

The evaluation of oxidative stress in patients with psoriasis vulgaris and atopic dermatitis by measuring the urinary level of 8-hydroxy-2'-deoxyguanosine

Junko Shimamoto MD | Teruo Kurokawa MD, PhD | Hideaki Tanizaki MD, PhD |
Shinichi Moriwaki MD 

Department of Dermatology, Osaka Medical College, Takatsuki, Japan

Correspondence

Shinichi Moriwaki, Department of Dermatology, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan.
Email: der002@osaka-med.ac.jp

Abstract

Objectives: Recent studies have revealed the relationship of oxidative stress to various medical disorders, such as cancer and ischemic heart disease. Atopic dermatitis (AD) and psoriasis vulgaris (PV) are chronic inflammatory dermatoses, and oxidative stress is presumed to be involved in the development of these diseases as well as their becoming refractory.

Methods: In this study, we collected urine samples from 40 AD patients, 25 PV patients, and 39 healthy volunteers (HVs). The level of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in each urine sample was measured and then compared among the groups. We also evaluated the relationship between the AD and PV severity and the urinary 8-OHdG level.

Results: We found that the urinary 8-OHdG level was significantly higher in the AD and PV groups than in the HV group. We did not, however, identify an association between the 8-OHdG level and the age, disease duration, or disease severity in the AD or PV groups.

Conclusions: Our results demonstrated an association between urinary 8-OHdG and the development of AD and PV, suggesting that both are oxidative stress-related diseases. Treatments or lifestyle improvements focused on anti-oxidation may therefore be vital for preventing these chronic dermatoses from developing and becoming refractory.

KEYWORDS

8-hydroxy-2'-deoxyguanosine, atopic dermatitis, oxidative stress, psoriasis vulgaris

1 | INTRODUCTION

Several recent studies have revealed that oxidative stress plays a vital role in the development and progression of various lifestyle-related diseases, such as cancer,¹ diabetes mellitus,² and cardiac failure,³ as

well as neurodegenerative disorders, including Parkinson's disease⁴ and cerebral apoplexy.⁵

The skin is the largest organ of the human body and has various functions that help sustain biological activity. Oxidative stress is therefore likely to be involved in the development, progression,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2019 The Authors. *Journal of Cutaneous Immunology and Allergy* published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society for Cutaneous Immunology and Allergy

and aggravation of chronic refractory dermatoses, which are typically characterized by a skin rash all over the body. Thus far, however, few reports with evidence sufficient to prove an association between dermatosis and oxidative stress have been published. Atopic dermatitis (AD) and psoriasis vulgaris (PV) are chronic refractory inflammatory dermatoses characterized by repeated cycles of remission and aggravation. Oxidative stress is thought to be closely involved in the development and progression of these two diseases.

8-hydroxy-2'-deoxyguanosine (8-OHdG)⁶ is a typical oxidative stress marker that is stable *in vivo*. It is generated by the oxidation of a constituent of DNA, namely the deoxyguanosine at the C-8 position. Damaged DNA secretes 8-OHdG into the blood by the action of the repair enzyme DNA glycosylase, and it is then excreted in urine. The urinary 8-OHdG level is reported to be elevated in patients with cancer and various medical disorders.

In the present study, we recruited patients with AD and PV. We measured the level of urinary 8-OHdG, a sensitive marker of oxidative stress, in order to investigate the correlation between oxidative stress and the development and severity of these diseases, particularly in terms of these diseases becoming refractory.

2 | METHODS

2.1 | Subjects

For this study, we recruited adult patients over 20 years of age who visited the Dermatology Department of Osaka Medical College Hospital to receive treatment between November 6, 2012, and September 10, 2018 (Table 1). Overall, the AD group comprised 40 atopic dermatitis patients (24 male and 16 female patients between 20 and 66 years old; mean age, 38.2 years old), and the PV group comprised 25 psoriasis vulgaris patients (14 male and 11 female patients between 28 and 82 years old; mean age, 57.2 years old).

We evaluated the disease severity in the AD and PV group patients using the SCORing Atopic Dermatitis (SCORAD) index and the Psoriasis Area and Severity Index (PASI), respectively. We also thoroughly interviewed all patients for details concerning their medical histories and current diseases in order to exclude patients who had a history of, or were being treated for, possible oxidative stress-related diseases, such as malignant organ tumors, cerebrovascular/circulatory system diseases, or collagen diseases. We did not, however, exclude patients with a history of AD-related diseases, such as bronchial asthma or allergic rhinitis,

TABLE 1 Details of subjects included in this study

Atopic dermatitis (AD) (N = 40)		Psoriasis vulgaris (PV) (N = 25)		Healthy volunteers (HVs) (N = 39)	
Characteristic	Value	Characteristic	Value	Characteristic	Value
Sex		Sex		Sex	
Male, n (%)	24 (60.0)	Male, n (%)	14 (56)	Male, n (%)	10 (25.6)
Female, n (%)	16 (40.0)	Female, n (%)	11 (44)	Female, n (%)	29 (74.3)
Age		Age		Age	
Mean ± SD (range), y	38.2 ± 11.0 (20-66)	Mean ± SD (range), y	57.2 ± 15.1 (28-82)	Mean ± SD (range), y	37.1 ± 9.8 (22-56)
Severity		Severity			
SCORAD INDEX, mean (range)	34 (2.4-88)	PASI SCORE, mean (range)	7.9 (0.6-30)		
Duration of AD		Duration of PV			
<5 y, n (%)	2 (5.0)	<5 y, n (%)	9 (36.0)		
5-9 y, n (%)	3 (7.5)	5-9 y, n (%)	4 (16.0)		
10-14 y, n (%)	4 (10.0)	10-14 y, n (%)	4 (16.0)		
15-19 y, n (%)	4 (10.0)	15-19 y, n (%)	3 (12.0)		
Over 20 y, n (%)	18 (45.0)	Over 20 y, n (%)	3 (12.0)		
Unknown, n (%)	9 (22.5)	Unknown, n (%)	2 (8.0)		
History of bronchial asthma		History of diabetes mellitus			
Yes, n (%)	11 (27.5)	Yes, n (%)	4 (16.0)		
No, n (%)	28 (70.0)	No, n (%)	19 (76.0)		
Unknown, n (%)	1 (2.5)	Unknown, n (%)	2 (8.0)		

Note: To assess the disease severity in the atopic dermatitis (AD) and psoriasis vulgaris (PV) groups, we used the SCORing Atopic Dermatitis index and Psoriasis Area and Severity Index, respectively. We also confirmed the presence/absence of a medical history of bronchial asthma in the AD group and diabetes in the PV group.

nor those with lifestyle diseases supposedly related to PV, like hypertension, diabetes mellitus, or lipid metabolism disorders. We also recruited 39 healthy volunteers (HVs; 10 male and 29 female subjects between 22 and 56 years old; mean age, 37.1 years old) as a control group.

The present study was approved by the research ethics committee of Osaka Medical College (No. 1098 and No. 2590). Before the study commenced, all of the subjects received an explanation at our clinic about the objective and the methods and gave their written consent.

2.2 | Measurement of the urinary 8-OHdG level

We collected 5 mL urine samples from all subjects, and these were centrifuged (1350 g for 5 minutes) to remove precipitates. Subsequently, 200 μ L urine samples were diluted twice with distilled water. The levels of 8-OHdG by immunochromatography and creatinine by the Jaffe method were then measured using the urinary oxidative stress marker measurement system ICR-001 (Techno Medica),⁷ and the creatinine-corrected 8-OHdG level (ng/mg Cre) was calculated. To reduce the influence of diurnal variation or measurement errors, we collected the samples during the morning and obtained the average of three independent 8-OHdG measurements for each sample.

2.3 | Statistical analyses

We compared the urinary 8-OHdG levels between the AD and HV groups and between the PV and HV groups using *t* tests. The relationship between the urinary 8-OHdG level and SCORAD index/PASI was analyzed using Pearson's correlation coefficient. We also conducted subgroup analyses of the AD, PV, and HV groups. The

urinary 8-OHdG values were compared according to the gender and age. The relationship between the urinary 8-OHdG level and disease duration was analyzed. Furthermore, the relationship between the urinary 8-OHdG level and the presence/absence of a history of bronchial asthma was analyzed in the AD group. Finally, the relationship between the urinary 8-OHdG level and the presence/absence of a history of diabetes mellitus was analyzed in the PV group using a *t* test. We conducted all statistical analyses using Microsoft Excel 2013.

3 | RESULTS

The following mean urinary 8-OHdG levels were obtained: 24.1 ng/mg Cre in the AD group ($n = 40$, standard deviation [SD]: 15.1 ng/mg Cre, minimum: 4.6 ng/mg Cre, maximum: 78.3 ng/mg Cre, median: 20.6 ng/mg Cre), 24.2 ng/mg Cre in the PV group ($n = 25$, SD: 13.6 ng/mg Cre, minimum: 8.5 ng/mg Cre, maximum: 65.2 ng/mg Cre, median: 20.8 ng/mg Cre), and 18.9 ng/mg Cre in the HV group ($n = 39$, SD: 7.2 ng/mg Cre, minimum: 9.0 ng/mg Cre, maximum: 33.7 ng/mg Cre, median: 17.3 ng/mg Cre). The urinary 8-OHdG level was significantly higher in the AD and PV groups than in the HV group ($P = .028$ for the AD group and $P = .042$ for the PV group, respectively; Figure 1). The correlation coefficient between the urinary 8-OHdG level and SCORAD index in the AD group was -0.16 . The correlation coefficient between the urinary 8-OHdG level and PASI in the PV group was -0.09 . Therefore, neither of these demonstrated a correlation (Figure 2).

In the AD, PV, and HV groups, no significant differences in the urinary 8-OHdG level were demonstrated according to the gender, age, or disease duration (Table 2). We analyzed the relationship between the urinary 8-OHdG level and the presence/absence of a history of bronchial asthma in the AD group. The mean urinary

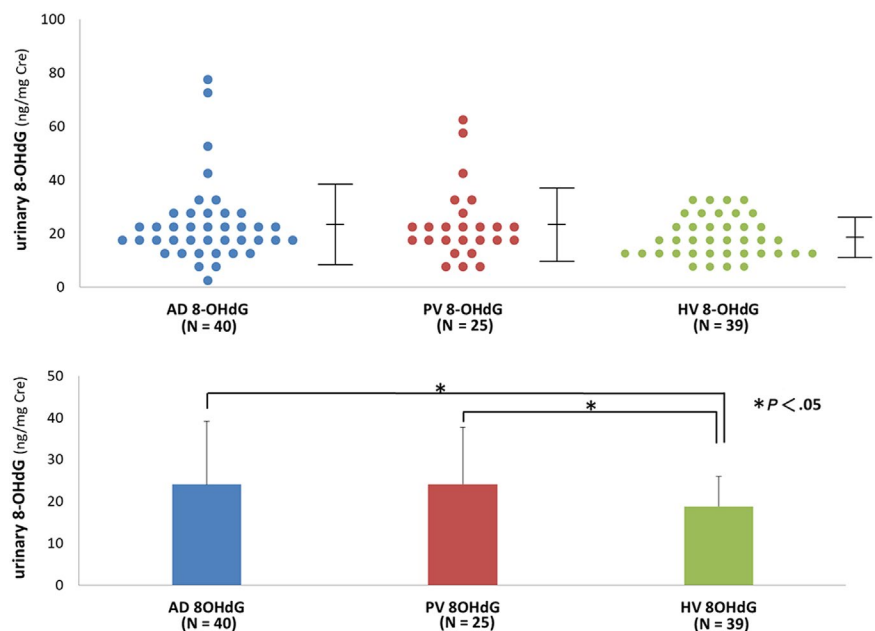


FIGURE 1 The urinary 8-OHdG levels of patients in the atopic dermatitis (AD; 40 patients), psoriasis vulgaris (PV; 25 patients), and healthy volunteer (HV; 39 volunteers) groups. The urinary 8-OHdG level was significantly higher in the AD and PV groups than in the HV group ($P = .028$ for the AD group and $P = .042$ for the PV group)

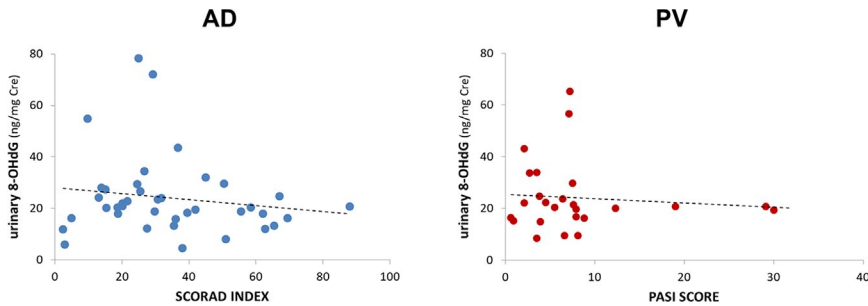


FIGURE 2 The association between urinary 8-OHdG levels and AD/PV disease severity. The correlation coefficient between the urinary 8-OHdG level and SCORAD index was -0.16 . The correlation coefficient between the urinary 8-OHdG level and PASI in the PV group was -0.09 . Therefore, neither of these demonstrated a correlation

TABLE 2 Summary of the urinary 8-OHdG levels in each group (40 atopic dermatitis patients, 25 psoriasis vulgaris patients, and 39 healthy volunteers) according to the disease type, gender, age, contraction/affection, and complications

Atopic dermatitis (AD) (N = 40)		Psoriasis vulgaris (PV) (N = 25)		Healthy volunteers (HVs) (N = 39)	
Characteristic	Urinary 8-OHdG (ng/mg Cre)	Characteristic	Urinary 8-OHdG (ng/mg Cre)	Characteristic	Urinary 8-OHdG (ng/mg Cre)
Total		Total		Total	
Mean \pm SD (range)	24.1 \pm 15.1 (4.6-78.3)	Mean \pm SD (range)	24.2 \pm 13.6 (8.5-65.2)	Mean \pm SD (range)	18.9 \pm 7.2 (9-33.7)
Sex		Sex		Sex	
Male (n = 24)	24.7	Male (n = 14)	23.6	Male (n = 10)	18.8
Female (n = 16)	23.3	Female (n = 11)	23.6	Female (n = 29)	18.9
Age		Age		Age	
20-29 y (n = 9)	23.7	20-29 y (n = 1)	65.2	20-29 y (n = 9)	18.4
30-39 y (n = 14)	20.0	30-39 y (n = 1)	21.4	30-39 y (n = 15)	17.2
40-49 y (n = 11)	29.6	40-49 y (n = 8)	21.8	40-49 y (n = 9)	21.4
50-59 y (n = 4)	21.1	50-59 y (n = 4)	24.8	50-59 y (n = 6)	20.1
60-69 y (n = 2)	29.7	60-69 y (n = 4)	32.5		
		70-79 y (n = 6)	15.2		
		80-89 y (n = 1)	22.3		
Duration of AD		Duration of PV			
<5 y (n = 2)	27.0	<5 y (n = 9)	28.4		
5-9 y (n = 3)	26.3	5-9 y (n = 4)	15.4		
10-14 y (n = 4)	14.2	10-14 y (n = 4)	24.9		
15-19 y (n = 4)	38.1	15-19 y (n = 3)	21.8		
Over 20 y (n = 18)	21.6	Over 20 y (n = 3)	27.6		
History of bronchial asthma		History of diabetes mellitus			
Yes (n = 11)	17.9	Yes (n = 4)	15.0		
No (n = 28)	26.7	No (n = 19)	25.2		

8-OHdG levels in the subgroups with and without a history of asthma were 17.9 and 26.7 ng/mg Cre, respectively. Thus, the mean urinary 8-OHdG level was significantly lower in the subgroup with a history of asthma than in the subgroup without a history ($P = .01$; Table 2).

Likewise, we analyzed the relationship between the urinary 8-OHdG level and the presence/absence of a history of diabetes mellitus in the PV group. The mean urinary 8-OHdG levels in the subgroups with and without a history of diabetes mellitus were 15.0 and 25.2 ng/mg Cre, respectively. Thus, the mean urinary 8-OHdG level was significantly lower in the subgroup with a

history of asthma than in the subgroup without a history ($P = .005$; Table 2).

4 | DISCUSSION

Urinary 8-OHdG is an oxidative stress marker that accurately reflects DNA damage by reactive oxygen species. The urinary 8-OHdG level is known to be elevated in several medical diseases, and it has been reported as a useful monitoring tool for evaluating the effectiveness of radiation treatment or chemotherapy in lung cancer.¹

Furthermore, its relationship with hypertensive disease progression has also been reported: The administration of an angiotensin II receptor blocker reduced the blood pressure and urinary 8-OHdG level.⁸ Many studies have suggested the involvement of oxidative stress in dermatosis, but few detailed clinical investigations on dermatosis patients have been conducted.

Atopic dermatitis and PV are both chronic inflammatory skin diseases. AD is a chronic skin disorder characterized by skin barrier dysfunction and excessive immunoglobulin E (IgE) production in response to various antigens. It is caused by a number of factors, such as congenital mutations in the filaggrin gene.⁹ PV typically affects middle-aged adults, manifesting as immunomodulation and inflammation in the epidermis and dermis with evident accelerated keratinocyte turnover, although the precise pathogenesis of this condition is unknown. Multiple genetic, external, and immunological factors are thought to be involved in its pathology.¹⁰ Given that both of these entities are dermatoses involving chronic inflammation, oxidative stress is likely to be involved in their development, progression, and tendency to become refractory.

In the present study, we recruited patients with AD and PV and measured their levels of urinary 8-OHdG, an accurate and easy-to-measure marker of oxidative stress. We found that the urinary 8-OHdG level was significantly higher in the AD and PV groups than in the HV group, suggesting that both diseases are oxidative stress-related. However, no correlation was identified between the urinary 8-OHdG level and AD or PV disease severity, as assessed by the SCORAD index and PASI. This may have been due to the limited number of patients included in the study or from the influence of other oxidative stress factors (eg, the presence of other oxidative stress-related diseases, such as hypertension, diabetes mellitus, bronchial asthma, or allergic rhinitis; or the smoking and drinking habits of the patients).

We also conducted subgroup analyses in the AD and PV groups to investigate the relationship between the urinary 8-OHdG level and the history of bronchial asthma and diabetes, respectively. Both bronchial asthma and diabetes mellitus are oxidative stress-related diseases, and we thus expected the urinary 8-OHdG levels to be elevated in the subgroups with a history of these diseases.^{2,11} However, our results showed significantly lower urinary 8-OHdG values in both the AD subgroup with a history of bronchial asthma and the PV subgroup with a history of diabetes mellitus than in the subgroups without such histories. We interviewed each patient at the time of the urine sample collection, and several patients were receiving treatment for bronchial asthma or diabetes. Thus, active oxygen species production may have been reduced due to these treatments, potentially leading to the observations of reduced urinary 8-OHdG levels. In addition, those differences are not significant ($P = .31$ for the AD subgroup with a history of bronchial asthma and $P = .08$ for the PV subgroup with a history of diabetes mellitus). The number of cases analyzed in each subgroup was small (11 patients in the AD group had bronchial asthma, and four patients in the PV group had diabetes mellitus), so a greater number of cases should be evaluated in future studies to draw a hard conclusion.

The urinary oxidative stress marker measurement system (ICR-001) we used in our investigation comprises desktop equipment capable of measuring the urinary 8-OHdG level relatively quickly and easily. Therefore, it would be suitable for use not only in large-scale facilities, like university hospitals, but also in smaller clinics. Though we could not determine the correlation between the urinary 8-OHdG level and AD/PV disease severity in the present study, the results of significantly elevated urinary level of 8-OHdG in both AD and PV cases imply the possibility of novel treatment options to these diseases, that is, anti-oxidation-oriented tailor-made treatments.

In the present study, we successfully demonstrated an association between the urinary 8-OHdG level and AD/PV development, suggesting that both diseases are oxidative stress-related. Our results also suggest that anti-oxidation-oriented treatment/medical guidance may be extremely valuable in preventing these chronic dermatoses from developing or becoming refractory. If associations between the urinary 8-OHdG level and other chronic refractory dermatoses, such as autoimmune bullous dermatoses, are identified and enough data are accumulated in future studies, urinary 8-OHdG measurements could be useful in dermatology clinics as an evaluation criterion for the treatment of various chronic dermatoses other than AD and PV.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Shinichi Moriwaki  <https://orcid.org/0000-0003-0803-9455>

REFERENCES

1. Erhola M, Toyokuni S, Okada K, Tanaka T, Hiai H, Ochi H, et al. Biomarker evidence of DNA oxidation in lung cancer patients: association of urinary 8-hydroxy-2'-deoxyguanosine excretion with radiotherapy, chemotherapy, and response to treatment. *FEBS Lett.* 1997;409:287-91.
2. Nishikawa T, Sasahara T, Kiritoshi S, Sonoda K, Senokuchi T, Matsuo T, et al. Evaluation of urinary 8-hydroxydeoxy-guanosine as a novel biomarker of macrovascular complications in type 2 diabetes. *Diabetes Care.* 2003;26:1507-12.
3. Suzuki S, Shishido T, Ishino M, Katoh S, Sasaki T, Nishiyama S, et al. 8-Hydroxy-2'-deoxyguanosine is a prognostic mediator for cardiac event. *Eur J Clin Invest.* 2011;41:759-66.
4. Seet R, Lee C, Lim E, Tan J, Quek A, Chong W, et al. Oxidative damage in Parkinson disease: measurement using accurate biomarkers. *Free Radic Biol Med.* 2010;48:560-6.
5. Mizukoshi G, Katsura K, Watanabe M, Katayama Y. Evaluation of therapeutic efficacy of free radical scavenger in patients with ischemic stroke. *Cereb Blood Flow Metab.* 2006;18:53-60.
6. Kasai H, Hayami H, Yamaizumi Z, Saito H, Nishimura S. Detection and identification of mutagens and carcinogens as their adducts with guanosine derivatives. *Nucleic Acids Res.* 1984;12:2127-36.
7. Kaneko K, Kimata T, Tuji S, Ohashi A, Imai Y, Sudo H, et al. Measurement of urinary 8-oxo-7,8-dihydro-2-deoxyguanosine in a novel point-of-care testing device to assess oxidative stress in children. *Clin Chim Acta.* 2012;413:1822-6.
8. Kuboki K, Iso K, Murakami E, Abe S, Araki E, Ueshiba H, et al. Effects of valsartan on inflammatory and oxidative stress markers



in hypertensive, hyperglycemic patients: an open-label, prospective study. *Curr Therap Res.* 2007;68:338–48.

9. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, et al. Japanese guidelines for atopic dermatitis 2017. *Allergol Int.* 2017;66:230–47.
10. Boehncke WH, Schön MP. Psoriasis. *Lancet.* 2015;386:983–94.
11. Montuschi P, Corradi M, Ciabattini G, Nightingale J, Kharitonov SA, Barnes PJ. Increased 8-isoprostane, a marker of oxidative stress, in exhaled condensate of asthma patients. *Am J Respir Crit Care Med.* 1999;160:216–20.

How to cite this article: Shimamoto J, Kurokawa T, Tanizaki H, Moriwaki S. The evaluation of oxidative stress in patients with psoriasis vulgaris and atopic dermatitis by measuring the urinary level of 8-hydroxy-2'-deoxyguanosine. *J Cutan Immunol Allergy.* 2019;2:163–168. <https://doi.org/10.1002/cia2.12088>