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# The effectiveness of cognitive behavioral therapy based on Cash's eight-step model in body image of women with psoriasis

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**Background:** Psoriasis is a chronic autoimmune, complex and progressive disease having various physical, psychological and social consequences. This study aimed to investigate the effect of cognitive behavioral therapy on body image in women with psoriasis.

**Methods:** The research was semi-experimental with pre-test and post-test design in both experimental and control groups, and follow-up after 3 months of intervention. The statistical population included women with psoriasis. A total of 60 patients were selected as available samples and randomly were divided into control and treatment (experiment) groups. The research tool was the cash's Body Image Questionnaire (1987). Data were analyzed by the SPSS 24 software using the repeated measures analysis of variance.

**Results:** Cognitive behavioral therapy guidance reduced the image body anxiety and its two sub-scales in women with psoriasis, and this effect was permanent after three months.

**Conclusion:** Using this therapeutic approach, we can help to reduce the concern of the body image in patients with psoriasis.

**Keywords:** cognitive behavioral therapy, body image, psoriasis

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## INTRODUCTION

Skin diseases are considered among the most common human diseases in society, which may result in serious functional defects <sup>1</sup>. Psoriasis (also known as psoriasis in French, which means oysters) is a chronic and systematic inflammation disease <sup>2</sup>. The most common form of psoriasis is psoriasis vulgaris, which occurs as a circular plaque in the extensor parts of the body such as elbows, the lower back, and around the navel <sup>3</sup>. The disease is mostly seen in two age groups having the most likelihood of occurrence, i.e. the age range of 16-22 years, as well as 57-60 years <sup>4</sup>. The newest statistical analyses have revealed that the increasing prevalence rate of the disease among adults living in the United

States (91.9%), Norway (8.5%) and the United Kingdom (2.2%), but the lowest prevalence rates have been found in Latin America, India, Africa (Egypt and Tanzania) and Asia (less than 5%) <sup>5</sup>. Inheritance and environment play important roles in the emergence of the disease <sup>6</sup>. The devastating effects of this disease on the patients life quality, and their psychological and social backgrounds are as considerable as the problems and restrictions seen in diseases such as cancer, heart disease and diabetes <sup>7</sup>. Psoriasis also causes many psychological issues such as lack of self-esteem <sup>8</sup>, depression <sup>9</sup>, sexual dysfunction <sup>10</sup>, anxiety and suicide <sup>11</sup>. In addition, one of the main disappointments in patients with psoriasis is their body dysmorphic disorder having a serious relationship with skin

defects caused by psoriasis<sup>12</sup>. Therefore, physical image is a psychological component that is affected by the disease. Physical image includes the emotion that a person has of his or her body's features and structures<sup>13</sup>. In other words, the body image is related to beliefs, perceptions, thoughts or feelings and individual behaviors about his/her physical appearance<sup>14</sup>. Factors such as physical development, individual interactions with the social environment, accidents, diseases, and injuries can influence individuals' physical image. It can also be a source of concern for individuals<sup>15</sup>. Researchers maintain that diseases altering the structure of the body can change the mental image of the body<sup>14</sup>. Negative body image is a factor found in disorders such as depression<sup>16</sup> and sexual dysfunction<sup>17</sup>, as well as in chronic diseases<sup>18</sup>, including psoriasis. Hence, there is a high correlation between the physical and psychological functions in chronic diseases, reducing self-esteem<sup>19</sup> and leading to poor self-concept<sup>20</sup>. The progressive development of psoriasis and its treatment process are the factors negatively affecting the patients' view of their physical image compared to their healthy counterparts<sup>12</sup>. This is likely to be a result of mood, sexual and familial disorders<sup>21</sup> and facial deformities (especially in patients whose their appearance is important in their careers)<sup>22</sup>. For most patients, facial changes are very painful and even more difficult to deal with than internal organ involvement<sup>23</sup>, since the deformity of the face always reminds individuals of their illness. Therefore, they use emotion-focused adaptive mechanisms (such as avoiding aggression, self-criticism, etc.) impairing adaptation<sup>24</sup>. Furthermore, the vaster the damages to the face and hands, the more concerned patients become about their body image<sup>25</sup>. Various methods such as exercising<sup>26</sup>, cosmetic surgery<sup>27</sup> and relaxation therapy<sup>28</sup> have been suggested to encounter body image dissatisfaction. However, cognitive-behavioral therapy seems to be one of the most effective treatments of body image dissatisfaction<sup>29</sup>. Cognitive-behavioral therapy is based on evidence, strategies, and techniques with relevant scientific findings and is carried out through altering the person's incompatible cognitions as one of the major causes of negative thoughts. The use of this method improves the patient's emotional distress and suspicious behaviors<sup>30</sup>. In general, the cognitive behavioral therapy for body image

disorder includes psychology training, self-monitoring, cognitive reconstruction, prevention of negative stimuli exposure, and rigorous training<sup>31</sup>. Research in the field of cognitive-behavioral psychotherapy has demonstrated its success in improving the psychological status of individuals, as Rayegan *et al.*<sup>32</sup> have reported the positive impact of cognitive-behavioral therapy (based on the Cash model) on the negative body image among female students. Various studies have confirmed the impact of cognitive and behavioral therapy, including increase in the quality of life in patients with irritable bowel syndrome (IBS)<sup>33</sup>, elevation in the acceptance, commitment, and marital satisfaction of young couples<sup>34</sup>, reduction in depression, and increase in the satisfaction with marriage in women with postpartum depression disorder<sup>35</sup>. In addition, it helps patients in the treatment process of insomnia disorder<sup>36</sup>, reduces the recurrence of depression<sup>37</sup>, and increases the acceptance and commitment of social phobia<sup>38</sup>. Regarding the vast spectrum of the effectiveness of cognitive-behavioral therapy, the main question of the present study is whether the group cognitive-behavioral therapy based on Cash's eight-step model is effective in improving negative body image in women with psoriasis.

## MATERIALS AND METHODS

The present study used a quasi-experimental design with a pre-test and post-test followed by a 6-week follow-up. The statistical population included all women with psoriasis referred to Razi Dermatology Hospital during the second semester of 2018. The inclusion criteria were 1. Passing at least one year since the diagnosis, 2. Having an age of 20-35 years old, 3. Being female, 4. Having a minimum education level of reading and writing. In addition, the exclusion criterion was absence in the intervention sessions for 3 times. Using the recorded patient information collected from offices of hospitals and after initial interviews with each patient (initiation and clinical diagnosis), 60 patients willing to be included in the study were selected by availability and purposeful sampling methods. The patients were randomly assigned to two experimental and control groups. Prior to the intervention and in a dedicated session, the ethical considerations were described for the patients. The



patients were familiarized with the nature and objectives of collaboration in the research, gave written informed consent forms, and they were informed that the researcher was committed to keeping all the information confidential. Six sessions of intervention were held for the experimental group (each session lasted 60 to 90 minutes, in a course of 3 weeks). The tools applied in this study included the following:

To collect data, a multidimensional body-self relations questionnaire (MBSRQ) was used, which consisted of two parts of demographic and personal information in 46 items. MBSRQ is a self-assessment scale made by Cash<sup>39</sup> to evaluate body image. There are six subscales in this instrument, including appearance evaluation (AE), appearance orientation (AO), fitness evaluation (FE), fitness orientation (FO), subjective weight (SW), and body areas satisfaction (BAS). The subscale of appearance evaluation involves seven questions with a score range of 7-35. The appearance orientation subscale has twelve questions with minimum and maximum scores of 12 and 60, respectively. The subscale of fitness evaluation has three questions with a score range of 3-15. The subscale of fitness orientation includes thirteen questions with a score range of 13-65. The subscale of subjective weight has two questions with a score range of 2-10. The subscale of body areas satisfaction consists of nine questions with a score range of 9-45. A number of items are reverse-scored questions. The total score obtained by summing subscale scores is considered the total score of body image, which will be in a range of 46 to 230. The individuals are requested to mark their degree of agreement with each question on a five-point scale (completely disagree to completely agree). The responses are scored from 1 to 5 based on the Likert scale. A higher score on MBSRQ indicates greater body satisfaction<sup>32</sup>.

Psychometric characteristics of this tool have been approved in many international studies like the one conducted by Annis *et al.*<sup>10</sup>. Rahati conducted research in Iran<sup>41,42</sup> and found a correlation (0.55) between body image and self-esteem ( $P < 0.001$ ). Cronbach's alpha values of 0.85, 0.60, 0.76, 0.46, 0.79, 0.80, and 0.81 were obtained for the total body image and subscales of AE, AO, FE, FO, SW, and BAS among 217 female subjects, respectively. During a study on 67 samples, the correlation coefficient between the scores of two tests during a two-week

interval was calculated to be 0.78 for appearance evaluation, 0.75 for appearance orientation, 0.71 for fitness evaluation, 0.69 for fitness orientation, 0.84 for subjective weight, and 0.89 for body areas satisfaction, which all indicate appropriate test-retest reliability of the scale. In addition, Cronbach's alpha values of the total scale and its subscales in the research conducted by Raghibi and Minakhani<sup>43</sup> were 0.74, 0.74, 0.80, 0.76, 0.66, 0.78, and 0.71, respectively. In this research, the reliability was confirmed via Cronbach's alpha with the values of 0.88, 0.80, 0.91, 0.84, 0.79, 0.90, and 0.82, respectively.

The intervention group, received cognitive-behavioral body image therapy based on the Cash's eight-step model in six sessions of 60 to 90 minutes during three weeks (twice a week), while the control group did not receive any training related to body image but regular care. After 6 weeks, the post-test was conducted on both groups by completing MBSRQ, measuring their weight, and calculating body mass index. The framework and content of cognitive-behavioral therapy sessions (Table 1) were designed and implemented based on Cash's eight-step model (2008). In the first session, a teamwork package was distributed to the subjects, and its summary on pamphlets was presented to the subjects to be reviewed.

The data obtained from 60 participants (30 in the intervention group and 30 in the control group) were analyzed using the IBM SPSS (Statistical Package for the Social Sciences) software version 24. First, we used the Shapiro-Wilk test to assure that the obtained data on the variables had a normal distribution; therefore, the condition of parametric tests is available. The entire comparisons were made between two domains, and the significance level was considered  $P < 0.05$ . To describe the sample, descriptive statistics including mean and standard deviation were used, and to compare dependent variables in both intervention and control groups, independent T-test was used. We applied Levene's Test to assess the homogeneity of variances of dependent variables calculated in both intervention and control groups as presuppositions in order to use the analysis of covariance (ANCOVA) test. This test was used to evaluate the effectiveness of cognitive-behavioral therapy in a total score of body image and its constructs. Furthermore, the effects of some intervening variables such

**Table 1.** Framework and contents of cognitive-behavioral therapy sessions

Session	Description
1st Session	Introduction, the definition of body image and the problems arising from body dissatisfaction, group discussion about appearance changes related to psoriasis; body image self-assessment tests
2nd Session	Recognizing negative body image roots in the past and present; training mindful self-monitoring technique; training body image ABCs; training to write a daily diary of body image; implementing mirror reflection technique
3rd Session	Reviewing assignments; training mindfulness and acceptance techniques; training systematic desensitization technique; recognizing and correcting current hypothesis related to the appearance; recognizing and correcting cognitive distortions of appearance
4th Session	Reviewing assignments; training, understanding, and confronting with body image evasive actions such as escaping and hiding; understanding, confronting, delaying, and restricting obsession techniques of appearance; the technique of exposure and response prevention
5th Session	Reviewing assignments; relaxation training; diaphragmatic breathing and mental imagery; training to meet body's rights; exercising positive and suitable physical activities; training to enjoy time following improvement of fitness and appearance, as well as amplifying sentence
6th Session	Reviewing assignments; training protective methods of positive body image; confronting with people who disturb the patients' body image; examining the participants' progress; continuing to use the skills acquired in training

as age, weight in the post-test stage, body mass index in the post-test stage, and education level were considered.

## RESULTS

Participants with a minimum age of 20 and a maximum age of 33 were selected in the intervention group. The mean and standard deviation values were calculated to be  $25.64 \pm 3.18$ . Furthermore, patients with a minimum age of 20 and a maximum age of 34 were selected in the control group. The mean and standard deviation values were calculated to be  $25.23 \pm 3.97$ . The results of the independent T-test showed no statistically significant difference between the two groups in terms of age ( $P = 0.681$ ).

Moreover, the minimum, maximum, and mean values of weight in the intervention group were 37.50, 87.00, and  $59.00 \pm 10.72$  kg, respectively. In addition, the mentioned values were 42.30, 85.20, and  $60.22 \pm 10.12$  kg in the control group, respectively. According to the results obtained from the independent T-test, there was no statistically significant difference between the two groups in terms of weight ( $P = 0.649$ ). In the intervention group, the mean height was  $158.19 \pm 8.23$  cm, which was in the range of 142.00 to 177.00 cm, while in the control group, it was  $159.15 \pm 6.63$  cm, which was in the range from 146.00 to 173.00 cm. The results obtained from the independent T-test showed no statistically significant difference between the two groups in terms of height ( $P = 0.620$ ). Moreover, the minimum and maximum values of the body mass index in the intervention group were 16.89 and 29.87, respectively, with the mean of  $23.74 \pm 3.39$ .

According to the results of the independent T-test ( $P = 0.878$ ), these values were not significantly different from those of the control group.

In addition, the Chi-square test showed no significant difference between the two groups of intervention and control in terms of education level ( $P = 0.7$ ).

The independent T-test showed that the scores of body image ( $P = 0.7$ ), appearance evaluation ( $P = 0.7$ ), appearance orientation ( $P = 0.5$ ), fitness evaluation ( $P = 0.8$ ), fitness orientation ( $P = 0.8$ ), subjective weight ( $P = 0.4$ ), and body areas satisfaction ( $P = 0.5$ ) were not significantly different between the two groups in the pre-test stage. In the post-test stage, however, there was a statistically significant difference in the subscale of appearance evaluation ( $P = 0.016$ ). Table 2 presents the mean and standard deviation of scores in the whole-body image and its constructs (in MBSRQ) in both intervention and control groups in pre-test and post-test stages.

Considering age, post-test weight, post-test body mass index, education level, and ethnicity variables as covariate and controlling the pre-test scores, the results of analysis of covariance (ANCOVA) for each variable demonstrated that the mean score of appearance evaluation ( $P = 0.0001$ ), mean score of body areas satisfaction ( $P = 0.0001$ ), and mean score of body image ( $P = 0.0001$ ) in the post-test stage in the intervention group were significantly higher than the corresponding scores in the control group. In other words, the cognitive-behavioral body image therapy changed the variables among the participants of the intervention group. Table 3 present a summary of the results of the analysis



**Table 2.** Mean and standard deviation of scores of whole-body image in both intervention and control groups in pre- and post-intervention stages

Variable Group	Intervention Group		Control Group	
	Pre-Intervention	Post- Intervention	Pre-Intervention	Post- Intervention
Appearance evaluation	22.61 ± 5.33	24.83 ± 4.43	23.10 ± 5.31	21.08 ± 5.15
Appearance orientation	47.54 ± 6.07	49.93 ± 5.77	46.60 ± 6.40	49.90 ± 6.28
Fitness evaluation	10.51 ± 2.77	10.06 ± 2.59	10.66 ± 2.60	10.53 ± 2.83
Fitness orientation	42.64 ± 8.96	41.74 ± 8.40	43.06 ± 9.20	41.46 ± 8.48
Subjective weight	5.87 ± 2.39	6.12 ± 2.20	6.33 ± 2.27	6.16 ± 2.24
Body areas satisfaction	30.29 ± 6.07	33.45 ± 5.39	31.26 ± 5.83	31.33 ± 5.12
Body image	159.48 ± 23.14	166.16 ± 20.81	161.03 ± 22.56	159.20 ± 22.39

**Table 3.** Results of analysis of covariance of the effectiveness of cognitive behavioral therapy in primiparous women's body image upon control of pre-test scores and some demographic variables

Origin of Changes	Total squares	Degree of freedom	Mean squares	The variance ratio test (F test)	P-Value	Degree of effectiveness	Test power
Age	89.55	1	89.55	1.29	0.26	0.025	0.20
Education level	196.75	1	196.75	2.44	0.10	0.054	0.38
Ethnicity	3.33	1	3.33	0.05	0.83	0.001	0.06
Post-test body mass index	91.51	1	91.51	1.32	0.26	0.026	0.20
Post-test weight	174.57	1	174.57	2.52	0.12	0.048	0.34
Group	984.29	1	984.29	14.18	0.00	0.221	0.59
Error	3471.03	50	69.42				
Total	1643777.00	61					

of covariance related to the effectiveness of the intervention in body image scores.

However, there was no significant difference between the intervention and control groups in the mean of appearance orientation ( $P = 0.4$ ), fitness evaluation ( $P = 0.5$ ), fitness orientation ( $P = 0.2$ ), and subjective weight ( $P = 0.3$ ) in the post-test stage via analysis of covariance test.

## DISCUSSION

This research was conducted to evaluate the effects of cognitive-behavioral therapy on the body image of women suffering from psoriasis who were referred to Razi Hospital in Tehran in 2018. The results demonstrated that group cognitive behavioral therapy based on Cash's eight-step model was a suitable method to improve total body image and some of its aspects among women with psoriasis. The findings of this study are in line with the results of previous studies focusing on the effect of cognitive-behavioral therapy on other groups, including the effectiveness of cognitive-behavioral therapy in negative body image<sup>44-46</sup>, body image of women under mastectomy<sup>47</sup>, and body image of Iranian girl students<sup>32</sup>.

To explain the findings, it can be mentioned

that psoriasis has many physical consequences altering the appearance and mental self-image. Accordingly, the perception of body image influences different aspects of one's life like inner experiences (feelings, behavioral desires, thoughts, etc.) in different situations<sup>48</sup>. Therefore, it is an essential factor in determining the way to interact with others<sup>15</sup>. An inappropriate perception of body image and dissatisfaction with it can lead to physical and psychological complications<sup>49</sup>. In this study, we attempted to inform our patients of the cognitive-behavioral psychotherapy group about their physical and psychological conditions by establishing an appropriate therapeutic relationship and empathizing with patients, along with raising their awareness<sup>50</sup>.

Raising awareness makes patients to be aware of their here-and-now experiences with interest and acceptance, changes their view on the usefulness of dealing and coping with his thoughts and emotions, and lead them to correct their unpleasant emotions. Therefore, patients will feel that they have more control over his/her emotions<sup>51</sup>. Raising awareness is based on the acceptance of unpleasant thoughts and different emotional states, and will dramatically enhance patients' ability to control the influence of their thoughts, in

addition to heightening their emotions. This will allow the patient to experience various thoughts and emotions without experiencing emotional disturbance<sup>52</sup>. When patients gain acceptance over their inner experiences, even painful and unpleasant emotions, thoughts, memories, and feelings, they do not find them to be intimidating or intolerable. Becoming aware of this strategy will help patients to change their relationship with their painful thoughts and feelings, and lessen their impact on their lives. In other words, psychological flexibility allows patients to respond to new experiences with openness and accept events as they are<sup>53</sup>. Raising awareness will assist the patients to cope with their negative thoughts (dissatisfaction and body image concern) impeding their emotional well-being and maintaining their emotional stability. Emotional stability enables patients not to focus on disturbing thoughts, and let them pass through their minds, thereby enabling them to overcome their negative spontaneous thoughts and emotions. Raising awareness and paying more attention to emotions and thoughts also make the patient to act more responsibly and effectively. Moreover, being in a group and listening to other patients' personal experiences determine where patients stand, thereby enabling them to cope with the catastrophe, because they achieve the notion that they are not the only ones suffering in this group. This interventional process gives them hope and, ultimately, the ability to regulate their behavior, thoughts, feelings, and performance, and lessen the psychological effects of the illness<sup>54</sup> such as body image and mental and behavioral components. For example, instead of avoiding oneself and others, patients engage in courageous behaviors, and instead of focusing on eliminating the traumatic factors of the disease and its consequences, patients accept emotions and thoughts and quit conflicting with them. Therefore, each of the components of cognitive-behavioral therapy can play a crucial role in reduction of anxiety about body image.

## CONCLUSIONS

The results confirmed the effectiveness of cognitive-behavioral therapy based on Cash's eight-step model in body image and several considerable body image constructs such as appearance evaluation and body areas satisfaction among

women suffering from psoriasis. We can use this appropriate treatment simply, for example, in the form of a self-study booklet to improve the problems associated with body image among different groups of patients. A positive mental image of the body will result in promoting patients' mental health, improving self-confidence, enhancing the degree of satisfaction and quality of their relationships, and finally experiencing a more pleasant life.

**Conflict of Interest:** None declared.

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# The quality of life and its related factors in patients with psoriasis

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**Background:** Psoriasis is a chronic disease that may affect patients' quality of life. We investigated the quality of life (QoL) and its related factors in psoriasis patients.

**Methods:** In this cross-sectional study, 123 patients with psoriasis vulgaris were enrolled, who were at the age of 18-55 years. The QoL was assessed by the psoriasis disability index (PDI) questionnaire. The stress associated with psoriasis was evaluated by the psoriasis life stress inventory (PLSI) questionnaire. The severity of the disease (SoD) was measured based on the psoriasis area and severity index (PASI) score.

**Results:** In this study, the mean age of the patients was  $40.77 \pm 0.73$  years, and the mean duration of the disease was  $8.7 \pm 8.23$  years. The average PASI score was 11.06, and the average PDI score was 11.98. The average PDI and PASI scores of smoker patients were significantly more than those of non-smokers ( $P = 0.017$ ). There was a strong relationship between all parts of QoL and PLSI scores, as well as between PASI and PLSI ( $P < 0.05$ ).

**Conclusions:** Psoriasis reduced our patients' quality of life. Thus, it is recommended that the QoL in psoriatic patients be evaluated. Stress management and psychological supporting methods are necessary for these patients.

**Keywords:** psoriasis, quality of life, life stress

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## INTRODUCTION

Psoriasis is an inflammatory systemic disorder having a chronic and relapsing course <sup>1</sup>. Stress may cause disability in psoriasis patients, resulting in major impacts on patients' quality of life (QoL), severity of disease (SoD), and therapeutic response <sup>2</sup>. Many patients have poor body image or low self-confidence, poor mental fitness, defamation feeling, shame and embarrassment due to their appearance <sup>3</sup>. Additionally, most patients report moderate to severe anxiety, anger, and depression. It appears that an increase in the severity of psoriasis is closely associated with the severity of depression and consequently with an increase in the number of suicidal thoughts <sup>4</sup>.

Assessment of patients' QoL allows evaluation of the effects of psoriasis and its treatment on their function <sup>3</sup>.

Owing to the lack of sufficient and new studies on the QoL of psoriasis patients in our country as well as potential negative effects of this disease on the patients' QoL, this study aimed to determine the QoL and its effective factors in Guilan Province, Iran.

## PARTICIPANTS AND METHODS

This analytical cross-sectional study was conducted in Guilan, Iran, from March 2016 till March 2017. A total of 123 patients with psoriasis referred to the educational dermatology clinic at Razi Hospital were enrolled. The inclusion criteria



were as follows: all patients with the vulgaris type of psoriasis confirmed by a dermatologist, and being aged between 18-55 years. Exclusion criteria were as follows: other autoimmune skin disorders (such as vitiligo, lichen planus, and alopecia areata), pregnancy and lactation. The data collection tool in this study was a questionnaire consisting of 4 parts:

### **General**

This included demographic characteristics (age, sex, body mass index), social history (marital status, educational level, occupation, housing status, income, smoking, alcohol intake, and substance abuse), and disease characteristics (duration of disease, involved regions, complications), history of other skin diseases, comorbidities, history of hospitalization, type of treatment, and sampling season.

### **Psoriasis Area and Severity Index (PASI)**

According to the PASI score, the patients were divided into three groups: mild ( $PASI > 12$ ), moderate ( $12 \leq PASI \leq 25$ ) and severe ( $PASI > 25$ )<sup>5</sup>.

### **Psoriasis Disability Index (PDI)**

PDI was used to evaluate the effects of psoriasis on patients' QoL. This part included 15 questions assessing five components of patients' QoL: daily activities, occupational conditions, interpersonal communications, leisure time, and treatment. All questions referred to the events of the last 4 weeks. Answers were scored from zero to 3 (zero: never, 1: little, 2: high, 3: very much); a higher score indicated lower QoL. The PDI was used in Persian.

### **15-item Psoriasis Life Stress Inventory (PLSI)**

This was used to measure the stresses associated with daily life events. The patients were requested to choose only one option (never: 0, mild: 1, moderate: 2, high: 3) based on the stress experienced during the last 4 weeks. Based on the overall score of PLSI, the patients were divided into two groups: high-stress (score  $\geq 10$ ) and low-stress (score  $< 10$ ).

Since the PLSI questionnaire had not been validated in our country, in this study, the

“backward-forward” method was used as a guide for intercultural adaptation to evaluate the validity of this questionnaire in both English and Persian languages. At this step, two bilingual experts translated the questionnaire from English into Persian. Then, the primary draft of the questionnaire was prepared. Subsequently, a bilingual expert translated the questionnaire from Persian into English, and the final version of the questionnaire was prepared. After this step, the research team compared the original English questionnaire to the final version. The Persian questionnaire was finally approved after few corrections. To evaluate the content validity of the Persian questionnaire, 10 dermatologists and psychologists were asked to independently determine the relevance of the items in the questionnaire with its overall content in terms of four criteria: simplicity, clarity, relevance, and necessity. After receiving the experts' opinion, content validity was calculated using Content Validity Index (CVI) and Content Validity Rate (CVR) coefficients for the translated questionnaire. The calculated CVI and CVR of each question were in the range of 0.7-1 and 0.8-1, respectively. Overall clarity, relevance, and simplicity of the questionnaire were 0.89, 0.91, and 0.86, respectively. Owing to the calculated CVR value of more than 0.62, no question was deleted from the questionnaire. In cases with the CVI between 0.7-0.9, questions were revised.

To determine the internal consistency, the Cronbach's alpha coefficient was calculated in 30 patients, which was 0.879. It was considered valid, since the value was higher than 0.7. The Ethics Committee of GUMS approved the study.

### **Statistical analysis**

All statistical analyses were conducted by the SPSS software version 18. Quantitative variables were described using mean and standard deviation, and qualitative variables were described using number and percentage. Normal distributions of the quantitative variables were measured using the Kolmogorov-Smirnov test. The total score of QoL and its components were compared to other variables using t-test, one-way ANOVA, Mann-Whitney test and Kruskal-Wallis test. Correlation between QoL and SoD was measured by the Spearman correlation coefficient. Linear regression with robust was used to assess the effects of

different variables on QoL. The significance level of all tests was considered a  $P$  value  $< 0.05$ .

## Ethics

The Ethical Committee of Guilan University of Medical Sciences approved the present study. All participants fulfilled informed consent.

## RESULTS

A total of 123 patients aged 18-55 years were enrolled (Tables 1 & 2). We found a significant

**Table 1.** Demographic characteristics of patients

Variables	N=123
Male/female	80/43
Age (mean $\pm$ SD) (years)	40.77 $\pm$ 10.73
Smoking	30 (24.4%)
Ex-smoker	11 (8.9%)
Alcohol use	11 (8.9%)
Drug abuse	8 (6.5%)
Body mass index (kg/m <sup>2</sup> )	
< 18.5	1 (0.8%)
18.5-24.9	37 (30.1%)
25-29.9	53 (43.1%)
> 30	32 (26%)
Level of education	
Less than High school	62 (50.4%)
High school	40 (32.5%)
Bachelor's degree	10 (8.1%)
Postgraduate degrees	11 (8.9%)
Occupation	
Unemployed	48 (39.0%)
Employed	61 (49.6%)
Retired	14 (11.4%)
Marital status	
Married	97 (78.9%)
Single	23 (18.7%)
Widowed	2 (1.6%)
Divorced	1 (0.8%)
Housing	
Personal property	90 (73.1%)
Leased	33 (26.9%)
Household income	
< 100 US dollars	37 (30.1%)
100-200 US dollars	61 (49.6%)
200-400 US dollars	22 (17.9%)
400 US dollars $\leq$	3 (2.4%)
Season of sampling	
Spring	37 (30.1%)
Summer	51 (41.5%)
Autumn	27 (22%)
Winter	8 (6.5%)

relationship between the patients' QoL and occupational conditions, disease complications, type of treatment, and substance abuse (Table 3).

There was an inverse but non-significant statistical correlation between age and QoL of the patients ( $r = -0.037$ ,  $P = 0.682$ ). Positive but non-significant statistical correlation was found between patients' QoL and body mass index (BMI) ( $r = 0.066$ ,  $P = 0.66$ ) as well as duration of the disease ( $r = 0.140$ ,  $P = 0.122$ ).

Furthermore, we found a significant positive correlation between most components of the patients' QoL, including daily activity, occupational conditions and leisure times, and severity of disease (SoD) ( $r = 0.294$ ,  $P = 0.001$ ;  $r = 0.298$ ,  $P = 0.001$ ;  $r = 0.267$ ,  $P = 0.003$ , respectively).

However, there was a positive non-significant correlation between other parts of the patients' QoL including personal communication and type of treatment, and SoD ( $r = 0.173$ ,  $P = 0.056$ ;  $r = 0.161$ ,  $P = 0.076$ , respectively). Moreover, we found a

**Table 2.** Patients' clinical characteristics

Variables	N=123
Regions of involvement	
Trunk	100 (81.3%)
Head	99 (80.4%)
Upper extremity	103 (83.7%)
Lower extremity	97 (78.8%)
Palmoplantar	29 (23.5%)
Psoriasis side effects	67 (54.5%)
History of other skin diseases	14 (11.4%)
A positive history of comorbidities	52 (42.3%)
History of hospitalization due to psoriasis	15 (12.2%)
Type of treatment	
Topical	63 (51.2%)
Systemic	4 (3.3%)
Both	49 (39.8%)
None of them	7 (5.7%)
Psoriasis severity	
Mild	83 (67.5%)
Moderate	31 (25.2%)
Severe	9 (7.3%)
Quality of life (mean $\pm$ SD)	
Daily activity (0-15)	5.35 $\pm$ 3.56
Occupational factors (0-9)	1.65 $\pm$ 2.53
Interpersonal communication (0-6)	1.05 $\pm$ 1.50
Leisure (0-12)	3.01 $\pm$ 3.02
Treatment (0-3)	0.89 $\pm$ 0.92
Total score (0-45)	11.98 $\pm$ 9.19
Psoriasis life stress inventory	
Low stress	32 (26.8%)
High stress	90 (73.2%)

**Table 3.** Patients' quality of life mean scores in terms of demographic and clinical characteristics

Variables	Mean ± SD	P
Sex		
Male	12.98 ± 10.16	0.278
Female	10.11 ± 6.79	
Smoking		
Yes	16.26 ± 11.22	0.017
Ex-smoker	13.45 ± 6.77	
No	10.21 ± 8.14	
Alcohol use		
Yes	11.54 ± 8.55	0.999
No	12.02 ± 9.29	
Drug abuse		
Yes	17.25 ± 9.61	0.079
No	11.61 ± 9.09	
Level of education		
Less than High school	11.46 ± 8.48	0.961
High school	12.17 ± 7.92	
Bachelor's degree	11.70 ± 10.17	
Postgraduate degrees	11.27 ± 10.85	
Occupation		
Unemployed	10.31 ± 6.68	0.002
Employed	14.26 ± 9.35	
Retired	6.35 ± 4.32	
Marital status		
Married	12.75 ± 9.61	0.298
Single	9.26 ± 7.26	
Widowed and divorced	8 ± 1	
Housing		
Personal property	11.39 ± 8.21	0.172
Leased	10.72 ± 9.45	
Household income		
< 100 US dollars	14.56 ± 11.30	0.535
100-200 US dollars	10.86 ± 8.57	
200-400 US dollars	10.72 ± 6.05	
400 US dollars ≤	12 ± 9.53	
Psoriasis side effects		
Yes	14.1 ± 10.31	0.015
No	9.44 ± 6.93	
History of other skin diseases		
Yes	11.14 ± 8.39	0.905
No	12.09 ± 9.32	
Comorbidities		
Yes	13.07 ± 9.02	0.144
No	11.18 ± 9.30	
History of hospitalization due to psoriasis		
Yes	16.53 ± 11.63	0.111
No	11.35 ± 8.68	
Type of treatment		
Topical	8.97 ± 7.52	< 0.001
Systemic	11.25 ± 11.41	
Both	16.88 ± 9.44	
None of them	5.29 ± 3.77	

significant correlation between the total score of QoL and SoD ( $r = 0.338$ ,  $P < 0.001$ ). In addition, there was a significant correlation between PLSI score and SoD ( $r = 0.378$ ,  $P < 0.001$ ).

Table 4 shows the mean scores of patients' QoL based on PASI and PLSI mean scores.

No significant statistical relationship was found between the patients' QoL in terms of daily activity, interpersonal communication and treatment, and SoD ( $P = 0.061$ ,  $0.458$ ,  $0.148$ , respectively). In addition, we found an association between PDI mean score in terms of occupational conditions, leisure times and overall score, and SoD ( $P = 0.002$ ,  $0.019$ ,  $0.006$ , respectively). These scores were higher in individuals with moderate SoD than in those with low SoD.

All components of QoL, including daily activity, occupational conditions, interpersonal communication, leisure times, type of treatment and total score, were significantly and positively correlated with the PLSI score ( $r = 0.553$ ,  $P < 0.001$ ;  $r = 0.466$ ,  $P < 0.001$ ;  $r = 0.481$ ,  $P < 0.001$ ;  $r = 0.654$ ,  $P < 0.001$ ;  $r = 0.477$ ,  $P < 0.001$ ;  $r = 0.707$ ,  $P < 0.001$ , respectively).

The mean score of all parts of QoL, including daily activity, occupational conditions, interpersonal communication, leisure times, type of treatment, total score and PASI score, were significantly higher in patients with high stress than in those with low stress ( $P < 0.001$  for all).

Based on the results of linear regression with robust correction, the QoL score in patients who received both topical and systemic treatment was 3.75 times more than those who received topical treatment ( $P = 0.004$ , 95% CI 1.198, 6.305,  $B = 3.75$ ). Stress is one of the determinants of low QoL in patients with psoriasis ( $P < 0.001$ , 95% CI 0.394, 0.654,  $B = 0.52$ ).

## DISCUSSION

In our study, there was no significant association between sex and QoL, similar to the reports by Zandi, *et al.*<sup>2</sup>, Milcic, *et al.*<sup>5</sup> and Nabaei, *et al.*<sup>3</sup>. In addition, age was not significantly associated with QoL in our patients, being consistent with the study conducted by Zandi *et al.* study<sup>2</sup>. However, in the study conducted by Javidi *et al.*<sup>6</sup>, the disability index was significantly higher in men aged 35-45 years, which could be due to the greater role of men in this middle age group in society and

**Table 4.** Patients' quality of life mean scores in terms of clinical disease severity and PLSI\* mean score

Quality of life	Daily activity	Occupational factors	Interpersonal communication	Leisure	Treatment	Total score
Psoriasis severity						
Mild	4.83 ± 3.58	1.15 ± 2.05	0.87 ± 1.27	2.53 ± 2.54	0.81 ± 0.82	10.21 ± 8.25
Moderate	6.41 ± 3.60	3.12 ± 3.18	1.54 ± 2.04	4.58 ± 3.73	1.19 ± 1.10	11.44 ± 6.14
Severe	6.55 ± 2.18	1.22 ± 2.38	1.00 ± 1.00	2.11 ± 2.75	0.55 ± 0.88	11.44 ± 6.14
P-value	0.061	0.002	0.458	0.019	0.148	0.006
PLSI						
Low stress	3.39 ± 2.74	0.48 ± 1.17	0.39 ± 0.74	1.09 ± 1.54	0.42 ± 0.56	5.78 ± 5.26
High stress	6.07 ± 3.57	2.08 ± 2.75	1.03 ± 1.63	3.72 ± 3.12	1.06 ± 0.96	14.25 ± 9.30
P-value	<0.001	0.002	0.003	<0.001	0.001	<0.001

\*Psoriasis Life Stress Inventory

economy and the more negative impact of the disease in this age group.

No significant relation was found between the levels of education and the QoL in our study, being consistent with the study conducted by Nabaei, *et al.*<sup>3</sup>. On the contrary, Milcic *et al.* showed that lower level of education decreased QoL (5).

Occupational status was significantly related to QoL in our patients. Workers have more stress due to their exposure to skin lesions, which may have more negative impacts on their QoL. Based on our knowledge, the relation between the PDI score and occupational status was not evaluated in prior studies.

The PDI score was higher than in married individuals than in single adults in our study, which could be due to familial and marital stress; however, there was no significant relationship between QoL and marital status. In the study conducted by Ansar *et al.*<sup>7</sup>, married subjects had a higher QoL than single subjects. Furthermore, in the study conducted by Nebaei *et al.*<sup>3</sup>, married patients had a better QoL. These differences in the results could be due to differences in sampling, location of the study and data collection tools.

In our study, the PDI score was higher in individuals living in their own homes, but there was no significant relationship between the status of housing and QoL. Another study evaluating this variable was not found.

There was no significant relationship between income status and QoL in our study, but Nabaei, *et al.* reported that psoriasis patients had a significantly lower income<sup>3</sup>. It should be noted that patients may report lower owing to their concern for data recording.

A lower number of our patients visited in

the winter may be justified due to bad weather conditions in our province. Lack of significant relation between season and QoL could be explained by the method of sample collection and the number of subjects referred to the hospital in each season.

In our study, smoker patients had a lower QoL. In the study by Ashkevari *et al.*, there was a statistically significant difference in the amounts of smoking in between the psoriasis group and the control group<sup>8</sup>. Fortes *et al.* showed that the risk of severe psoriasis in people who consumed more than 20 cigarettes per day was two times more than those who consumed 10 cigarettes or less<sup>9</sup>. Psoriasis results from disturbances in the immune system. Nicotine may induce a range of intrinsic and adaptive immune responses, affecting the function of antigen-presenting cells. These cells increase the function of the immune system cells by releasing pro-inflammatory cytokines associated with the pathogenesis of psoriasis<sup>8</sup>; Therefore, the relation between QoL and smoking was predictable.

There was no significant relationship between drug abuse and QoL in our patients. According to the previous studies, alcohol consumption may be associated with the risk of progression or worsening of the disease<sup>10</sup>. Nevertheless, in our study, due to the low number of people who consumed alcohol because of religious issues, the relation between alcohol and QoL may not be well appraised; this can be true for the use of other erotic drugs. There was no similar study investigating the relation between alcohol, drug abuse, and QoL in psoriasis patients.

The duration of the disease was not significantly associated with QoL in our study, being consistent with the studies conducted by Zandi, *et al.*<sup>2</sup> and Milcic, *et al.*<sup>5</sup>.

Psoriasis patients with disease complications had a lower QoL in our study, being in line with the results obtained by Firooz *et al.*<sup>11</sup> and Rosen, *et al.*<sup>12</sup>. However, nail involvement in our study was considered a complication of the disease and therefore it was not possible to assess the relation between nail involvement and QoL separately. Furthermore, in our study, nail involvement was determined just based on clinical examination without any laboratory investigation for fungal infections, which could be one of the limitations of our study. Moreover, joint involvement was considered based on patients' history and physical examination, but in other studies, arthropathy was confirmed by a rheumatologist.

There was no significant relation between other skin diseases and the QoL in our patients. We found no study describing the relation between the history of other skin diseases and QoL in psoriasis patients.

No significant relationship between the incidence of comorbidities and the QoL of patients was found, which may be owing to the rapid initiation of the treatment for comorbid diseases.

Although the QoL score was higher in patients with a history of hospitalization, it did not show a significant relation, which may be due to the low number of patients with a history of admission.

In our study, there was a significant relationship between QoL and type of treatment; therefore, those patients received both topical and systemic treatment compared to patients who used only topical therapy. Additionally, patients who did not receive any treatment had lower QoL. Therefore, it could be concluded that SoD is higher in those who used both types of treatment. Furthermore, lower QoL for these patients could be due to frequent referring for more treatment. In the study conducted by Fortune *et al.*<sup>13</sup>, similar to our study, QoL was lower in those who used both systemic and topical treatments, compared to patients who used only systemic therapy or topical treatment, but the difference was not significant.

The mean PDI score in patients with moderate psoriasis was significantly different from that in patients with mild psoriasis. However, this score was lower in patients with severe psoriasis than in those with moderate psoriasis, which could be due to the lower number of people with severe psoriasis. There was also a significant correlation

between the total score of the PDI and the PASI score. In other words, patients with a more severe disease had lower QoL.

In general, patients with higher SoD had more problems in hairdressing, bathing or some clothing. In terms of occupational status, higher SoD could result in absence from work or avoidance of some activities in the workplace. In another study on the occupational function of patients with severe psoriasis, the occupational inefficiency was significantly higher in the course of the disease<sup>14</sup>.

In our study, patients with a higher SoD had more problems in exercising and swimming.

The lack of relationship between interpersonal communication and SoD in our patients may be explained by the fact that the disease has been accepted by their spouses, friends, and relatives; therefore, they have been able to become compatible with their disease. The lack of effect on sexual intercourse in most patients could be explained by the culture of society and patients' embarrassment.

The treatment was not significantly related to SoD; it might be concluded that patients have been able to adapt themselves over time.

In the study conducted by Milcic *et al.*<sup>5</sup>, the components of daily activity, occupational condition and leisure time were significantly associated with QoL, being consistent with our results. In the study by Kumar *et al.*<sup>15</sup>, there was a significant correlation between PASI and PDI overall score, but none of the components was separately investigated. In the study by Nabaei *et al.*<sup>3</sup>, the PDI score was significantly higher in severe psoriasis than in mild or moderate psoriasis.

In our study, there was a significant relationship between all aspects of QoL and its total score, and stress. Patients with higher stress had lower QoL. There was also a significant relationship between SoD and stress. Milcic *et al.* reported a significant correlation between all aspects of QoL and stress, being similar to our result. Moreover, SoD was higher in the high-stress group than in the low-stress group, and no significant correlation was found between PASI and PLSI<sup>5</sup>, being inconsistent with our study. Fortune *et al.* reported that all components of QoL were at a significantly higher level in the high-stress group than in the low-stress group<sup>13</sup>; this was inconsistent with our results indicating no significant difference in QoL between high-stress and low-stress groups.



## CONCLUSION

The results of our study indicated a significant association between SoD and QoL. Disease-related stress was another reason for the low QoL of the patients, and psoriasis had a devastating effect on different aspects of life. To reduce psoriasis patients' stress, we suggest that they should be under the supervision of a psychologist and monitored by psychiatrists; however, their skin lesions should be managed.

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# Comparison of serum levels of calcium, vitamin-D, phosphorous and C-reactive protein in acne patients versus healthy subjects

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## INTRODUCTION

Acne vulgaris is considered a common skin disease in which sebaceous glands' inflammation and obstruction lead to involvement of chest, back, and face <sup>1-3</sup>. The genetic has been regarded as one of the main contributing factors to acne <sup>4</sup>. Four related mechanisms include follicular proliferation and ruptures, sebum production, inflammation,

**Background:** Acne vulgaris is among common bothersome skin problems. Recognition of contributing factors would help to prevent acne. Some dietary and inflammatory factors are among suggested etiologies. Accordingly, in this study, the serum levels of calcium, vitamin D, phosphorous and C-reactive protein (CRP) were determined and compared in acne patients and healthy subjects.

**Methods:** In this case-control study, 144 consecutive subjects with and without acne (moderate-very severe) referred to Rasoul Akram Hospital in 2016 were enrolled. In this regard, the serum calcium, phosphorous, CRP, vitamin D were determined in the subjects and compared between the groups.

**Results:** The results indicated that serum CRP, calcium, and phosphorous level were alike between the groups ( $P > 0.05$ ) without any relation to acne severity except CRP. The serum vitamin D level was significantly different ( $P = 0.0001$ ), but it was not associated with acne severity. Serum calcium levels of males were significantly higher in both groups.

**Conclusions:** Based on our results, it may be concluded that calcium, phosphorous, and CRP levels are not associated with acne incidence, but the serum vitamin D is related to acne presentation. CRP levels were positively associated with acne vulgaris severity.

**Keywords:** acne vulgaris, calcium, vitamin D (Vit D), C-reactive protein (CRP)

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and coryne-bacterium presence <sup>5,6</sup>. Acne is usually observed in adolescence due to sex hormone role in the middle of the second decade of life <sup>6-8</sup>. Androgens level, genetic, corticosteroids, chemical agents, and psychiatric factors are among the aggravating factors for acne <sup>9-11</sup>. Antibiotics such as tetracycline <sup>12-14</sup> and retinoid <sup>15</sup> are the main therapeutic options. Although, these modalities are effective in the treatment of the patients, the

therapeutic outcomes are not favorable in some cases. In these cases, other etiologies such as mineral and vitamin deficiencies are proposed to be important. Some micronutrients or inflammation-related factors such as zinc, calcium, vitamin D, phosphorous, and C reactive protein (CRP) are among suggested markers. Regarding some controversies or few studies in this area<sup>16-21</sup>, this study was conducted to determine and compare the serum levels of calcium, vitamin D, phosphorous, and CRP in acne patients and healthy subjects.

## PARTICIPANTS AND METHODS

### Participants and study design

In this case-control study, 144 consecutive subjects with and without acne (72 cases and 72 controls), referred to Rasoul Akram Hospital in 2016 were enrolled. Additionally, the serum calcium, phosphorous, CRP and vitamin D were determined in the subjects by the ELISA method, and compared between the groups, based on acne severity. The control group was selected from healthy personnel without acne through clinical examination. The severity was determined according to the following items:

- Mild acne: fewer than 20 comedones, or fewer than 15 inflammatory lesions, or a total lesion count more than 30;
- Moderate acne: 20-100 comedones, or 15-50 inflammatory lesions, or a total lesion count of 30-125;

- Severe acne: more than 5 cysts, or comedone count more than 100, or a total inflammatory count more than 50, or a total lesion count more than 125.

### Statistical methods

Data of the 144 patients (72 subjects in each group) were analyzed using the SPSS software (version 24.0). The tests used for comparisons included Independent-Sample-T, Mann-Whitney-U, ANOVA, Kruskal-Wallis, and Pearson tests. The significance level was considered 0.05.

### Ethical considerations

The written informed consent was obtained from all participants.

## RESULTS

The mean age was  $25.5 \pm 7.9$  and  $26.4 \pm 8.8$  years in both case and control groups, respectively ( $P > 0.05$ ); in each group, 50% were male. Table 1 shows the acne severity. Duration was less than one year, 1-5 years, 5-10 years, and more than 10 years in 34.7%, 23.6%, 16.7%, and 25%, respectively.

As Table 2 shows, dairy intake (diary product usage divided based on frequency of use and considered as multiple times in a day (very much), daily (much), most days in a week (medium), 2-3 times in week in a week (few), less than 2 days in a week or even no use (very few)) was higher

**Table 1.** Acne grading in the case group

		Grade			Total
		Moderate	Severe	Very severe	
Group	Case	18 25.0%	24 33.3%	30 41.7%	72 100.0%
Total		18 25.0%	24 33.3%	30 41.7%	72 100.0%

**Table 2.** Dairy intake in the two groups

		Dairy Products Consumable Ratio					Total
		Very few	Few	Medium	Much	Very much	
Group	Case	Count 11	15	26	15	5	72
		% Within Group 15.3%	20.8%	36.1%	20.8%	6.9%	100.0%
	Control	Count 21	30	18	3	0	72
		% Within Group 29.2%	41.7%	25.0%	4.2%	.0%	100.0%
Total		Count 32	45	44	18	5	144
		% Within Group 22.2%	31.3%	30.6%	12.5%	3.5%	100.0%

in the case group ( $P = 0.0001$ ). In case and control groups, sun exposure longer than three hours was 48.6% and 27.8%, respectively, with a significant difference ( $P = 0.010$ ). Calcium, phosphorus and CRP levels were not significantly different between the two groups. The only serum marker differed between the groups was vitamin D ( $P = 0.001$ ) (Table 3).

The age was not related to vitamin D, CRP, calcium and phosphorous ( $P > 0.05$ ). The gender was not associated with determined serum markers except calcium that was higher in males in both case and control groups. ( $P = 0.0001$  and  $P = 0.003$ ,

respectively). Although, the CRP level was not different between the case and control groups, it was positively associated with acne severity or its grade ( $P = 0.034$ ). Other serum factors were not related to acne severity ( $P > 0.05$ ). The only factor relevant to sun exposure in both groups was the serum vitamin D level ( $P = 0.0001$ ). Furthermore, calcium ( $P = 0.0001$ ) and phosphorous ( $P = 0.042$ ) were associated with the dairy intake in the two groups. Duration of acne was not associated with serum markers levels ( $P > 0.05$ ).

The determined serum levels were not relevant to acne severity, except CRP ( $P = 0.034$ ) (Tables 4 and 5).

**Table 3.** Serum levels of vitamin and minerals in the two groups

Group	Mean	Std. Deviation
Ca (mg/dl)		
Case	9.59	.64
Control	9.40	.61
Phosphorous (mg/dl)		
Case	3.19	.96
Control	3.31	.53
VitD (ng/ml)		
Case	29.30	16.21
Control	20.39	14.89
CRP (mg/l)		
Case	6.95	3.11
Control	6.36	2.23

## DISCUSSION

Acne is a common dermatological disease worldwide, particularly in adolescents. Determination of the related factors can help to plan a better program to reduce the burden of acne. According to our findings, between calcium, phosphorous, CRP, and vitamin D indices, only the serum vitamin D level was related to acne. Interestingly, the patients with acne had higher serum levels of vitamin D. In other words, vitamin D can reduce the acne rate, being inconsistent

**Table 4.** Association of gender with serum parameters

Group	Gender	Ca (mg/dl)	Phosphorous (mg/dl)	VitD (ng/ml)	CRP (mg/l)
Case	Female				
	Mean	9.31	3.39	31.51	6.69
	Std. Deviation	.41	1.18	17.57	3.13
	Male				
	Mean	9.88	3.00	27.08	7.21
	Std. Deviation	.71	.63	14.64	3.11
Control	Female				
	Mean	9.20	3.33	23.46	6.50
	Std. Deviation	.52	.57	16.08	3.00
	Male				
	Mean	9.61	3.29	17.32	6.22
	Std. Deviation	.62	.49	13.11	1.05

**Table 5.** Association of acne severity with serum parameters

Group	Grade	Ca (mg/dl)	Phosphorous (mg/dl)	VitD (ng/ml)	CRP (mg/l)
Case	Moderate/Severe				
	Mean	9.58	3.18	26.67	6.30
	Std. Deviation	0.60	0.51	15.83	1.82
	Very Severe				
	Mean	9.62	3.21	32.97	7.87
	Std. Deviation	0.70	1.37	16.27	4.19

with some other studies. Our study showed that patients with acne had higher exposure to the sun or higher intake of dairy products that may explain the higher levels of vitamin D in the case group; future studies with participant matching need to be conducted in these regard. Namazi *et al.* reported that CRP levels (as an indicator of systemic effect of acne) were not significantly different between acne patients and controls even in very severe clinical forms<sup>21</sup>. We also found that CRP levels were not different between the acne patients and controls; however, we found a positive correlation between the acne severity and CRP levels.

Toosi *et al.* showed that the mean vitamin D level was 8.4 ng/ml and 10.4 ng/ml in both case and control groups, respectively, which was not statistically different<sup>22</sup>. There was no significant relation between severity of disease, BMI, age at onset of disease, duration of disease, and serum 25(OH) D levels. Contrary to the study conducted by Toosi *et al.*<sup>22</sup>, our results indicated that the control group had significantly lower vitamin D levels. Moreover, we did not find any correlation between vitamin D and demographic characteristics of the patients, as well as between vitamin D and acne. Two related studies in Turkey and Korea demonstrated that patients with acne had lower levels of vitamin D; the latter study reported an inverse correlation between the acne severity and serum levels of vitamin D, being inconsistent with our results; this result is justified by the above-mentioned probable confounders<sup>23,24</sup>.

In conclusion, to the best of our knowledge, calcium, phosphorous, and CRP levels are not associated with acne, but the serum vitamin D is relevant to acne. Furthermore, among these determined factors, CRP is the only factor related to acne severity.

Calcium level is higher in males with higher exposure to the sun, based on cultural or occupational condition in our country that may differ in other countries with different nutritional habits and different sun exposure. Owing to the high prevalence of acne, it is recommended that the probable related factors be focused to better manage or prevent acne vulgaris, since there are many related articles in this regard<sup>25</sup>.

However, more comprehensive matched studies with a larger sample size are required to obtain more definite results particularly with consideration

of confounding factors.

Considering the high prevalence and great burden of acne vulgaris there are many articles emphasizing on acne associations<sup>25</sup>, treatments<sup>26-29</sup> and management of its complications especially scars<sup>30-32</sup>. In this study, one of the controversial associations of acne vulgaris is studied and discussed.

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# Immunohistochemical analysis of T-cell subsets in the inflammatory infiltrates of alopecia areata and its comparison with androgenetic alopecia

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**Background:** Androgenic hair loss (AGA) and alopecia areata (AA) are common conditions which sometimes are histologically difficult to differentiate. This study was conducted to detect differentiating features of these two disorders with IHC analysis of T-cell subsets in the inflammatory infiltrates of alopecia areata and androgenetic alopecia.

**Methods:** This cross-sectional study was conducted at Shohada-e-Tajrish Hospital in 2018. Twenty-eight cases of alopecia areata and 32 androgenic hair loss cases were evaluated. H&E and IHC staining for CD3, CD4, and CD8+ T-lymphocytes were performed. Lymphocytic densities were graded in a quintet grading system. The inflammation density in various areas of skin tissue was evaluated. Statistical analysis was performed using SPSS version 21.

**Results:** Peribulbar lymphocytic infiltration was seen in 88.5% of AA patients and 12.5% of AGA patients ( $P = 0.000$ ). Presence of melanin, pigmented casts, and lymphocytes in follicular stela were in favor of AA diagnosis. CD3, CD4, and CD8+ T-cells in follicular stela, peri-bulbar, and subcutaneous regions were higher and denser in AA patients, while CD3 and CD4+ T-cells around sebaceous ducts were in favor of AGA diagnosis.

**Conclusion:** Peribulbar lymphocytic infiltration is among the most important differentiating features of AA and AGA. Infiltration of T-cells in various regions of skin tissue has high diagnostic value. Histologic and immunohistochemical evaluation of skin tissues according to these factors can differentiate these two entities with high precision.

**Keywords:** hair loss, alopecia areata, androgenetic alopecia

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## INTRODUCTION

Alopecia is a common dermatologic complaint around the world which is categorized into several conditions. Alopecia areata (AA) is a prevalent disorder with a prevalence of 0.7-3.8% among patients referring to dermatology clinics<sup>1,2</sup>. It is estimated that AA is present in 0.1-0.2% of US general population<sup>3</sup>, which is associated with a

life-long risk of 1.7%<sup>4</sup>. Another form of alopecia is known as androgenetic (AGA) which involves nearly 50% of men and approximately half of women over 40 years of age<sup>5</sup>. Due to the fact that both of these entities are so common, definite diagnosis of these disorders is essential.

Differentiation of AA and AGA by histopathology is a challenging issue because both of them are characterized by increases in catagen/telogen ratio

and follicular miniaturization<sup>6</sup>. In cases of hair loss in androgen-dependant regions, this choice between AA and AGA grows more difficult. To make a specific diagnosis, some histologic keys are present. In either disorders, follicular miniaturization or changes in catagen/telogen ratio and empty follicular fibrous tracts which are known as empty stela are found<sup>7-9</sup>. In some cases, lymphocytes might be detected in stela. In more complex cases, presence of melanin in stela of AA patients might complicate the diagnosis. Identification of pigmented casts, especially in brunette, leads to more challenging diagnostic puzzles<sup>6,10</sup>.

Traditionally, detection of peribulbar lymphocytic infiltration, in addition to eosinophils, approved a diagnosis of AA. But, peribulbar infiltration is routinely not found in subacute AA where an evident follicular miniaturization and increase in catagen/telogen ratio must be present to meet the requirements of AA diagnosis<sup>8</sup>. A shift of higher than 50% in catagen/telogen ratio and evident follicular miniaturization with a terminal/vellus ratio of more than 1:7 is essential for making such diagnosis<sup>7,11</sup>. The hard problem is where terminal/vellus ratio is higher than 1:1 but lower than 1:7 in addition to a catagen/telogen shift between 20 to 50 percent; in such settings, histologic discrimination between AA and AGA is very problematical. So, using additional methods to reach an accurate and certain diagnosis is necessary. Several studies have demonstrated that T-cell lymphocyte infiltration in AA is confirmed<sup>9</sup>, but the details of this infiltration is not extensively reviewed. In addition, status of lymphocytic infiltration in AGA is not clarified well. Thus, we aimed to evaluate and compare the presence and distribution of CD3, C4, and CD8 lymphocytic infiltrations and other pathologic features between AA and AGA samples to determine whether these parameters could contribute to better distinguishing AA from AGA or not.

## MATERIALS AND METHODS

This cross-sectional study was conducted on biopsies performed from 2011 to 2017 at Shohada-e-Tajrish Hospital in Tehran; 28 cases of AA and 32 cases of AGA were reviewed. The final diagnosis of all cases was confirmed by two independent expert histopathologists. In all cases, a 4-mm punch biopsy was performed. An expert laboratory technician

performed the process of IHC staining for CD3, CD4, and CD8 markers. H&E staining had been performed on 5- $\mu$ m sections. H&E findings included peribulbar lymphocytic infiltration, eosinophils, and lymphocytes in fibrous tracts, melanin, and pigmented casts in fibrous tracts, hyperkeratosis, and dilatation of follicles' opening and follicular miniaturization. Lymphocytic densities were graded in a quintet grading system (0: no infiltration, trace: scant lymphocytic infiltration, 1+: mild lymphocytic infiltration, 2+: moderate lymphocytic infiltration and 3+: severe lymphocytic infiltration). These lymphocytic infiltrations were evaluated in follicular epithelium, papillary dermis, reticular dermis, subcutis, peri-bulbar dermis, peri-sebaceous ducts, and empty follicular fibrous tracts (stela). Patients' age and gender were also recorded.

All acquired data were analyzed in SPSS software (version 20, SPSS Inc., Chicago, IL, USA). Descriptive analysis of data was performed in form of overall and in-group frequency and percentage of parameters. For comparison of parameters between two groups, t-test, chi-square test, or U-Mann Whitney test were used as needed. Parameters' cut-off for discrimination between two diagnoses were determined with ROC curve analysis, and their associated AUC, sensitivity, and specificity were calculated. P-value < 0.05 was considered as statistically significant.

## RESULTS

We reviewed 32 AGA and 28 AA patients. Mean age of the patients was  $39.3 \pm 14.77$  and  $31.17 \pm 14.00$  years for AGA and AA groups, respectively ( $P = 0.040$ ). Gender distribution of patients in each group was as follows: 26 (81.3%) females and 6 (18.8%) males in the AGA group (female-to-male ratio = 4.3:1) and 23 (82.1%) females and 5 (17.9%) males in the AA group (female-to-male ratio = 4.6:1) ( $P = 0.929$ ).

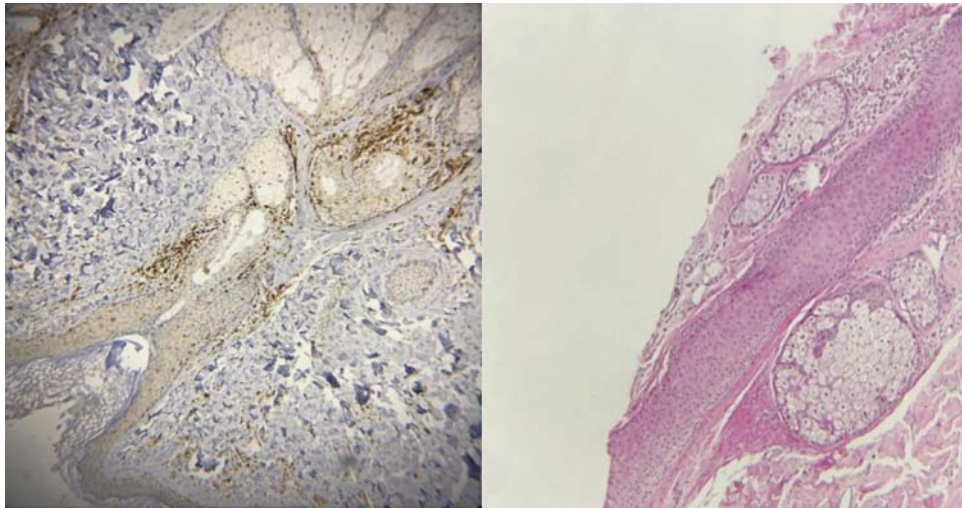
Overall inflammation density in AGA patients was trace in 12 (37.5%) patients, 1+ in 15 (46.9%) patients, and 2+ in 5 (15.6%) patients, while in AA patients, 4 (14.3%) cases of trace, 17 (60.7%) cases of 1+, and 7 (25%) cases of 2+ inflammation density was seen ( $P = 0.122$ ). The overall inflammation severity was not statistically significant between two groups. Peribulbar lymphocytic infiltration density showed significant difference between

two groups as in the AGA group; there was no infiltration in 28 (87.5%) cases and trace infiltration in 4 (12.5%) cases, but in AA patients, 3 cases (11.5%) showed no evidence of infiltration; 10 (38.5%) cases had trace infiltration; 7 patients (26.9%) had 1+; and 6 patients (23.1%) had 2+ infiltration densities ( $P = 0.000$ ). Figure 1 depicts lymphocytic infiltration around sebaceous ducts in H&E and CD4 IHC staining in a case of AGA.

Further findings from H&E examination and comparison between two groups of AGA and AA

in different parameters are shown in Table 1.

Analysis of inflammation density with CD3, CD4, and CD8+ T-lymphocytes reveals that there is no difference between AA and AGA in reticular dermis and follicular epithellium. While inflammation density in stela, peribulbar, and subcutaneous regions is significantly in favor of AA diagnosis (all CD3, CD4, and CD8+ T-lymphocytes), inflammation in peri-sebaceous duct regions (CD3 and CD4+ lymphocytes) is highly suggestive of AGA. Figure 2 shows infiltration of CD3+ lymphocytes in stela and

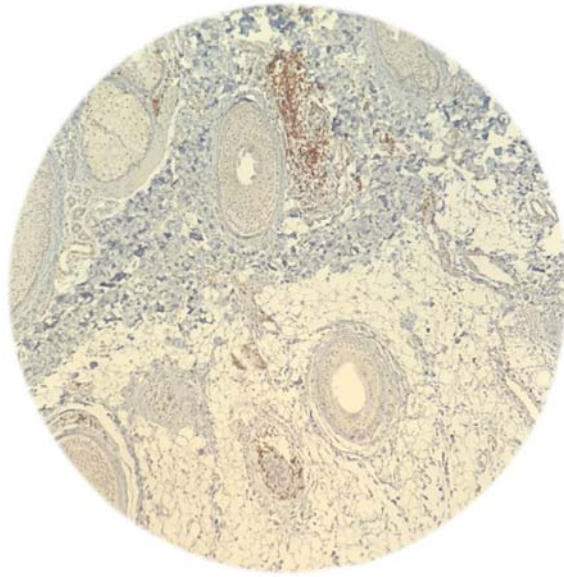


**Figure 1.** Lymphocytic infiltration around sebaceous ducts in a case of AGA, CD4 IHC staining and H&E staining ( $\times 100$ )

**Table 1.** Comparison of H&E study findings in AA and AGA groups

Parameters	Infiltration grading	AGA	AA	P-value
Peribulbar lymphocytic infiltration	0	28 (87.5%)	3 (11.5%)	0.000
	Trace	4 (12.5%)	10 (38.5%)	
	1+	-	7 (26.9%)	
	2+	-	6 (23.1%)	
Presence of eosinophils in stela	Present	2 (6.3%)	5 (17.9%)	0.162
	Absent	30 (93.8%)	23 (82.1%)	
Melanin in stela	Present	6 (18.8%)	14 (50%)	0.010
	Absent	26 (81.3%)	14 (50%)	
Lymphocytes in stela	0	14 (43.8%)	5 (17.9%)	0.001
	Trace	18 (56.3%)	12 (42.9%)	
	1+	-	10 (35.7%)	
	2+	-	1 (3.6%)	
Pigmented casts in stela	Present	-	4 (14.3%)	0.027
	Absent	32 (100%)	24 (85.7%)	
Follicular miniaturization	Present	28 (87.5%)	17 (60.7%)	0.017
	Absent	4 (12.5%)	11 (39.3%)	
Hyperkeratosis	Present	24 (75%)	20 (71.4%)	0.755
	Absent	8 (25%)	8 (28.6%)	
Dilatation of follicles' opening	Present	22 (68.8%)	24 (88.9%)	0.063
	Absent	10 (31.3%)	3 (11.1%)	





**Figure 2.** Infiltration of CD3+ lymphocytes in stela and peribulbar region in a patient with AA diagnosis ( $\times 100$ )

peribulbar region in a patient with AA diagnosis. The practical details are listed in Table 2.

To differentiate between two diagnoses, it is essential to establish a cut-off value for parameters which were significantly different between AA and AGA. We evaluated sensitivity, specificity, and AUC of these parameters for distinguishing between AA and AGA based on these cut-off values. The best parameter for this purpose was peribulbar lymphocytic infiltration with AUC of 0.911, sensitivity of 88.5%, and specificity of 87.5%. The details are thoroughly reviewed in Table 3.

## DISCUSSION

Since the time Headington<sup>12</sup> suggested punch biopsy sectioning in 1984, this procedure has got growing popularity among pathologists because it allows visualization of all follicles present in biopsy, so it makes morphologic and quantitative assessment feasible<sup>13</sup>. But still, using this procedure

**Table 2.** Details of immunohistochemical staining for CD3 and CD4+ T-lymphocytes

IHC staining/region	Alopecia type	0	Trace	1+	2+	3+	P-value
CD3/stela	AGA	8 (25%)	24 (75%)	-	-	-	0.000
	AA	1 (3.6%)	10 (35.7%)	13 (46.4%)	2 (7.1%)	2 (7.1%)	
CD3/peribulbar	AGA	27 (84.4%)	5 (15.6%)	-	-	-	0.000
	AA	4 (15.4%)	9 (34.6%)	7 (26.9%)	5 (19.2%)	1 (3.8%)	
CD3/reticular dermis	AGA	-	24 (75%)	7 (21.9%)	1 (3.1%)	-	0.468
	AA	-	17 (60.7%)	9 (32.1%)	2 (7.1%)	-	
CD3/subcutaneous	AGA	30 (93.8%)	2 (6.3%)	-	-	-	0.001
	AA	14 (51.9%)	10 (37%)	3 (11.1%)	-	-	
CD3/follicular epithelium	AGA	2 (6.3%)	27 (84.4%)	2 (6.3%)	1 (3.1%)	-	0.501
	AA	3 (10.7%)	21 (75%)	4 (14.3%)	-	-	
CD3/peri-sebaceous duct	AGA	3 (9.4%)	13 (40.6%)	11 (34.4%)	5 (15.6%)	-	0.013
	AA	6 (21.4%)	19 (67.9%)	2 (7.1%)	1 (3.6%)	-	
CD4/peri-sebaceous duct	AGA	-	8 (25%)	14 (43.8%)	10 (31.3%)	-	0.006
	AA	1 (3.6%)	18 (64.3%)	7 (25%)	2 (7.1%)	-	

**Table 3.** Sensitivity, specificity and AUC of cut-off values for distinguishing AA from AGA

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI
Peribulbar lymphocytic infiltration	Trace	88.5	87.5	0.911	0.828-0.994
Melanin in stela	Presence of melanin	50	81.2	0.656	0.515-0.797
Lymphocytes in stela	Presence of lymphocytes	82.1	43.7	0.740	0.612-0.868
Follicular miniaturization	Presence of miniaturization	60.7	12.5	0.366	0.233-0.510
Pigment casts	Presence of casts	14.3	100	0.571	0.424-0.719
CD3 in stela	Trace	60.7	100	0.835	0.729-0.941
Peribulbar CD3	Trace	84.6	84.4	0.884	0.789-0.979
Subcutaneous CD3	Trace	48.1	93.7	0.713	0.576-0.850
Peri-sebaceous duct CD3	Trace	78.6	9.4	0.292	0.160-0.424
Peri-sebaceous duct CD4	1+	32.1	25	0.258	0.131-0.384

AUC: Area under the curve



needs high levels of expertise and precision, and in some cases, differentiation of several types of alopecias becomes so challenging. As mentioned above, in this study we aimed to assess the challenging diagnosis of AGA and AA.

Overall, histologically distinguishing of two alopecias, especially in the absence of perifollicular inflammation, is very tough because both AGA and AA show hair follicles' miniaturization<sup>14</sup>. In our study, miniaturization in AGA is significantly higher than AA (87.5% vs. 60.7%). In Whiting *et al.*<sup>15</sup> and Dy *et al.*'s<sup>10</sup> studies, a higher rate of miniaturization in AA was seen, but this rate was not statistically significant. On the other hand, Horenstein *et al.*<sup>16</sup> and Miteva *et al.*<sup>17</sup> reported, similarly, a higher rate of miniaturization in AGA in comparison to AA. Conflicts between various studies could be attributed to the region where biopsy was taken. As hair follicles' miniaturization is a slow process which is mainly found in the center of lesions, miniaturization in margin of lesions might occur later in the process.

One of the important morphologic parameters which was clearly higher in areata alopecia was peribulbar inflammation. This can also be seen in syphilitic alopecia and lupus, but it is very rare in AGA<sup>18</sup>. Peribulbar inflammation was seen in 88.5% of AA patients, while only 12.5% of AGA patients showed peribulbar inflammation. This feature is usually reported in early stages of AA, so there are broadly variable reports of 12 to 100% regarding the occurrence of this feature<sup>16,18,19-24</sup>.

Another differential feature in our study was the presence of pigmented casts and melanin depositions. Pigmented cast was not seen in any case of AGA, but 14.3% of AA patients showed these casts ( $P = 0.027$ ). Melanin in stela was also detected in 50% of AA patients and 18.8% of AGA patients, which is an approximately three-fold ratio ( $P = 0.010$ ). It is reported that the type and location of pigmented casts and melanin depositions vary between two disorders. In AA, pigmented casts are usually larger and higher in number and are located in peribulbar region, while in AGA, they are found in telogen/catagen follicles<sup>25</sup>. Peckham *et al.*<sup>8</sup> reported that in 84% of AA patients, melanin was found in stela and it is a key diagnostic feature of AA. In an Indian study by Singh *et al.*, in 83% of horizontal biopsies and 80% of vertical biopsies in AA, melanin was found<sup>19</sup>.

Presence of eosinophils in perifollicular region is considered an important diagnostic feature in the literature. In our study, 17.9% of AA and 6.3% of AGA patients showed eosinophils in perifollicular region ( $P = 0.162$ ). Elston *et al.*<sup>26</sup> found eosinophils in 53% of AA patients, while this rate in Peckham *et al.*'s study<sup>8</sup> was 44%. As mentioned earlier, this rate was much lower in our study. Chaitra *et al.*<sup>22</sup> and Singh *et al.*<sup>19</sup> reported no evidence of eosinophil in their evaluations.

Lymphocytes in stela were also suggested as an indicator of AA. In the current study, 82.1% of AA patients had such symptoms, while in AGA, only 56.3% had lymphocytes in stela ( $P = 0.001$ ). In various studies of AA, 41 to 94 % of patients had lymphocytes in stela<sup>8,17,19</sup>.

Dilatation of follicles' opening was seen in 68.8% of AGA patients and 88.9% of AA patients. This difference was not statistically significant ( $P = 0.063$ ). Miteva *et al.*<sup>17</sup> found this feature in 91% of patients with incognita alopecia. Muller *et al.*<sup>24</sup> also found this condition in 58% of AA patients. There are no reports on this feature in AGA studies. The role of this feature in discrimination of these two disorders needs further investigations.

Immunohistochemical staining for CD3, CD4, and CD8+ T-lymphocytes revealed no difference between AA and AGA in reticular dermis and follicular epithelium. While inflammation density in stela, peribulbar, and subcutaneous regions is significant in favor of AA diagnosis (all CD3, CD4, and CD8+ T-lymphocytes), inflammation in peri-sebaceous duct regions (CD3 and CD4+ lymphocytes) is highly suggestive of AGA. Previous studies have reported that perifollicular inflammation was present in 14.3-100% of AA patients<sup>17,20,22,23</sup>, while in AGA patients, this rate was 0-85%<sup>11,17,27</sup>. The majority report sets forth the following finding of fact: inflammation in AA is more severe than AGA. What we found in our study was that severity of inflammation depends on the region of study in the tissue; in some parts, inflammation of AA is more severe, and in some other parts, AGA is more inflamed. It is speculated that in AA, the underlying cause of inflammation is the nature of the disease but in AGA, coincidence of seborrheic capitis; inflammation due to sun light or application of some topical agents on the skin leads to inflammation. ROC curve analysis showed that these parameters contribute to distinguishing

AA from AGA, to some various degrees. The most helpful parameters in our study were peribulbar lymphocytic infiltration in H&E stained slides, CD3+ lymphocytes in peribulbar region, and stela in IHC stained slides (AUCs of 0.911, 0.884, and 0.835, respectively). Other studies have also emphasized the importance of these parameters for more accurate diagnosis. Kolivras *et al.*<sup>5</sup> showed that CD3+ lymphocytes are reliable histopathologic keys in favor of AA diagnosis (sensitivity and specificity of CD3 staining in that study was higher than 80% for various regions; when two regions were combined, this rate reached almost 100%). In a study by Kamyab *et al.*<sup>28</sup>, it was revealed that inflammation density of AA was higher than AGA regarding CD3 (specificity of 86.7% and sensitivity of 96.7%) and CD8 (specificity of 50% and sensitivity of 86.6%) staining. It was also mentioned that intrafollicular CD3 and CD8 stained T-cell infiltrations were significantly higher in AA samples in comparison to AGA samples (P-values of 0.017 and < 0.000, respectively).

The main limitation of the study is its relatively small sample size which did not allow comparison of alopecias with different degrees of clinical severity. Recruitment of total duration of disease from the onset in further analyses can lead to more comprehensive results.

## CONCLUSIONS

Peribulbar lymphocytic infiltration is the most reliable parameter in distinguishing AA from AGA. Staining for CD3 (T-lymphocytes' cell marker) has significant diagnostic value in establishing accurate diagnosis.

**Conflict of Interest:** None declared.

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# Determination of serum levels of zinc in acne vulgaris patients: a case control study

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**Background:** Acne vulgaris is a dermatologic disorder with a wide variety of distribution and presentation. Its high prevalence and important cosmetic and psychological concerns focusing on contributing factors would be of great value for better approach and prevention of acne vulgaris. There are many articles that argue the role of some dietary and inflammatory factors in acne vulgaris. In this study, the serum levels of zinc in acne patients were determined and compared with healthy subjects.

**Methods:** In this age and gender matched case-control study, 200 consecutive subjects with and without acne (moderate-very severe) referring to Rasoul Akram Hospital, 2016, were enrolled, and their serum zinc levels were determined and compared across the groups.

**Results:** Serum zinc levels were alike across the groups ( $P > 0.05$ ), and the severity of acne was not related to zinc level. The levels of zinc were significantly different between genders in the case group (men had lower levels). In female patients with acne, the level of zinc was inversely correlated with acne severity.

**Conclusion:** Zinc is not related to acne incidence or its grade, but men with acne have lower levels of zinc compared with women. Also, acne severity in women is inversely correlated with zinc level. It can be assumed that zinc supplementation may be a good trend in men with acne or alleviate the severity of acne in women, which needs more evaluation and work up.

**Keywords:** acne vulgaris, serum, zinc

Iran J Dermatol 2020; 23: 28-31

## INTRODUCTION

Acne vulgaris is a common skin disorder with inflammation of sebaceous glands and an obstruction of follicular unit with keratin which leads to acne lesion formation especially in the chest, back, and face <sup>1-3</sup>. Genetic factors are considered the main contributing factors <sup>4</sup>. Four related mechanisms include follicular proliferation and ruptures, sebum production, inflammation, and coryne-bacterium

presence <sup>5,6</sup>. Acne is usually seen in adolescence due to the sex hormone role in mid second decade of life <sup>6-8</sup>. Aggravating factors for acne include androgens level, genetic, corticosteroids, chemical agents, and psychiatric factors <sup>9-11</sup>. Antibiotics such as tetracycline <sup>12-14</sup> and also retinoid <sup>15</sup> are the main therapeutic options. However, these modalities are effective in the treatment of patients. In some cases, the therapeutic outcomes are not favorable; in such cases, other etiologies such as mineral and

vitamin deficiencies are proposed to be important. Some micronutrients or inflammation-related factors like zinc, calcium, vitamin D, phosphorous, and CRP are among suggested markers. Taking into account controversies or limited number of studies relating to the subject<sup>16-21</sup>, we aimed to determine the serum level of zinc and compare it in acne patients with healthy subjects.

## PARTICIPANTS AND METHODS

### Participants and study design

In this age and gender matched case-control study, 200 consecutive subjects with and without acne (100 cases and 100 controls) in Rasoul Akram Hospital in 2016 were enrolled, and their serum zinc levels were determined by ELISA method and compared across the groups, based on acne severity. The control group was among health care personnel who had no acne in clinical examination. The severity was determined according to the following items:

- Mild acne: fewer than 20 comedones, or fewer than 15 inflammatory lesions, or a total lesion count lower than 30;
- Moderate acne: 20-100 comedones, or 15-50 inflammatory lesions, or a total lesion count of 30-125;
- Severe acne: more than five cysts, or comedone count greater than 100, or a total inflammatory count greater than 50, or a total lesion count greater than 125.

### Statistical methods

Data analysis of data from 200 patients (100 subjects in each group) was done using SPSS software (version 24.0). The tests for comparisons were Independent Samples t-Test, Mann-Whitney-U, ANOVA, Kruskal-Wallis, and Pearson tests. The significance level was considered 0.05.

### Ethical considerations

The written informed consent was obtained from all participants.

## RESULTS

This case-control study was an age and gender matched one conducted on 200 participants (100 cases and 100 controls). In each group, 50 male and 50 female participants were enrolled. The mean age of the participants in the case and control group was 25.38 and 25.60 years old, respectively. In the case group, 27% of the patients had moderate acne, and 32% and 41% of the patients had severe and very severe acne, respectively. Table 1 shows the acne duration time among patients in the case group.

The level of zinc was not significantly different between two groups. Also, the level of zinc was not related to the patients' age ( $P > 0.05$ ).

The zinc level was significantly different between males and females in the case group ( $P = 0.0001$ ) (Table 2).

There was not any relationship between the

**Table 1.** The acne duration time among the acne patients

Group	Time				Total
	Less than 1 year	Between one to five years	Between five to ten years	More than ten years	
Case					
Count	34	27	18	21	100
% within group	34.0%	27.0%	18.0%	21.0%	100.0%
Total					
Count	34	27	18	21	100
% within group	34.0%	27.0%	18.0%	21.0%	100.0%

**Table 2.** Zinc levels ( $\mu\text{g}/\text{dL}$ ) based on gender in the case and control groups

Group		Sex	N	Mean	Std. Deviation	Std. Error Mean
Case	Zinc	Female	50	96.30	17.53	2.48
		Male	50	74.95	21.83	3.09
Control	Zinc	Female	50	82.96	15.08	2.13
		Male	50	83.94	16.75	2.37



**Table 3.** Zinc levels ( $\mu\text{g/dL}$ ) related to acne severity and based on gender

Sex	Grade	Mean	Std. Deviation
Female	Moderate	112.62	21.69
	Severe	91.52	16.09
	Very Severe	92.80	12.12
Male	Moderate	70.61	21.80
	Severe	69.03	20.10
	Very Severe	83.20	21.60

zinc level, acne grading, and duration ( $P > 0.05$ ). In women with acne, the zinc level was inversely correlated with severity of acne ( $P = 0.003$ ) (Table 3).

## DISCUSSION

Acne is a common dermatological disease worldwide especially in adolescents. Determination of related factors would lead to better programming for reduction of acne burden. We found that zinc level is not related to acne presentation or its severity, but men with acne had lower levels of zinc, and zinc level in women was related to acne severity.

Ozuguz *et al.* reported that among 150 patients with and without acne, the zinc level was lower in the acne group especially in more severe cases<sup>16</sup>. However, in our study, the zinc level was not related to the acne and disease severity; but in women with acne, we found similar results regarding the zinc level and severity.

Kaymak *et al.* reported that serum zinc level was low in 54% and 10% of acne and control groups, respectively, which is in contrast to our findings<sup>17</sup>.

El-Saaie *et al.* similarly reported no difference between zinc levels in acne patients and control group<sup>18</sup>.

Amer *et al.* reported that serum zinc level was lower in acne patients versus control group, especially in severe acne cases, which is not also in line with the findings of the current study, except for the correlation of zinc level and acne severity in females<sup>19</sup>. Moreover, Michaëlsson *et al.* conversely reported that zinc level was lower in acne cases; they assessed a larger sample size, over 170 patients<sup>20</sup>.

Because of high prevalence of acne, it sounds good to focus on probable related factors for better management or prevention of acne vulgaris, and there are many articles in this regard<sup>22</sup>.

Since acne is one of the most common skin problems, research on its associations<sup>22</sup>, novel therapeutic options and related-consequences, is really of great value. So in this case-control study we focused on zinc level as one of the controversial previously proposed associated factors with acne incidence and severity.

## CONCLUSION

It may be concluded that zinc level is not different between acne patients and healthy controls and also is not related to acne severity. It can be supposed that zinc supplementation is possibly a good trend in men with acne or to alleviate the severity of acne in women, which needs more evaluation and work up. Further studies with larger sample size are required to attain more definite results, especially with consideration of confounding factors.

## Acknowledgement

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**Conflict of Interest:** None declared.

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## Serum parameters, diet and body mass index in acne vulgaris: a mini review

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Skin as an outer layer of body and a main connection between the body and the environment is a way that pathogens can access the body; Therefore, it has a crucial protecting role for the body because of obstacle functioning and microbiota. Factors that seem to commonly contribute to the disease are follicular hyperkeratinization, propionibacterium acnes, sebum production, and inflammation; however, pathogenesis of acne vulgaris as an inflammatory skin disorder is still poorly understood. Google Scholar and PubMed databases were searched for all related articles, using the key words of zinc, diet, vitamin D, BMI, and acne vulgaris.

**Keywords:** diet, zinc, vitamin D, acne vulgaris

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### INTRODUCTION

Skin as an outer layer of the body and a main connection between the body and the environment is a way that pathogens access the body, hence it has a main protecting role for body because of obstacle functioning and microbiota <sup>1</sup>. Acne is one of the main etiologies for dermatological consultation and is an inflammatory disease in pilosebaceous follicle occurring commonly in adolescents and sometimes in adults. It is associated with hyperseborrhoea altering the epithelium of the follicle with formation of comedones; a modification of propionibacterium acnes causes an activation of the innate immunity and subsequent inflammation <sup>1</sup>. Pathogenesis of acne vulgaris as an inflammatory skin disorder

is still poorly understood <sup>1</sup>. Factors that seem to commonly contribute to the disease are follicular hyperkeratinization, propionibacterium acnes, sebum production, and inflammation; however, involvement of some factors like obesity and diet in the disease is currently being more understood <sup>2</sup>. Although the association between dairy intake and acne is less convincing than that between a high glycemic diet and acne, both merit considerations, when providing any dietary advice, the roles of antioxidants, omega-3 fatty acids, zinc, vitamin A, dietary fiber, and iodine in the course of acne, remain unclear. The association between acne and diet is highly controversial, and numerous studies during the last decade have led dermatologists to reflect on a potential link between diet and acne <sup>3</sup>.

Studies on the influence of diet in acne formation are unconvincing and usually focused chiefly on specific foods such as milk that is considered artificial in diet category <sup>2,4</sup>. In this study, we reviewed the literature focusing on the association between diet and BMI in acne vulgaris.

## MATERIALS AND METHODS

We reviewed English articles reported in the literature from 2008 to 2019 in order to find associations between diet and BMI in acne vulgaris. Google Scholar and PubMed databases were searched, using the key words zinc, diet, vitamin D, BMI, and acne vulgaris.

## RESULTS AND DISCUSSION

The first studies about the effect of milk have been conducted many years ago; However, there has been no conclusive evidence that milk and dairy products have comedogenic effects <sup>3</sup>. The probable cause of possible comedogenic effects of milk and its products is the hormonal content produced by cows during pregnancy, and it is declaimed that the constituent of milk which mostly stimulates the pilosebaceous unit is insulin-like growth factor 1 (IGF-1), whose concentration in the blood varies depending on the severity of acne <sup>2,3</sup>. Acne is affected not only by hormones but also by some biochemical associations between the hormones and the pilosebaceous unit. Hence, addition of exogenous hormones derived from the diet to the pool of endogenous hormones may have a significant effect <sup>3</sup>.

Chocolate has usually been considered as a factor that may relate to exacerbation of acne, but there are few evidences supporting this negative impact on the skin, and dermatologists have frequently observed that patients have new acne lesions few days after ingestion of products containing chocolate <sup>3</sup>. However, there is no data and evidence about the type of chocolate consumed by subjects and the cocoa percentage in consumed samples which may affect the results. Dark chocolate contains more antioxidants derivatives than milk chocolate, which would implicate that it may have less comedogenic effects. The question of whether chocolate aggravates acne lesions, is yet to be clear <sup>3</sup>.

Reactive oxygen species produced by leukocytes

contribute to inflammatory progression of acne and reactive oxygen species that are normally removed by cellular antioxidants such as glucose-6-phosphate dehydrogenase and catalase, both of which are presented in little amounts in acne patients. It has been suggested that oxidative stress may be implicated in the origin of acne, and antioxidant drug effects (or antioxidant supplements) may be valuable adjuvant in acne treatment <sup>3</sup>. Studies on this matter are crucial to support the theory of the positive role of antioxidants in acne therapy, but effects of such substances in the course of acne are not yet fully explored.

Zinc is a micronutrient that is necessary for functioning and development of the human skin tissue. It has been also shown to be bacteriostatic against *Propionibacterium acnes*, to inhibit chemotaxis, and to reduce production of pro-inflammatory cytokine – tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) <sup>3</sup>. Some studies have established that patients with acne often are zinc-deficient, and the oral supplementation would have positive effects on the treatment of acne vulgaris <sup>3</sup>.

Retinol and vitamin A derivatives are found principally in products with animal origin, while products of plant origin contain mainly provitamin products. The main sources for it are the milk and dairy products, liver, eggs, and oils derived from them. Vitamin A is a fat-soluble vitamin stored in the liver and may be effective in prevention of acne in high-dosages <sup>3</sup>.

Vitamin D regulates the immune system and also proliferates and differentiates keratinocytes and sebocytes. The effect of vitamin D is not only limited to calcium homeostasis, but it is also important in the regulation of the cell growth, immune system, and cell differentiation. Human sebocytes and keratinocytes are some target cells for biologically active vitamin D metabolites by nuclear vitamin D receptors. Hence, it has anti-comedogenic and antioxidant properties, and vitamin D deficiency may facilitate the pathogenesis of acne and may play a potential role in pathogenesis of acne vulgaris, or acne vulgaris may have a negative effect on vitamin D synthesis <sup>4,5</sup>.

Regarding body mass index (BMI) and acne severity, there are many controversies based on different geographic populations as well as age and gender related categories. However, this correlation has not been completely supported

by many articles in spite of some correlations in many sub-group analyses <sup>6</sup>.

High prevalence and great burden of acne makes it as one of most important areas of scientific research especially regarding its correlations <sup>6</sup>, therapies <sup>7-10</sup> and complications like acne scars <sup>11-13</sup>. In this review, we briefly focused on some associations of inflammatory acne.

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## A young girl with H syndrome and coeliac disease

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H syndrome is an autosomal recessive genodermatosis with reports dating back to the last decade. This syndrome is caused by mutations in the SCL29A3 gene. The clinical characteristics of this syndrome consist of dermatological manifestations, including hyperpigmented, hypertrichotic, and indurated patches and plaques. It affects various systems by causing heart anomalies, hepatosplenomegaly, hypogonadism, and low height.

This is the case of a 19-year-old girl from the northwest of Iran who was born of a cousin marriage. The primary manifestations included low height, underdeveloped secondary sex characteristics, and typical dermatological manifestations. This patient was examined mostly because of digestive and endocrine problems and thus had not been subject to extensive dermatological examinations until the skin biopsies mirrored manifestations similar to histiocytoses (e.g., Rosai-Dorfman disease and granuloma annulare). The patient was eventually diagnosed with H syndrome by a dermatologist from the clinical symptoms.

H syndrome is an autosomal recessive genodermatosis that affects different organs and is diagnosed by a set of typical and systemic cutaneous symptoms and biopsies. In this patient, an endoscopic examination of the upper gastrointestinal tract was carried out due to reports of anemia. A biopsy of the atrophic duodenum region revealed the existence of coeliac disease. However, the comorbidity of coeliac disease and H syndrome has not been previously reported.

**Keywords:** hyperpigmentation; hypertrichosis; hypogonadism

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### INTRODUCTION

H syndrome was originally defined in 2008<sup>1</sup>. H syndrome is an autosomal recessive genodermatosis with systemic manifestations. Hyperpigmented, hypertrichotic, and indurated patches and plaques comprise the cutaneous pathognomonic characteristics of this condition and form its hallmark. Generally appearing on the inner thighs, these patches and plaques cause prevalent disorders in different systems such as low height (short stature), hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, hyperglycemia/diabetes mellitus, skeletal anomalies (fixed flexion contractures, hallux valgus), etc<sup>1,2</sup>.

H syndrome is a rare autosomal recessive disorder caused by mutations in the SLC29A3 gene. This gene encodes the human nucleoside transporter (hENT3) of the ENT3 family<sup>3</sup>. Given the various manifestations of H syndrome, it can be wrongly diagnosed. Hence, having further knowledge of this syndrome is important. This patient was a case from the northwest of Iran that was reported due to the rarity of this disease and the diversity of the symptoms.

### CASE PRESENTATION

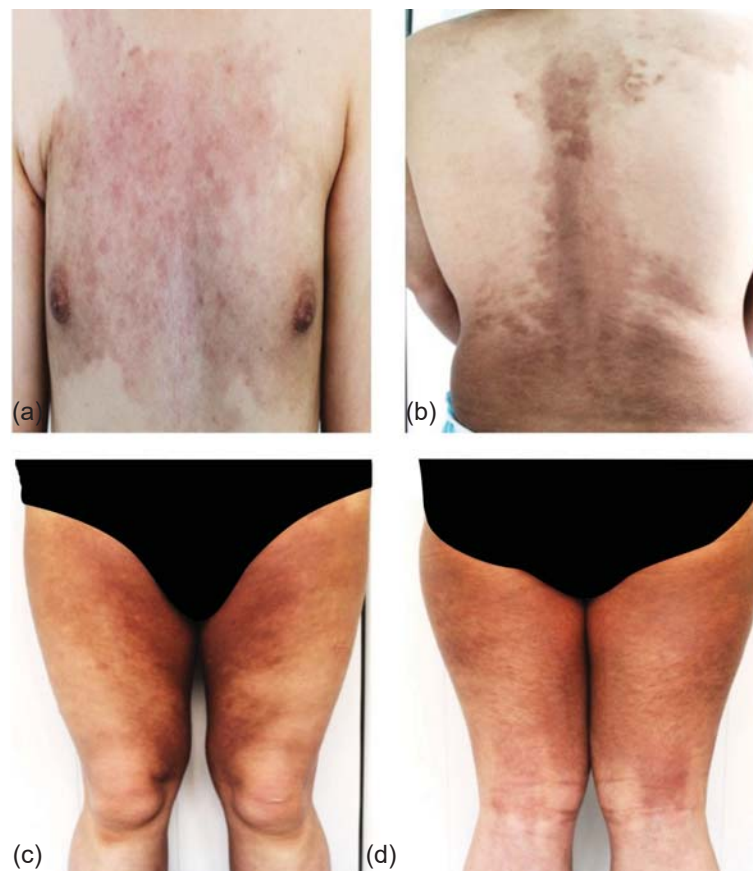
A single 19-year-old girl, the third child of a healthy couple in a cousin marriage, visited the

dermatology clinic of Sina Hospital (Tabriz, Iran) with complaints about cutaneous conditions that had manifested as progressive hyperpigmented patches and plaques as well as hypertrichosis and induration on the arms and thighs from the age of 2. This patient was born as a full-term neonate through natural childbirth at home. The mother received no prenatal care, and no post-birth examination of the neonate's health and gender were carried out. The other two children in this family had no similar conditions nor do they had a history of specialized diseases. The assessment of the patient's growth indicators at the health center revealed height and weight growth retardation considering the patient's age. For instance, at the age of 6, her height and weight were 97 cm and 16.5 kg, respectively (chronologic age: 6 years and 10 months; height age: 3 years and 3 months, and weight age: 3 years and 8 months). Hyperpigmented patches manifested symmetrically with hypertrichosis and mild induration on the

inner thighs and arms at the age of 2. The condition progressed slowly and gradually from the age of 2, spreading to the anterior and posterior sides of the patient's trunk. The patient had been subjected to pubertal induction for 4 years using 0.625 mg conjugated estrogens due to a lack of secondary sex characteristics and primary amenorrhea at the age of 15. However, the treatment did not change the manifestation of the secondary sex characteristics, and the patient had also been diagnosed with hypogonadotropic hypogonadism.

## CLINICAL FINDINGS

The physical examination revealed the presence of plaques with hyperpigmented and indurated centers and hypertrichotic patches with erythematous irregular margins on the chest, abdomen, and back along the spinous process and proximal to the upper and lower limbs, with the knees being spared (Figure 1). These conditions were asymptomatic.



**Figure 1.** Clinical findings: Symmetrical hyperpigmented, hypertrichotic skin lesions on the chest wall (a), back (b), front side of thighs (c), and back side of thighs (d).

The patient had a normal karyotype (normal female, 46xx) and normal mental capacity. She also had normal vital signs. A cardiac auscultation revealed a decrease in the heart sounds and a high heart rate ( $90 <$ ). A 2x2cm lymph node and a scar on the right axillary lymph node were observed in the lymph nodes examination. Her thelarche was in Tanner I stage (prepubertal). In an abdominal examination, the liver was felt 4 cm below the costal margin. In a genital examination, large and indurated labia majora were recorded, and the pubis region was indurated; there was also no vaginal opening. A skeletal examination indicated a short stature (height: 138 cm, and weight: 40 kg), hallux valgus, and lateral tibial torsion.

Since the patient suffered from hypochromic microcytic anemia, an endoscopic examination of the upper gastrointestinal tract was carried out, revealing duodenal mucosal atrophy (D1, D2). Coeliac disease was also found through biopsies. The MRI (with and without contrast) results showed a normal pituitary gland. In ultrasonography, the uterus and ovaries were found to be normal. In the abdomen and pelvis ultrasound assessments, the liver span was 142cm, but the spleen was oversized (span = 142). An examination of the kidneys showed mild hydronephrosis, and cardiomegaly was observed in the CXR. The echocardiography showed right atrium hypertrophy (RAH), right ventricular hypertrophy (RVH), and pulmonary hypertension. Trans-esophageal echocardiograph (TEE) results confirmed the following cardiac conditions: lipomatous hypertrophic change of IAS (inter-atrial septum) cystic mass anterior to PA, most interrupted IVC probably with lung origination without connection to cardiac chamber, and RVH.

Considering the patient's cutaneous manifestations, several differential diagnoses were considered, such as Winchester syndrome, hemochromatosis, POEM's syndrome, Beker's nevus, and morphea. Consequently, the patient



**Figure 2.** Proliferation of histiocytes between collagen bundles; basal layer hyperpigmentation (x40)

underwent a skin biopsy based on these differential diagnoses. The histopathologic evaluation showed widespread fibrosis with proliferation of histiocytes between normal and necrotic collagen bundles and acanthosis with basal layer hyperpigmentation in the epidermis, similar to granuloma annulare and Rosai-Dorfman disease (Figure 2) (Tables 1-3).

**Table 2.** Classification of common clinical findings by the rate of prevalence about patients with H syndrome based on a study of 79 patients <sup>2</sup>

Clinical findings	Prevalence
Cutaneous hyperpigmentation accompanied by hypertrichosis and induration	68%
Flexion contractures of the fingers and toes	56%
Sensorineural hearing loss	53%
Short stature	49%
Hepatomegaly	43%
Splenomegaly	39%

**Table 1.** Results of paraclinical tests for the patient

Test	Results	
CBC (Complete blood count)	Hb:9.8, serum iron:23, MCH:20.3	Anemia
Serology	Anti EMA IgG:143, Anti Giliadin (IgG)>100, TTG (IgG):3.5, ESR:80-100	Increased
Endocrinology	FSH: 6.3, LH: 11.9, Testosterone: 0.09, Estradiol: 50.7	Normal
Thyroid function test	TSH: 2.3, FT4:8.7	Normal
Liver function test	SGOT (AST):9, SGPT (ALT):12, T.Bili:0.5, D.Bili:0.1	Normal
Lipid profile	HDL: 29, Cholesterol:115, Triglyceride:132	Normal

**Table 3.** Clinical findings of our patient

Findings	Clinical manifestations in current patient
Cutaneous	Cutaneous hyperpigmentation with hypertichosis and induration on upper and lower limbs, abdomen, back, buttocks
Musculoskeletal	Hallux valgus, lateral tibial torsion, short stature (138cm)
Cardiovascular	RVH, RAH, pulmonary hypertension, cardiomegaly, lipomatous hypertrophic change of IAS
Hematological	Axillary lymphadenopathy, splenomegaly
Endocrine	Hypogonadism

RVH: Right ventricular hypertrophy

RAE:Right atrial enlargement

IAS:interatrial septum

## DISCUSSION

Most reported cases of H syndrome are in Middle Eastern countries although there are reports of this syndrome in other parts of the world <sup>2</sup>. The determining factor in the discovery of the cause of H syndrome was the mutation in SLC29A3, which encodes protein hENT3. This protein belongs to the ENT3 family, which plays a major role in the mitochondrial membrane and functions of these organelles <sup>3</sup>.

The patient was suffering from hypochromic and microcytic anemia and was diagnosed with coeliac disease through endoscopy of the upper gastrointestinal tract; serologic measurements also showed increased levels in anti-Gliadin (IgG) (> 100) and TTG (IgG) (:3.5). This condition was improved by a gluten-free diet. Various degrees of anemia have been reported in other H syndrome patients, and one patient was diagnosed with immune hemolytic anemia <sup>4</sup>.

IDDM and hearing loss may occur at early ages prior to the onset of cutaneous conditions <sup>5,6</sup>. However, this patient did not suffer from hearing loss or diabetes mellitus. Previous studies have shown a wide range of cardiac conditions in H syndrome patients: ASD (atrial septal defect), VSD (ventricular septal defect), MVP (mitral valve prolapse), cardiomegaly, pulmonary hypertension, left ventricular dilation <sup>1</sup>, acute coronary syndrome <sup>7</sup>, pericarditis, left superior vena cava, pericardial effusion, and pulmonary stenosis <sup>3,8</sup>. The diversity of the heart anomalies in H syndrome patients mirrors the role hENT3 plays in the normal function and structure of the heart <sup>9</sup>. Regarding the heart anomalies, pericardial conditions are the most prevalent cardiovascular anomalies in patients with H syndrome <sup>2</sup>. However, this patient was not diagnosed with any pericardial condition, but lipomatous hypertrophy of IAS

was diagnosed, which has not previously been reported as a prevalent cardiac condition among H syndrome patients. H syndrome is a new form of histiocytosis, and it is considered a histiocytic genodermatosis <sup>5</sup>. From a histopathological point of view, H syndrome is similar to Rosai-Dorfman disease; patients always have high ESR and histiocytic pathologic results <sup>5</sup>. In a biopsy of the cutaneous lesions caused by Rosai-Dorfman, dermal infiltration of large histiocytes was observed along with lymphocytes, plasma cells, and several neutrophils <sup>10</sup>. In addition, histopathological assessments of the cutaneous lesions in H syndrome cases revealed the widespread fibrosis in the derm and subcutaneous fat as well as cells similar to histiocytes with irregular nuclei and nodular aggregation of lymphocytes and scattered plasma cells <sup>11</sup>. A comparison has been drawn between the clinical symptoms and histopathologic characteristics of these two diseases in another study <sup>10</sup> (Table 4).

## CONCLUSION

H syndrome must be taken seriously in patients with typical cutaneous manifestations, disorders in various organs, and endocrine pathologies. The symptoms of H syndrome range from mild to severe. This condition is difficult to diagnose due to similarities between this syndrome and diseases with similar symptoms (especially with similar cutaneous manifestations). In this patient, typical cutaneous manifestations, short stature, delayed puberty, and hypogonadism were indicative of H syndrome. She had developed anemia due to malabsorption caused by coeliac disease. Therefore, considering the multiple reports of anemia in this patient, if endoscopic examinations had been conducted, perhaps coeliac disease would have been considered the cause of anemia and the resulting

**Table 4.** Comparison of clinical and histopathologic features of familial Rosai-Dorfman disease and H syndrome <sup>10</sup>

Tissue	Familial Rosai-Dorfman Disease	H syndrome
Inheritance	Autosomal recessive	Autosomal recessive
Skin	Hyperpigmentation of lower extremities	Hyperpigmentation and indurated hypertrichotic patches on the lower abdomen and lower extremities
Heart	Atrial septal defect	Pulmonary stenosis, patent ductus arteriosus
Ear	Sensorineural deafness	Sensorineural deafness
Abdomen	Hepatosplenomegaly	Hepatosplenomegaly
Growth	Short stature	Short stature
Endocrine	-	Diabetes mellitus Hypogonadism Gynecomastia
Eye	Uveitis, eyelid swellings	Exophthalmos
Hands	-	Camptodactyly, flexion contractures
Feet	-	Hallux valgus fixed flexion contractures of toe joints
Hematological anomalies	Bone marrow showing nonclonal myeloproliferative process, with numerous monocytes and histiocytes and moderate myelofibrosis	Red cell aplasia due to myelofibrosis
Lymph nodes	Cervical, submandibular, inguinal lymphadenopathy	-

diagnosis of H syndrome might not have occurred. This report is an attempt to increase awareness in medical practice about different manifestations of H syndrome.

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**Conflict of Interest:** None declared.

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## Cutaneous necrosis following brown recluse spider bite

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### Dear Editor,

Arachnids are a large class of Arthropods that inhabit all around the planet Earth and consist of varied species<sup>1</sup>. One of the orders of this class is the Araneae. Spiders that belong to the Araneae order live free and are easily identified through having four pairs of legs, chelicerae, and fangs<sup>2</sup>. At the current time, more than 46000 species of spiders have been discovered all over the world<sup>3</sup>. The number of species discovered in Iran is nearly 600. Many species of spiders are harmless to humans and their habitation in proximity to humans does not pose any dangers. However, a number of species are venomous and their bite can cause various complications<sup>4</sup>. Of spiders that are vital from the viewpoint of medicine, *Loxosceles* (Sicariidae) and *Latrodectus* (Theridiidae) should be noted<sup>5</sup>. These spiders reside in some zones of the world including Iran<sup>6</sup>. Sicariidae consists of about 139 species classifies into *Loxosceles* and *Sicarius*. The species of the genus *Sicarius* are found in South America and Africa but *Loxosceles* spiders - also known as recluse spiders- have a global distribution<sup>4</sup>.

In this paper, we reported a case of loxoscelism with cutaneous necrosis following a brown recluse spider bite. He was a 35-year-old male living in Qom city. In June 2018 and after about 48 hours of the bite, the patient requested medical aid. Upon examination of the site of injury on his right calf, two adjacent wounds were seen. The injury was 3 cm in diameter and a bruise was evident around it that was about 12 cm wide. Pain, inflammation, and severe sensitivity were noted in the area of the injury and the patient reported dizziness, fever, and general sensitivity. An ultrasound scan of the injured leg was requested showing reduced surface echogenicity. Blood screening showed an increase in the platelets and white cell count (leukocytosis) with a positive CRP.

At this time, the treatment protocol started with the prescription of intravenous antibiotics and subcutaneous pain killers. Treatment continued until day 17 (Figure 1). From this day on, the wound almost healed. The spider that bit the patient was found and identified as *Loxosceles sp.* using valid diagnostic keys in the laboratory of the Department of Medical Entomology affiliated with Tehran University of Medical Sciences (Figure 2).



Figure 1. Skin erythema, ulceration and necrosis following bites from *Loxosceles sp.*



**Figure 2.** Brown recluse spider (*Loxosceles* sp.).

This is the first case report of loxoscelism due to recluse spider biting in Qom Province. The patient, who was a construction worker, sought medical assistance two days after the bite with an intense pain along with other symptoms. These spiders are found in urban regions, deserts, caves, and mountainous as well as residential areas. The characteristics of this spider include a violin shaped mark on the cephalothorax which can be seen with the unarmored eye<sup>4</sup>. Brown recluse spiders (*Loxosceles* spp.) are often found in temperate and tropical areas of the United States, Europe, and Africa, and in some limited areas of Asia. *Loxosceles rufescens* are reported from Europe, some parts of Australia and in the western Mediterranean region of Palestine<sup>7</sup>. In recent years, loxoscelism has been reported in some regions of Iran such as Bandar Abbas, Kashan, Khorasan Province, northeast of Iran, and Charkhab Cave, southern Iran<sup>8</sup>. Moreover, *Loxosceles rufescens* was also reported in many regions of Iran, including Alborz, Tehran, Razavi Khorasan, Fars, Mazandaran, and Hormozgan<sup>4</sup>. In this study, the patient was referred to the emergency department 48 hours after the bite with intense pain as well as other symptoms such as a wound, inflammation, severe sensitivity, dizziness, fever, elevated platelets and white cell count (leukocytosis), hypertension, nausea, and irritation. Based on previous studies, the brown recluse spider venom contains sphingomyelinase D, and sometimes hyaluronidase, alkaline-phosphatase, phosphohydrolase, protease, and some other enzymes<sup>7,9</sup>. Spider bite symptoms are very different based on the site of bite, spider species, and symptoms such as erythema, pain, and macula at the site of bite. Inflammation and skin necrosis are also observed in some cases, and in cases of fewer complications, such as coagulopathy and disseminated intravascular coagulation (DIC),

vascular bleeding and renal failure are observed, which can sometimes lead to death<sup>7,10</sup>. According to this case, Qom is one of the risk areas for spider bites. In these cases, symptoms such as erythema, pain, fever, and macula are very common in the bite site. Also, inflammation and skin necrosis are observed in some cases, which may be similar to symptoms of many other diseases. For timely diagnosis and treatment of injuries caused by spider bites, adequate training should be given to general physicians and hospital staff.

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