Journal of
Medical Sciences

Research Paper

Gastrointestinal Dysfunction Symptoms and Lipids Profile in Patients with Various Severities of Acne Vulgaris

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According to an old notion, the axis of "brain-gut-skin" plays a significant role in the pathogenesis of acne vulgaris. This study aimed to compare gastrointestinal dysfunction symptoms in patients with different severities of acne vulgaris with their normal counterparts. In this cross-sectional, case-control study, 120 adolescents and young adults were recruited from two teaching dermatological clinics over a one-year period (2012-2013). These participants were 30 normal subjects (controls), 30 patients with mild acne vulgaris, 30 patients with moderate acne vulgaris and 30 patients with severe acne vulgaris. Frequency of gastrointestinal dysfunction symptoms including halitosis, gastric reflux, abdominal bloating, abdominal discomfort, constipation and diarrhea was compared between the controls and the patients. Serum lipids profile was also compared between the patients and the controls. All the four studied groups were matched for their members' age and sex. Controls and the cases with mild acne vulgaris were comparable in terms of the frequency of gastrointestinal symptoms. Frequencies of abdominal bloating (30% vs. 10%, p = 0.05) and constipation (36.7% vs. 13.3%, p = 0.04) were significantly higher in the group with moderate acne comparing with the controls. They were also significant more frequent in the patients with severe acne comparing with the controls (40%, p = 0.01 and 46.7%, p = 0.01, respectively). Comparing with the controls, serum lipids profile was significantly deranged only in the cases with severe acne vulgaris. This study showed that gastrointestinal dysfunction is associated with moderate-to-sever acne vulgaris. In addition, serum lipids profile may be abnormal only in severe acne vulgaris.

Key words: Acne vulgaris, gastrointestinal dysfunction, serum lipids profile

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INTRODUCTION

Acne vulgaris is a very common skin disease, commonly seen in adolescents and young adults. The lesions may occur on any part of the body; but the face, head and upper torso are the most common involved regions (Dawson and Dellavalle, 2013; Feinberg and Shwayder, 2013). Due to the importance of the target population, there are numerous ongoing studies all over the world aiming to promote prevention and treatment of acne vulgaris (Babaeinejad *et al.*, 2011; Fouladi, 2012; Khodaeiani *et al.*, 2012; Babaeinejad and Fouladi, 2013; Goforoushan *et al.*, 2013; Khodaeiani *et al.*, 2013; Kapoor and Saraf, 2011).

The pilosebaceous unit (Fouladi, 2013), microbial agents (Somi *et al.*, 2008; Murillo and Raoult, 2013) and hormonal factors (Navali *et al.*, 2011; Deepika *et al.*, 2012) are the key elements in the pathogenesis of acne vulgaris. However, scientists believe that there are still diverse other known and known underlying etiologies in development and exacerbating of the lesions of acne vulgaris, which yet to be defined (Titus and Hodge, 2012). One of these less studied probable contributors is the psychological factor. The notion of "brain-gut-skin" was first described by Stokes and Pillsbury in 1930. According to their hypothesis, there is an interconnection between these three major organ systems (Bowe and Logan, 2011). To the best of our knowledge, there is only a relevant study in the literature. In this cross-sectional study, it was shown that patients with seborrheic diseases (including acne vulgaris) experience gastrointestinal manifestations including halitosis, gastric reflux, abdominal bloating and constipation more likely than their healthy counterparts (Zhang *et al.*, 2008). The authors, as mentioned before, did not focus on acne vulgaris and its severity. The objective of the present study is to investigate a possible association between gastrointestinal symptoms with acne vulgaris and its severity in a well-designed, case-control setting for the first time.

MATERIALS AND METHODS

In this cross-sectional, case-control study, 120 adolescents and young adults were recruited from two referral dermatological clinics in Tabriz over a one-year period (2012-2013). The studied population was categorized into four groups:

- Controls: Including 30 individuals without current or previous acne vulgaris
- Patients with mild acne vulgaris according to the Evaluator Global Severity Score (EGSS) (Eichenfield *et al.*, 2010) (n = 30)

- Patients with moderate acne vulgaris according to the EGSS (n = 30)
- Patients with severe acne vulgaris according to the EGSS (n = 30)

Subjects with known gastrointestinal disease and those with previous anti-acne treatment were not included. Routine diet of the studied population was similar.

A questionnaire containing two parts and adequate information regarding the questions were handed to each participant. In the first part, demographics of the participants (age and sex) were inquired. In the second part, the presence or absence of gastrointestinal symptoms including halitosis, gastric reflux, abdominal bloating, abdominal discomfort, constipation and diarrhea was investigated.

The inquired symptoms were defined as follows:

- **Halitosis:** Any unpleasant odor of the breath and the mouth air (Aylikci and Colak, 2013)
- **Gastric reflux:** Regurgitation of the contents of the stomach into the mouth (Gul, 2013)
- **Abdominal bloating:** A subjective sensation of swelling of the abdomen with or without burping, borborygmi or flatus (Daneshpajouhnejad *et al.*, 2012)
- **Abdominal discomfort:** Frequent abdominal pain/tenderness before or after meal
- **Constipation:** Presence of at least two of the following: (1) Straining (25% of defecations at the minimum); (2) Hard/lumpy stools (25% of defecations at the minimum); (3) Sensation of incomplete defecation (25% of defecations at the minimum); (4) Sensation of obstruction (25% of defecations at the minimum); (5) Using manual maneuvers (25% of defecations at the minimum) and (6) <three defecations/week (Longstreth *et al.*, 2006)
- **Diarrhea:** Frequent loose or watery stools (fecal output>200 g day^{-1} on western diet) (Longstreth *et al.*, 2006)

Presence of at least one of the above-mentioned symptoms indicated gastrointestinal dysfunction in the present study. Frequency of gastrointestinal symptoms was compared between the controls and the groups of the patients with acne vulgaris.

Serum lipids profile (including serum levels of total cholesterol, low-density lipoprotein or LDL, high-density lipoprotein or HDL and triglyceride) was determined on the venous blood samples obtained from the participants after at least 12 h fasting. For this purpose, previously published standard laboratory methods were employed

(Arora *et al.*, 2010). Finally, the results were compared between the controls and the cases with different severity of acne vulgaris.

Statistical analysis: Data were shown as mean±standard deviation and frequency (%). The SPSS software for Windows (ver.16) was used. Independent samples t test (for age and lipids profile) and the Chi-square/Fisher's exact tests (for sex and the frequency of gastrointestinal symptoms) were employed for analyzing. P = 0.05 was considered statistically significant.

RESULTS

Demographics: In the control group, there were 17 males (56.7%) and 13 females (43.3%) with a mean age of 22.63±3.37 years (range: 18-30).

In the group with mild acne vulgaris, there were 19 males (63.3%) and 11 females (36.7%) with a mean age of 23.90±4.23 years (range: 18-30). In the group with moderate acne vulgaris, there were 18 males (60%) and 12 females (40%) with a mean age of 23.53±3.97 years (range: 18-30). In the group with severe acne vulgaris, there were 19 males (63.3%) and 11 females (36.7%) with a mean age of 24.23±3.74 years (range: 18-30). These four groups were comparable in terms of sex (Chi-square test p = 0.96) and age (One-way ANOVA p = 0.12). Demographics of the studied population are summarized in Table 1.

Serum lipid profile
Total cholesterol level: Mean serum total cholesterol level was 187.78±2.45 mg dL^{-1} in the controls, 189.23±4.12 mg dL^{-1} in the patients with mild acne vulgaris, 190.34±4.43 mg dL^{-1} in the patients with moderate acne vulgaris and 218.22±6.01 mg dL^{-1} in the patients with severe acne vulgaris. Based on the result of One-way ANOVA test there was a significant difference between the groups (p = 0.02). Based on post hoc analysis, however, only the mean serum level of total cholesterol was significantly higher in the cases with severe acne vulgaris in comparison with the controls (p = 0.03).

LDL-cholesterol level: Mean serum LDL-cholesterol level was 122.46±7.13 mg dL^{-1} in the controls, 126.89±4.32 mg dL^{-1} in the patients with mild acne

vulgaris, 128.22±4.12 mg dL^{-1} in the patients with moderate acne vulgaris and 149.65±5.12 mg dL^{-1} in the patients with severe acne vulgaris. Based on the result of One-way ANOVA test there was a significant difference between the groups (p = 0.001). Based on post hoc analysis, however, only the mean serum level of LDL-cholesterol was significantly higher in the cases with severe acne vulgaris in comparison with the controls (p = 0.01).

HDL-cholesterol level: Mean serum HDL-cholesterol level was 43.45±1.12 mg dL^{-1} in the controls, 39.12±0.23 mg dL^{-1} in the patients with mild acne vulgaris, 37.12±1.02 mg dL^{-1} in the patients with moderate acne vulgaris and 33.89±0.89 mg dL^{-1} in the patients with severe acne vulgaris. Based on the result of One-way ANOVA test there was a significant difference between the groups (p = 0.001). Based on post hoc analysis, however, only the mean serum level of HDL-cholesterol was significantly lower in the cases with severe acne vulgaris in comparison with the controls (p = 0.003).

Triglyceride level: Mean serum triglyceride level was 139.12±3.11 mg dL^{-1} in the controls, 139.34±4.12 mg dL^{-1} in the patients with mild acne vulgaris, 142.34±3.23 mg dL^{-1} in the patients with moderate acne vulgaris and 156.02±5.14 mg dL^{-1} in the patients with severe acne vulgaris. Based on the result of One-way ANOVA test there was a significant difference between the groups (p = 0.03). Based on post hoc analysis, however, only the mean serum level of triglyceride was significantly higher in the cases with severe acne vulgaris in comparison with the controls (p = 0.04). Serum lipid profile of the studied groups are summarized and compared in Table 2.

Gastrointestinal symptoms
Controls: In the control group, halitosis was positive in 3 cases (10%), gastric reflux in 3 cases (10%), abdominal bloating in 3 cases (10%), abdominal discomfort in 2 cases (6.7%), constipation in 4 cases (13.3%), diarrhea in 1 case (3.3%) and any gastrointestinal dysfunction symptom in 11 cases (36.7%).

Patients with mild acne vulgaris vs. controls: In the group with mild acne vulgaris, halitosis was positive in 2 cases (6.7%), gastric reflux in 3 cases (10%), abdominal

Table 1: Demographics of the studied population including patients with mild, moderate and severe acne vulgaris and their normal counterparts (controls)

Variable	Mild acne (n = 30)	Moderate acne (n = 30)	Severe acne (n = 30)	Control (n = 30)	p-value
Sex					
Male	19 (63.3)	18 (60)	19 (63.3)	17 (56.7)	0.96
Female	11 (36.7)	12 (40)	11 (36.7)	13 (43.3)	
Age (year)	23.90±4.23	23.53±3.97	24.23±3.74	22.63±3.37	0.12

Data are presented as mean±standard deviation and frequency (%), p-value = 0.05 is statistically significant

Table 2: Serum lipid profile of the studied population including patients with mild, moderate and severe acne vulgaris and their normal counterparts (controls)

Variable	Mild acne (n = 30)	Moderate acne (n = 30)	Severe acne (n = 30)	Control (n = 30)	p-value
Total cholesterol	189.23±4.12	190.34±4.43	218.22±6.01	187.78±2.45	**0.02**
LDL	126.89±4.32	128.22±4.12	149.65±5.12	122.46±7.13	**0.01**
HDL	39.12±0.23	37.12±1.02	33.89±0.89	43.45±1.12	**0.001**
Triglyceride	139.34±4.12	142.34±3.23	156.02±5.14	139.12±3.11	**0.03**

Data are presented as mean±standard deviation, p-value = 0.05 is statistically significant (bold), HDL: High-density lipoprotein, LDL: Low-density lipoprotein

bloating in 6 cases (20%), abdominal discomfort in 2 cases (6.7%), constipation in 7 cases (23.3%), diarrhea in 2 cases (6.7%) and any gastrointestinal dysfunction symptom in 16 cases (53.3%).

Comparing the controls with the patients with mild acne vulgaris, there was not a significant difference between the two groups in terms of halitosis (Fisher's exact test p = 0.50), gastric reflux (Chi-square test p = 0.67), abdominal bloating (Chi-square test p = 0.47), abdominal discomfort (Chi-square test p = 0.69), constipation (Chi-square test p = 0.32) and any gastrointestinal dysfunction symptom (Chi-square test p = 0.19).

Patients with moderate acne vulgaris vs. controls: In the group with moderate acne vulgaris, halitosis was positive in 4 cases (13.3%), gastric reflux in cases (10%), abdominal bloating in 9 cases (30%), abdominal discomfort in 3 cases (10%), constipation in 11 cases (36.7%), diarrhea in 3 cases (10%) and any gastrointestinal dysfunction symptom in 18 cases (60%).

Comparing the controls with the patients with moderate acne vulgaris, there was not a significant difference between the two groups in terms of halitosis (Fisher's exact test p = 0.50), gastric reflux (Chi-square test p = 0.67), abdominal discomfort (Fisher's exact test p = 0.50) and any gastrointestinal dysfunction symptom (Chi-square test p = 0.07). Frequencies of abdominal bloating (Fisher's exact test p = 0.05) and constipation (Chi-square test p = 0.04) were significantly higher in the group with moderate acne comparing with those in the controls.

Patients with severe acne vulgaris vs. controls: In the group with severe acne vulgaris, halitosis was positive in 6 cases (20%), gastric reflux in 4 cases (13.3%), abdominal bloating in 12 cases (40%), abdominal discomfort in 5 cases (16.7%), constipation in 14 cases (46.7%), diarrhea in 4 cases (13.3%) and any gastrointestinal dysfunction symptom in 20 cases (66.7%).

Comparing the controls with the patients with severe acne vulgaris, there was not a significant difference between the two groups in terms of halitosis (Fisher's exact test p = 0.47), gastric reflux (Fisher's exact test p = 0.50) and abdominal discomfort (Fisher's exact test p = 0.42).

Frequencies of abdominal bloating (Fisher's exact test p = 0.01), constipation (Chi-square test p = 0.01) and any gastrointestinal dysfunction symptom (Chi-square test p = 0.02) were significantly higher in the group with severe acne comparing with those in the controls.

Percentages of the mentioned gastrointestinal symptoms in the four studied groups are shown in Fig. 1.

DISCUSSION

Psychological complications, such as depression and anxiety, are frequent in patients with acne vulgaris (Uhlenhake *et al.*, 2010). On the other hand, it has been suggested that acne vulgaris predisposes patients to gastrointestinal upset. It is now over 70 years that according to these findings, the term "brain-gut-skin" has been proposed (Bowe and Logan, 2011).

In the present study, gastrointestinal manifestations in acne vulgaris were investigated. Based on this investigation, frequency of the cases with abdominal bloating and constipation was significantly higher in the cases with moderate and severe acne vulgaris comparing with the controls. Comparing with the cases mild acne vulgaris and the controls, however, the differences did not reach a statistical level of significance (Fig. 1).

These findings are in line with the results of a previous study by Zhang *et al.* (2008). In this study, they had been evaluated over 13000 adolescents and found that gastrointestinal symptoms were significantly higher in the patients with diseases of the sebaceous glands, including acne vulgaris.

Unlike Zhang's study, in the present work the role of the severity of acne vulgaris was examined for the first time in the literature. Interestingly, there was a positive correlation between the number of gastrointestinal manifestations and the severity of acne vulgaris. This finding further corroborates the hypothesis of "brain-gut-skin" axis. According to this theory, both functional integrity of the intestine and its microbial inhabitants play a role in psychological symptoms and skin inflammation. On the other hand, both mental status and skin involvement can alter the intestinal microbial flora, which in turn, enhances systemic and local inflammation. This is a "vicious cycle" which has been theorized in the
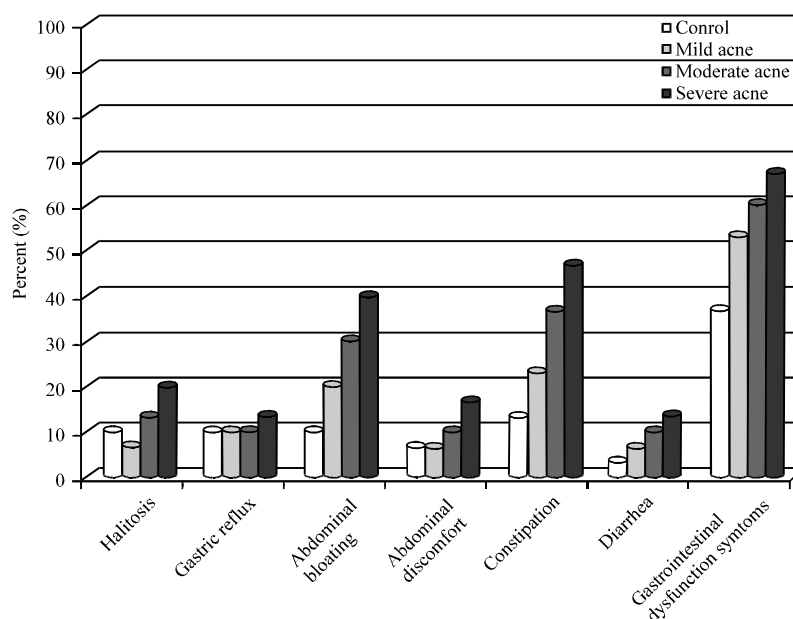
Fig. 1: Percentage of gastrointestinal symptoms in the studied population including patients with mild, moderate and severe acne vulgaris and their normal counterparts (controls)

interconnection between the gut and the skin in patients with acne vulgaris (Bowe and Logan, 2011).

Small Intestinal Bacterial Over growth (SIBO) is another key element that may further connect acne vulgaris and gastrointestinal malfunction. In this condition, mild gastrointestinal manifestations, such as those investigated in the present work, exist (Bures *et al.*, 2010; Lombardo *et al.*, 2010). It has been shown that SIBO is more prevalent in patients with acne vulgaris in comparison with uninvolved people (Bowe and Logan, 2011).

It has been previously reported that psychological stress stops normal flowing in the intestine. This condition promotes bacterial overgrowth and compromise the intestinal barrier (Wang and Wu, 2005). This finding sheds more light on the association between gastrointestinal complaints and acne vulgaris.

In available data, a particular emphasis exists on the connection between constipation and psychological compromise. Accordingly, chronic constipation is associated with significant alteration to the intestinal microflora (Attaluri *et al.*, 2010). Depression, on the other hand, promotes constipation and further deteriorates intestinal permeability and normal function (Hillila *et al.*, 2008; Maes *et al.*, 2008). This mutual relation may justify the place of acne vulgaris in this interconnection between constipation and psychological involvement.

Difference between acne patients and normal controls in terms of their intestinal microflora is another

hint for an association between the skin and the gut. For example, a Russian study by Volkova *et al.* (2001) has shown that 54% of patients with acne vulgaris had significant changes in the intestinal microflora. This may also justify why adding probiotics to the diet of patients with acne vulgaris can play role in therapy (Kim *et al.*, 2010).

According to recent data, probiotics can reduce systemic inflammation and oxidative stress, two factors that have been accused of playing pivotal role in pathogenesis of acne vulgaris (Mikelsaar and Zilmer, 2009; Bowe and Logan, 2010; Fu *et al.*, 2010).

In the present study serum lipid profile of the patients with different severities of acne vulgaris was also compared with the controls. Accordingly, serum lipid profile abnormalities were only present in the cases with severe acne vulgaris. These findings are in conformity with the results of two previously performed studies in this regard (Abulnaja, 2009; Arora *et al.*, 2010).

Overall, although the notion of association between acne vulgaris and gastrointestinal system dates back to more than 50 years ago, there is significant scarcity of data in this regard. The current study is the first one that examines this association emphasizing the severity of acne. Gut microbes, oxidative stress, inflammation, glycemic control and neurotransmitters all may have role in this connection (Bowe and Logan, 2011), indicating a very complex entity. Further studies are needed to elucidate the role of these possible contributors individually.

CONCLUSION

Gastrointestinal dysfunction symptoms including abdominal bloating and constipation are significantly more frequent in the patients with moderate-to-severe acne vulgaris comparing with their unaffected counterparts.

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