

High Sensitivity C-Reactive Protein Level and Psoriasis Severity in Thai Patients

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Background: Psoriasis vulgaris severity have been widely assessed by psoriasis area severity index (PASI) score. However, it may not be the best measure because of the high variability and inability to tell the other aspect of the disease including co-morbidity and cardiovascular risk.

Objective: To determine the correlation between high sensitivity C-reactive protein (hs-CRP) level and psoriasis severity and to determine co-morbidities of psoriasis patients.

Material and Method: One hundred eighty psoriasis patients and thirty control patients were enrolled in the present cross-sectional study. Fasting venous blood were collected and analyzed for fasting plasma glucose, hemoglobin A1c, lipid profile, and hs-CRP. The psoriasis patients were assessed for skin severity by PASI scoring. The correlation was assessed by regression analysis.

Results: The hs-CRP level was found significantly higher in the psoriasis group (p -value <0.001). The hs-CRP level significantly correlated with PASI score by using multivariate regression analysis.

Conclusion: This correlation between hs-CRP level and the psoriasis severity has led to the proposition that hs-CRP be used as a biomarker for overall inflammation including skin severity and cardiovascular risk factor in psoriasis.

Keywords: Psoriasis vulgaris, Severity score, PASI score, hs-CRP, High sensitivity C-reactive protein

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Psoriasis vulgaris, the chronic inflammatory skin disease, exact cause is unknown, polygenic predisposition and environmental factors can aggravate the disease. Overall incidence is around 1-3% depends on nationalities, lower incidence in Asian around 0.3%^(1,2). In Thailand, although the exact prevalence and incidence of psoriasis have not been reported, chronic plaque type psoriasis visiting outpatient department of the Institute of Dermatology is average 1,800 patients per year. The treatment of disease depends on the severity, mild disease can successfully be controlled with topical treatment, whereas severe disease should be controlled with systemic drugs or phototherapy. Various scoring systems such as psoriasis area severity index (PASI), body surface area (BSA), patient global assessment score have been used to assess severity of psoriasis, but there is no best tool in terms of accuracy and consistency⁽³⁾. The PASI score, the most commonly used system, has high content

validity, nevertheless, this system is subjective, difficult to interpret due to nonlinear scaling, time-consuming, and has high intra and inter-rater variability, and other comorbidities are not evaluated^(3,4). Consequently, various biomarkers have been widely investigated to represent the skin severity, prediction of the future prognosis or find more objective and more accurate method. Among them high sensitivity C-reactive protein (hs-CRP) is one of the most potential^(5,6). According to lack of the study of hs-CRP in Asian psoriasis patients, the present study focused on the correlation of psoriasis severity and hs-CRP level in Thai patients.

Material and Method

Study population

The present cross-sectional study recruited 180 plaque type psoriasis patients at the outpatient clinic and phototherapy unit of the Institute of Dermatology, and 30 non-psoriasis patients as the control group between September 2013 and June 2014. The psoriasis patients aged 18 years and older diagnosed based on clinical manifestation of psoriasis were included. The control group enrolled volunteer

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patients without any inflammatory skin lesion, diagnosed nevus or benign skin tumor undergoing excision or electrocautery. The patients with any of these following features, having sign of acute or chronic infection, autoimmune diseases, systemic vasculitis, previous history of myocardial infarction, having symptom and sign of arthritis including psoriatic arthritis, previous history of active cancer, tumor embolization, or surgery, burn wound, and bony fracture within three months were excluded. The study protocol was approved by the Ethic Committee of Institute of Dermatology and all participants gave informed consent.

Intervention

All participants met the criteria were recorded their medical and personal information. The clinical parameters including the resting blood pressure, body weight, height, waist, and hip circumference were measured and body mass index (BMI) was calculated. Furthermore, the psoriasis patients were assessed the disease severity by BSA and PASI score by the first author at time of enrollment. The PASI score was calculated by grading the plaques based on three parameters, redness (R), thickness (T), and scaliness (S). The severity was rated for each index on a 0-4 scale (0 for no involvement; 4 for severe involvement) and divided into four regions, head (h), upper extremities (u), trunk (t), and lower extremities (l). In each of these areas (A), the affected area was graded on a 0 to 6 scale (0, no involvement; 1, 1 to 9%; 2, 10 to 29%; 3, 30 to 49%; 4, 50 to 69%; 5, 70 to 89%; 6 for 90 to 100%). The PASI score can then be calculated as $PASI = 0.1 \times (Rh+Th+Sh) \times Ah + 0.2 \times (Ru+Tu+Su) \times Au + 0.3 \times (Rt+Tt+St) \times At + 0.4 \times (Rl+Tl+Sl) \times Al^{(4)}$. The BMI was calculated using the formula of weight (kg)/height (m)². Patients were classified as overweight if BMI is 25.0 to 29.9 kg/m², and obesity if BMI greater than 30 kg/m².

Laboratory investigation

The venous blood samples were collected from both groups to determine glucose, hemoglobin A1c (HbA1c), total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, hs-CRP, following an overnight fasting at least eight hours. Fasting plasma glucose level was measured by the glucose oxidase method, the lipid profile and hs-CRP level were measured by immunonephelometric assay (BNPRO spec, Nephelometry, Siemens, Germany).

Statistical analysis

The statistical analysis was performed using SPSS version 16.0. According to non-Gaussian distribution of majority of data, we assessed median \pm interquartile range (IQR) for descriptive data, nonparametric test, including Mann-Whitney test, and Kruskal Wallis test for comparing difference between groups. Correlation between PASI score and hs-CRP were assessed by simple regression and multivariate logistic regression analysis, with PASI score as a dependent variable. The factors of age, diabetes, hyperlipidemia, high LDL/HDL ratio, hypertension, and metabolic syndrome were included into multivariate regression analysis. The correlation was demonstrated as odds ratios (OR) with 95% confidence intervals (CI). Diabetes mellitus defined as fasting glucose greater than 126 mg/dL and/or HbA1c greater than 6.5% or currently on hypoglycemic drug. Hypertension defined as currently intake of antihypertensive drug, repeated resting diastolic blood pressure greater than 90 mmHg or repeated resting systolic blood pressure greater than 140 mmHg. Hyperlipidemia defined as currently intake lipid lowering drugs, total cholesterol greater than 240 mg/dL. Metabolic syndrome was defined as criteria of the International Diabetes Federation/National Heart, Lung, Blood Institute/World Heart Federation Joint Interim, which require at least three scores of 1) waist circumference (South Asian greater than 80 cm, male greater than 90 cm), 2) triglyceride level greater than 150 mg/dL or currently on treatment, 3) reduced HDL (female less than 50 mg/dL, male less than 40 mg/dL) or currently on treatment, 4) systolic blood pressure greater than 130 mmHg or diastolic blood pressure greater than 85 mmHg or currently on antihypertensive drug, and 5) fasting blood sugar greater than 100 mg/dL or currently on treatment. The *p*-value less than 0.05 was considered statistical significance.

Results

One hundred eighty Thai psoriasis patients were included in this study and 55.6% were male and 44.4% were female. The average age was 41.5 \pm 25.8 years, with 10 \pm 11.0 year-duration of the disease. Their occupation were government officers (13.3%), private companies (34%), own businesses (22.8%), laborers (6.7%), unemployed (13.9%), students (8.3%), half of them graduated at least with a bachelor's degree. Eighty percent had family history of psoriasis. Most of patients had mild disease (PASI less than 10) 153, the others had moderate (PASI 10 to 20) 24, and severe diseases (PASI greater than 20) 3.

The median PASI score was 4.6 ± 4.9 and the BSA involvement was 5.5 ± 7 . The main treatment in last four weeks was topical steroid and coal tar derivative (95%, 83.3%). Only 12.1% were currently on systemic treatment, which methotrexate was the main drug (7.7%), and 19.4% on phototherapy (18.8% NB-UVB, 0.6% PUVA). Nail involvement was found in 81.7%, including onycholysis (66.7%), subungual hyperkeratosis (51.1%), oil spot/salmon patch (28.3%), dystrophic nail (16.1%), pitting nail (35.6%). The control group was 30 non-psoriasis patients, diagnosed as seborrheic keratosis (60%), nevus (30%), and other benign skin tumors (10%). The authors assessed the difference between the psoriasis and the control group (Table 1), which demonstrated significant higher of body mass index, systolic and diastolic blood pressure, diabetes, obesity, and metabolic syndrome in psoriasis

Table 1. Demographic data and difference between psoriasis and control group

Details	Psoriasis (n = 180)	Control (n = 30)	p-value
Sex (male/female)	100/80	10/20	0.024
Age (years), median \pm IQR	41.5 \pm 25.8	40.0 \pm 28.3	0.796
Smoking, n (%)	40 (22.2)	2 (6.7)	0.071
Alcohol, n (%)	30 (16.7)	2 (6.7)	0.175
BMI, median \pm IQR	25.9 \pm 6.4	22.0 \pm 5.0	<0.001
SBP, median \pm IQR	123.0 \pm 20.0	114.5 \pm 19.3	0.001
DBP, median \pm IQR	80.0 \pm 13.0	70.0 \pm 15.3	<0.001
Diabetes, n (%)	27 (15.0)	0	0.023
Hypertension, n (%)	67 (37.2)	5 (16.7)	0.090
Hyperlipidemia, n (%)	153 (35.0)	16 (23.0)	0.207
Metabolic syndrome, n (%)	59 (32.8)	2 (6.7)	0.003
Obesity, n (%)	40 (22.2)	6 (3.3)	<0.001

BMI = body mass index; DBP = diastolic blood pressure; IQR = interquartile range; SBP = systolic blood pressure

Table 2. Lab results and difference between psoriasis and control group

Lab	Psoriasis (n = 180)	Control (n = 30)	p-value
hs-CRP (mg/L), median \pm IQR	2.4 \pm 4.8	0.8 \pm 1.1	<0.001
FBS (mg/dl), median \pm IQR	89.0 \pm 17.0	85.0 \pm 14.8	0.071
Total cholesterol (mg/dL), median \pm IQR	215.0 \pm 48.8	186.0 \pm 45.8	<0.001
LDL/HDL ratio, median \pm IQR	3.0 \pm 1.7	2.3 \pm 1.0	<0.001
Triglyceride (mg/dL), median \pm IQR	115.5 \pm 101.3	65.0 \pm 59.3	0.827
LDL (mg/dL), median \pm IQR	141.0 \pm 47.0	115.5 \pm 37.3	<0.001
HDL (mg/dL), median \pm IQR	47.0 \pm 16.8	53.0 \pm 24.3	0.001

FBS = fasting blood sugar; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein; IQR = interquartile range; LDL = low-density lipoprotein

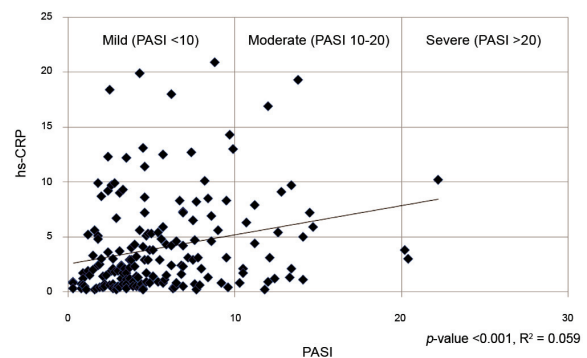


Fig. 1 Demonstrating the correlation between PASI score and hs-CRP level by using simple regression analysis (n = 177, exclude outlier).

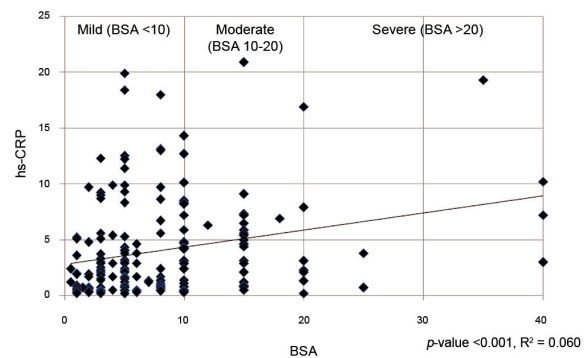


Fig. 2 Demonstrating the correlation between BSA and hs-CRP level by using simple regression analysis (n = 176, exclude outlier).

group. For the co-morbidities, in addition to the Table 1, benign prostate hyperplasia (1.1%), chronic obstructive pulmonary disease (0.56%), and port wine stain (0.56%) were found in psoriasis patients. For the blood test, we found total cholesterol, LDL, LDL/HDL ratio greater than three in psoriasis group were significantly higher, while HDL was found significantly lower. The hs-CRP level also revealed significant

higher in psoriasis group. The PASI score was found correlated to hs-CRP level as shown in Fig. 1 by simple regression analysis as well as correlation of BSA and hs-CRP (Fig. 2). Multivariate logistic regression analysis was performed with stepwise inclusion of age, BMI, alcoholic drinking, smoking, diabetes, dyslipidemia, L/H ratio greater than three, hypertension, metabolic syndrome, which can be confounding risk factors to PASI score, the dependent variable. The analysis showed no significant correlation between these factors and PASI score and confirmed significant correlation between hs-CRP and PASI score after controlling other confounding factors (OR 3.22, 95% CI 1.23-8.48, *p*-value = 0.018) (Table 3).

Discussion

C-reactive protein, an acute phase reactant protein, is produced from hepatocyte within hours after being stimulated from inflammation, infection, tissue damage, and decrease rapidly after the stimulating factor has been eliminated or responded to treatment⁽⁷⁾. Due to its nature of short half-life, it could be useful for daily monitoring. This biomarker used for assess the disease activity of many diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic vasculitis, rheumatic fever, and acute pancreatitis, therefore the inflammatory skin disease like psoriasis without psoriatic arthritis may also be used. Although, it has nonspecific property, its sensitivity for inflammation highlighted investigators to explore the role for assessing the skin severity. The hs-CRP can detect CRP level less than 5 mg/L. The median level of hs-CRP in Thai healthy persons is 1.8 mg/L (range 0.2 to 7.9), which is higher than our control group, but still lower than psoriasis group⁽⁸⁾. The result of the present study demonstrated the correlation between PASI score and hs-CRP level, similar to the previous studies, which performed in Caucasian. Roch-Pereira et al studied various markers comparing between control group, mild psoriasis (PASI less than 3), and severe psoriasis (PASI greater than 3) demonstrating that the level of hs-CRP has been the most striking difference among groups and proposed the level of hs-CRP more than 0.69 mg/L could be the marker of worsening psoriasis⁽⁵⁾. Kanelleas et al found level of hs-CRP was the only marker correlated with PASI score both before and after treated with etanercept and the more difference of hs-CRP level revealed the more treatment response⁽⁶⁾. The retrospective study of Strober et al showed the association between skin activity and hs-CRP, independent of BMI, age and sex

Table 3. Demonstrating the multivariate logistic regression analysis between PASI score and other factors (n = 180)

	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Age	0.99	0.96-1.02	0.509	0.99	0.96-1.02	0.606	0.99	0.96-1.02	0.610	0.99	0.96-1.02	0.478	0.99	0.96-1.02	0.454	0.99	0.95-1.02	0.369
BMI	0.75	0.29-1.95	0.553	0.73	0.28-1.91	0.519	0.79	0.30-2.14	0.647	0.89	0.32-2.46	0.816	0.70	0.23-2.12	0.531	1.03	0.33-3.22	0.966
Alcoholic drinking	1.09	0.34-3.51	0.881	1.08	0.34-3.46	0.897	1.06	0.33-3.39	0.917	1.11	0.35-3.54	0.861	1.08	0.34-3.41	0.893	0.77	0.24-2.51	0.661
Smoking	0.76	0.21-2.69	0.670	0.76	0.22-2.69	0.672	0.78	0.22-2.74	0.698	0.69	0.19-2.49	0.573	0.66	0.19-2.36	0.527	0.68	0.19-2.41	0.551
Diabetes				0.70	0.19-2.62	0.598	0.68	0.18-2.54	0.561	0.61	0.16-2.35	0.475	0.80	0.19-3.41	0.766	0.74	0.17-3.24	0.689
Dyslipidemia							0.89	0.24-3.32	0.857	0.89	0.24-3.35	0.866	0.98	0.26-3.69	0.972	0.77	0.20-3.04	0.713
L/H ratio >3							1.42	0.55-3.68	0.470	1.32	0.50-3.47	0.571	1.41	0.54-3.74	0.485	1.50	0.55-4.08	0.426
Hypertension										1.69	0.60-4.77	0.318	2.31	0.71-7.55	0.166	2.35	0.72-7.61	0.156
Metabolic syndrome													0.49	0.13-1.83	0.286	0.43	0.11-1.64	0.218
hs-CRP level																3.22	1.23-8.48	0.018

BMI = body mass index; hs-CRP = high sensitivity C-reactive protein; IQR = interquartile range; PASI = Psoriasis Area and Severity Index

and hs-CRP level reduced significantly difference in the etanercept treated group at twelfth week compared with control group⁽⁹⁾. Coimbra et al performed cross-sectional study in plaque type psoriasis patients treated with various kinds of treatment, which only hs-CRP associated to severity of disease and longitudinal study showed significant decrease hs-CRP level when treated with PUVA and NBUVB⁽¹⁰⁾. Chodorowska et al studied all types of psoriasis treated with various kinds of treatment found significant higher hs-CRP level compare to control group both before and after treatment, which hs-CRP level markedly reduced after treated with ciclosporin⁽¹¹⁾. The recent study from Turkey also found significant higher level of hs-CRP in psoriasis and proposed the new markers, vaspin and vascular adhesion protein-1 (VAP-1), for severity of disease⁽¹²⁾. However, the recent study in Japanese plaque type psoriasis found significant higher hs-CRP level over control group, but no significant correlation with PASI score, similar to the study of Sergeant et al, which included all types of psoriasis including psoriasis arthritis with various kinds of treatment^(13,14). The possible explanation for correlation between hs-CRP level and psoriasis severity is, keratinocytes in psoriasis lesion secreted interleukin-1 and tumor necrosis factor- α , which can stimulate hepatocytes to produce hs-CRP into the circulation, so mild psoriasis will have lower level of this marker than severe disease.

In the present study, psoriasis patients had 32.8% metabolic syndrome, which higher than the general Thai population (20%) but lower than the previous studies which was 49.25%, may be due to their higher mean age (50.04 \pm 13.81 years), and all types of psoriasis and psoriatic arthritis were included^(16,17). This previous study also showed the odds ratio of 2.24 (p -value <0.001) after controlling for age, sex, smoking and alcoholic consumption, and other metabolic component including high blood pressure and abdominal obesity were significantly higher in psoriasis group, similar to our study. These emphasized the association among psoriasis and metabolic syndrome, which increased cardiovascular risk in psoriasis patients. Furthermore, hs-CRP level can predict cardiovascular risk in the future including cerebrovascular and peripheral arterial disease. The Centers for Disease Control and Prevention and the American Heart Association defined hs-CRP less than 1 mg/L as a low risk, 1-3 mg/L as intermediate risk and more than 3 mg/L as high risk for cardiovascular event, which the latter group revealed relative odds of 2.0 (95% CI 1.6-2.5) for major coronary events compare

to the low risk group⁽¹⁸⁾. In the present study almost half of psoriasis patients (43.3%) had intermediate to high risk of cardiovascular event in the future, so this emphasized the importance of screening other metabolic co-morbidities for early detection and treatment, in order to reduce cardiovascular event mainly myocardial infarction (meta-analysis of cohort study: OR = 1.25 (95% CI 1.03-1.52)), which is known as the leading cause of death in psoriasis^(19,20). Another marker for increasing atherosclerosis risk is LDL/HDL ratio more than 3, which found 48.9% in psoriasis group, comparing 10.3% in control group, which was significant difference between group (p -value = 0.001)⁽¹⁵⁾. The limitation of the present study is that hs-CRP is not a specific marker, although it represents inflammatory burden of psoriasis, the other causes of inflammation and infection must be prior excluded. From the regression analysis, the prediction ability of hs-CRP for severity is quite low as 5.9%, so further study is needed to clarify the association of hs-CRP and the severity when the clinical symptom is improved after treatment, and whether the cardiovascular risk factor can decrease if hs-CRP reduced to normal level, to confirm the association of hs-CRP and psoriasis severity. In fact, hs-CRP test is simple blood test, inexpensive (250 bath/test), and also available in majority of secondary care hospitals in Thailand. Taken together, hs-CRP is a potential marker that can be used for grading psoriasis severity with great cost-effectiveness. Additional work will be imperative to validate this marker in larger cohort.

Conclusion

The present study found significant correlation between hs-CRP and psoriasis severity, defined as PASI score. Whether, this marker can be comparable to PASI score needs further investigation. In spite of the limitation of the cross-sectional study, its investigator independent and more accuracy may make this marker be valuable in clinical practice and research in the future.

What is already known on this topic?

The high sensitivity C-reactive protein has proven effective in the process to evaluate the association between psoriasis severity and cardiovascular risk in studies among Caucasian.

What this study adds?

This is the second study in Asian psoriasis patients that showed significant correlation between

hs-CRP level and PASI score, contrasted to the previous Japanese study.

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Potential conflicts of interest

None.

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ระดับซีรีแอคทีฟโปรตีนความไวสูงและความรุนแรงของโรคสะเก็ดเงินในผู้ป่วยชาวไทย

รวีพันธุ์ เอื้อรัตนวงศ์, สมชาย เอื้อรัตนวงศ์, จักรพงษ์ ชุณหเสวี, ประภาวรรณ เขาวะวณิช

ภูมิหลัง: โรคสะเก็ดเงินเป็นโรคการอักเสบของผิวหนังที่พบบ่อย การประเมินความรุนแรงของผื่นเพื่อเลือกแนวทางการรักษาและติดตามอาการนั้นโดยทั่วไปนิยมใช้วิธี PASI score แต่วิธีนี้ยังมีข้อจำกัดในแง่ความแตกต่างระหว่างผู้ประเมิน และเป็นเพียงการประเมินผื่นผิวหนังไม่สามารถบอกความรุนแรงของโรคในองค์รวม เช่น ภาวะโรคร่วม ความเสี่ยงในการเกิดโรคหลอดเลือดหัวใจในอนาคตได้

วัตถุประสงค์: เพื่อเปรียบเทียบความสัมพันธ์ของระดับ high sensitivity C-reactive protein (hs-CRP) กับความรุนแรงของโรคสะเก็ดเงิน และเพื่อหาความชุกโรคร่วม เช่น โรคเบาหวาน ความดันโลหิตสูง โรคไขมันในเลือดสูง โรคอ้วนลงพุง ในผู้ป่วยสะเก็ดเงิน

วัสดุและวิธีการ: ผู้ป่วยสะเก็ดเงินจำนวน 180 ราย และกลุ่มควบคุมจำนวน 30 ราย ได้รับการเจาะเลือดหาระดับน้ำตาลก่อนอาหาร น้ำตาลสะสม ระดับไขมัน และระดับ hs-CRP และประเมินความสัมพันธ์ด้วยวิธีการวิเคราะห์แบบถดถอย

ผลการศึกษา: จากการศึกษาพบว่าระดับ hs-CRP ในกลุ่มผู้ป่วยสะเก็ดเงินสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) และพบความสัมพันธ์ระหว่างระดับ hs-CRP และความรุนแรงของโรคสะเก็ดเงินซึ่งประเมินโดย PASI score

สรุป: ระดับ hs-CRP อาจใช้เป็นตัวชี้วัดความรุนแรงของโรคสะเก็ดเงินได้ โดยสามารถบอกการอักเสบของผื่นผิวหนังและเป็นตัวบ่งชี้ความเสี่ยงในการเกิดโรคหลอดเลือดได้