Evaluation of Lewis phenotypes in patients with psoriasis

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Background: It seems that there are similar associated diseases in psoriasis and Lewis (b) negative phenotypes such as diabetes mellitus, cardiovascular events, and metabolic syndrome. Therefore, we decided to evaluate the frequency of Lewis phenotypes in patients with chronic plaque type psoriasis. A limited number of studies have been previously conducted in this regard.

Methods: Fifty patients and 100 age and gender matched control subjects were selected as the study population. Two milliliter of venous blood was collected from each subject to find out the Lewis phenotype and in subjects with the Le (a-b-) phenotype, saliva was collected to determine the secretory status. All individuals with the Le (a-b-) phenotype were typed as non-secretor in their saliva by the hemagglutination inhibition assay; therefore, in this study, Lewis (b) positive individuals were considered as secretor and Lewis (b) negative as non-secretor phenotypes.

Results: There was a significant difference in the secretory status or Lewis phenotypes between the two groups. ABH non-secretory status Le (a-b-) and Le (a+b-) together or Lewis b negative phenotypes were found in 78% (39 of 50) of the patients and 26% (26 out of 100) of the healthy controls (P<0.0001). The Le (a-b-) phenotype regardless of the secretory status was found in 14 patients with psoriasis (28.0%) and five healthy controls (5.0%), indicating a statistically significant difference (P=<0.0001).

Conclusions: Individuals with Lewis b negative phenotypes or non-secretors are at risk of developing psoriasis. Inheriting Le/b antigen may have a protective role in patients with psoriasis.

Keywords: psoriasis, Lewis phenotypes, secretor, non-secretor, risk factor

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INTRODUCTION

Psoriasis is a chronic and recurrent inflammatory skin disease characterized by erythrosquamous plaques, especially on the extensor surfaces of the body and scalp. Skin and joint manifestations affect approximately 2% of the population. Chronic plaque type psoriasis has been associated with cardiovascular disease, diabetes mellitus, and an increased risk for atherothrombotic events including coronary artery disease and stroke. Patients with psoriasis have a 5-year shorter life expectancy [1-3].

There are some suggested genetic and environmental risk factors for developing psoriasis. The strongest association is with HLA-Cw*06 and a number of genes including IL12B and IL23R have recently been confirmed. Environmental risk factors including streptococcal pharyngitis, stressful life events, low humidity, drugs, HIV infection, trauma, smoking, and obesity have been associated with psoriasis [4].

Non-secretor individuals lack ABO blood group antigens in their saliva and other body secretions. These cell- surface fucosylated oligosaccharides

participate in several biological processes such as tissue differentiation, cell movement, inflammation, and bacterial adhesion. Saliva and other secretions of ABH secretors contain substantially more diverse carbohydrates than non-secretors that may be involved in the above-mentioned functions. Also, their exposure to endogenous and exogenous antigens are more than secretors and they are more susceptible to inflammatory diseases [5,6].

Based on genetic inheritance, ABH (the precursor to the ABO blood group antigens, present in people with all common blood types, is called the H antigen), the Lewis blood group system, and the secretor status are linked with each other. A secretor is defined as a person who secretes blood group antigens into body fluids and secretions like the saliva, milk, semen, amniotic fluid, etc. If people are ABH secretors, they secrete antigens according to their blood groups; for example, group O individuals secrete H antigen and group A individuals secrete A and H antigens, etc [5].

There are two main antigens in the Lewis blood group system, Le/a and Le/b, with four phenotypes: Le (a+b-), Le (a-b+), Le (a-b-), and Le (a+b+). The Lewis gene is located on chromosome 19 and is very close to the secretor gene. Fucosyltransferase 3 (FUT3) is the product of Lewis gene and fucosyltransferase 2 is the enzyme synthesized by the secretor gene. The function of both enzymes is adding fucose to the sugar moiety of glycolipid and glycoprotein. The H substance in secretions is formed by the action of fucosyltransferase 2 on type one precursor oligosaccharide chain and then fucosyltransferase 3 will produce Le/b by adding fucose to this H substance; therefore, all individuals with Le/b in their phenotypes are secretors. In non-secretors, the Le/a antigen can be produced by adding fucose to type one oligosaccharide chain. Simultaneous inheritance of secretor and Lewis gene can lead to the Le (a-b+) phenotype except in a variant of secretor gene which is prevalent in Japan, china, and Southeast Asia phenotyped as Le(a+b+), because of the weak action of Fuc2 on the precursor type one chain. In the absence of Lewis gene, null phenotype with no Lewis antigen can form Le (a-b-). To evaluate the secretory status in these cases, the presence of the H substance can be checked in the plasma or saliva [5,7].

The purpose of our study was to analyze the frequency of Lewis phenotypes in psoriasis.

PARTICIPANTS AND METHODS

A total of 50 patients and 100 healthy subjects as the control group were selected as the study population. Patients were visited in the Department of Dermatology of Shohada-e-Tajrish Hospital affiliated with Shahid Beheshti University of Medical Sciences during 2013-2014. Patients with a clinical diagnosis of chronic plaque psoriasis lasting more than 6 months were included in the study. All fifty patients had chronic plaque type psoriasis. Patients with a history of other inflammatory diseases, psoriatic arthropathy, ischemic heart disease, diabetes mellitus (Fasting blodd sugar [FBS]>110 mg/dl), hypertension (BP>140/90 mmHg), dyslipidemia (trig;ycerides >160 mg/dl, cholestrol > 240 mg/dl), metabolic syndrome diagnosed with the presence of three or more criteria of the National Cholesterol Education Program's Adult Panel III (ATP III) [8] and diseases due to hypercoagulable states (deep vein thrombosis, myocardial infarction, stroke, etc.) were excluded. Demographic factors such as age, gender, and the duration of disease were recorded. This study was approved by the Ethic Committee of the university and all the patients and controls signed informed consent forms.

Two milliliter of venous blood was collected from each patient and control in EDTA containing tubes. Red blood cells were washed 3 times with 5% saline solution for Lewis blood group antigen typing. Lewis blood grouping was performed by the tube test using standard commercial antiserum; for each specimen, 2 tubes containing one drop of anti Le/a and anti Le/b and 2 drops of 5% RBC suspension were used. After 10 minutes incubation at room temperature, the tubes were centrifuged at 3000 rpm for 30 seconds and observed for agglutination. With regards to the reaction pattern of anti-Le/a and anti -Le/b with the red cell suspension, four phenotypes were observed: Le (a+b-), Le (a-b+), Le (a+b+) and Le (a-b-). For determining the secretory status of Le (a-b-), the saliva was checked for the presence of the H substance. For this purpose, 3 ml saliva was collected in a glass tube and boiled for 5 minutes to destroy saliva enzymes. Then, the hemagglutination inhibition method was used to detect the secretory state. Two drops of filtrated saliva and one drop of anti H (extracted from ulex europaeus lectin) was mixed and incubated for

20 minutes at room temperature. In the second step, group O cells (an indicator cell) were added; then, the tubes were centrifuged at 3000 rpm for 30 seconds. Anti- H agglutinates O cells but if the saliva contains the H substance, it is neutralized and cannot agglutinate O indicator cells. Therefore, positive agglutinated tubes were classified as non-secretor and negative ones as secretor [9].

All statistical analyses were performed using the statistical software SPSS 16.0.0. (SPSS Inc. Chicago, IL, U.S.A.). Two-sided *P*-values less than 0.05 were considered statistically significant. Continuous variables are expressed as mean (SD) or as median with minimal to maximal range (min-max). Categorical data are presented as number (percentage).

RESULTS

Fifty patients with psoriasis and 100 healthy individuals were recruited to this study. Baseline demographics and clinical characteristics of the study participants are summarized in table 1. The two groups were similar in age and gender (table 1).

The distribution of the Lewis phenotypes was significantly different between the two groups ($P<0.0001$ and table 2). The Le (a+b-) phenotype was observed with a higher frequency in patients with psoriasis in comparison with healthy controls ($P<0.001$, table 2). In addition, the Le (a-b-) phenotype was found with a higher frequency in psoriatic patients compared to healthy individuals ($P<0.0001$, Table 2). However, the Le (a-b+) phenotype was observed with a lower frequency in patients compared to controls (table 2). The two groups were significantly different with respect to the ABH non-secretor status which was found in 78% (39 out of 50 patients) and 26% (26 out of 100 controls) of the patients with psoriasis and healthy individuals, respectively ($P<0.0001$, table 2).

There was no significant association between the non-secretor status and the duration of the disease in psoriatic patients (median (range): 3 years (0.5-20) in non-secretors vs. 7 years (0.17-12) in secretors; $P=0.52$). The mean age at the onset of disease was not significantly different between

Table 1. Baseline demographic and clinical characteristics of patients with psoriasis and healthy controls

Characteristic	Patients (n=50)	Controls (n=100)	*P*-value
Gender			
Female	29 (58%)	57 (57%)	0.91
Male	21 (42%)	43 (43%)	
Age, years			
Mean±SD	43.12±10.89	43.25±11.26	0.94
Median (range)	42.5 (23-63)	43 (23-68)	
Age at onset of disease, year			
Mean±SD	37.93±12.00	-	
Duration of disease , year			
Median (range)	3 (0.5-20)	-	

Values are no. (%) unless otherwise noted.

Table 2. Distribution of ABO blood types, Lewis phenotypes and secretory status of patients with psoriasis and healthy controls.

	Patients with psoriasis (n=50)	Healthy controls (n=100)	*P*-value*
Lewis phenotypes			
Le (a+b-)	25 (50%)	21 (21%)	<.001
Le (a-b+)	9 (18%)	66 (66%)	<.0001
Le (a-b-)	14 (28%)	5 (5%)	<.0001
Le (a+b+)	2 (4%)	8 (8%)	0.35
Secretion phenotypes			
Non-secretor	39 (78%)	26 (26%)	<.0001
Secretor	11 (22%)	74 (74%)	

Values are no. (%) unless otherwise noted.
Note: A indicates A blood group; B, B blood group; O, O blood group; AB, AB blood group.
**P*-value for comparing the proportions between the two groups

non-secretor and secretor patients (38.58±12.16 years in non-secretors vs. 35.64±11.66 years in secretors; *P*=0.47).

The frequency distribution of the ABO blood types did not differ significantly between the two groups (Table 2).

DISCUSSION

It has already been demonstrated by several studies that a non- secretory state may directly or indirectly have a role on the etiology and pathogenesis of certain diseases. There are limited similar studies in psoriasis patients.

Gunput *et al.* reported that complement activation was significantly higher in secretors than in non-secretors. Activation of the complement can be effective in bacterial clearance and inhibiting colonization [10]. Nurjadi *et al.* showed that histo-blood group antigens may play an important role in modulating *Staphylococcus aurous* colonization; they found that individuals in the O/non-secretor group were at increased risk of carrying *S. aureus* in their throat while in contrast, colonization of *S. aureus* was prevented in the O/secretor group [11].

There are several reports about the higher prevalence of *Candida* spp. carriers and persistent candida infection in ABH non-secretors than secretors [12]. There is a study about a low level of IgA in the saliva and intestinal mucosa of non-secretor individuals. IgA has a characteristic role in mucosal immunity and is important in tolerance and protection against infections [13].

According to the mentioned studies, there might be an accelerated immune response due to chronic exposure to different antigens in non-secretor subjects. Although the role of histo-blood group antigens in psoriasis is not clear, it seems that more exposure to some microorganisms in non-secretor patients could trigger the immune response so these individuals may be prone to some inflammatory diseases such as psoriasis [5].

Without considering the secretory status, in some studies, the Lewis null phenotype Le (a-b-) is considered a genetic marker of susceptibility to several diseases such as ischemic heart disease, hyper coagulate state, diabetes mellitus, metabolic syndrome, autoimmune diseases including ankylosing spondylitis, psoriatic arthritis, etc. [2,3,5,14].

The result from NHLBI Family Heart Study showed that Le (a-b-) people were high risk for the development of ischemic heart diseases while individuals with a secretory phenotype were found to be protected against the development of ischemic heart diseases. It was suggested that the Le (a-b-) phenotype had the highest level of factor VIII and Von Willbrand factor and they might be at a higher risk for future thrombotic events and heart disease [15].

Lewis negative individuals are also at the greatest risk of developing diabetes and metabolic syndrome; Le (a-b-) men and syndrome X share a close genetic association on chromosome 19, so the Le (a-b-) phenotype is a genetic marker of insulin resistance syndrome [16].

Many previous studies have shown that psoriatic patients are at risk of developing atherothrombotic events, heart disease, metabolic syndrome, and dyslipidemia [1-3]. Lewis double negative ones Le (a-b-) are at the greatest risk of developing the same diseases as psoriatic patients; therefore, susceptibility to similar diseases in psoriatic patients and individuals with the Le (a-b-) phenotype suggests that the Lewis null phenotype gene may have an association with psoriasis [5].

Zhukova *et al.* tested some blood related genes in psoriatic patients and found that homozygosis for recessive allele Le was the risk factor for the development of psoriasis [17].

In this study, we found a higher frequency of the Le/b negative phenotypes, including Le (a-b-) and Le (a+b-) with a non-secretory status in our patients. It can be suggested that Lewis b negative people are at risk of developing psoriasis; therefore, inheriting the Le/b antigen may have a protective role in patients with psoriasis. In the future, we intend to have a prolonged fallow-up of these patients to confirm the theory that Lewis b negative individuals with psoriasis may be at an increased risk of psoriasis-associated diseases such as metabolic syndrome, and diabetes mellitus.

We suggest further investigation of Lewis phenotypes in patients with other types of psoriasis. Further studies on the role of histo-blood group antigens in the mechanism of psoriasis can result in a better understanding of this association.

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