have not changed the thiol-disulphide balance. This may indicate that the reduced protein level is used to reduce OS.

In our study, despite the presence of undisturbed thiol-disulphide balance in PR patients, the total protein values of the patients were significantly lower than the controls. However, the albumin and thiol disulphide parameters were found to be similar to the control group.

In this study, the 77% of the patients applied during the first 15 days of the disease and a negative relation was found only between disease period and disulphide/total thiol. Since native thiols play a role in the immune response as the disease duration is prolonged, the conversion of native thiol/disulphide may be reduced. The balance is disturbed as the period of PR prolonged. It may be that the presence of oxidative stress has not been adequately demonstrated since most of the patients apply early stage of PR. Whether or not

OS is effective in the continuation of PR is not fully explained, as the number of patients with long-term disease is not sufficient. Since only one blood sample is taken from the patients during this study, the issue of how the OS process after the disappearance of the lesions cannot be explained.

Another finding identified is that, native and total thiols decreased with age in PR [45]. This situation supports the OS relationship with aging [49,50]. By suppressing the immunity system excessive psychological stress can facilitate the development of PR [1].

Another result achieved in this study is that psychological stress story was present in 67% (n=35) of the PR patient group. Psychological stress can affect PR itself and also PR's acute skin lesions can cause the patient to have stress, so this might also cause the increase of OS [1]. The presence of high levels of native thiols in patients who had stress history supports this hypothesis. It has been asserted that PR appears mostly in cases where the immunity system is weakened. Whether the stress suppresses the immune system or the immune system triggers the stress is not fully understood.

The autoimmune hypothesis has also been suggested in the etiopathogenesis of PR. The presence of autoimmune markers can be explained by genetics. People with the same HLA halo types develop genetic predisposition by triggering a viral infection. Recently, hypothesis has been suggested that PR is an autoimmune disease that develops in genetically predisposed individuals [37]. In many diseases, OS is not the direct reason. It develops as secondary to the disease and may play a role in its pathogenesis.

Antioxidant treatment may also be beneficial in PR, which is mostly of viral origin. However in this study OS was affected but it did not distorted.

CONCLUSION

The reason of PR diseases is not known yet. According to the data obtained this OS and its etiopathogenesis related study, it can be said that in PR the thiol/disulphide homeostasis is affected but the total balance is not disturbed. Further researches are needed to support these findings.

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