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Report

Analysis of 3702 patients with acne vulgaris and concomitant comorbidities in Turkey: a multi-centered, prospective, controlled study

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Abstract

Background Acne vulgaris is a chronic inflammatory skin disease that affects the pilosebaceous unit. Although it is considered to be a skin-limited disease, different clinical studies have recently been published in which the disease is accompanied by systemic symptoms. In this study, systemic comorbidities accompanying acne vulgaris and the relationship between existing comorbidities and disease severity are investigated.

Methods This prospective multicenter study was conducted by the Turkish Society of Dermatology Acne Study Group. Twelve dermatology clinics and 14 clinicians throughout Turkey participated in the study. A structured physician-administered questionnaire was used to collect patient demographics, clinical findings, and lifestyle data. Physicians recorded each participant's medical history, including current and past comorbidities, duration of any comorbidity, smoking, and drinking. Body mass index (BMI) was calculated.

Results There were 3022 patients in the adolescent acne group and 897 in the control group. The incidence of nonmigraine headache in adolescents with acne was significantly higher than in the nonacne group ($P = 0.019$). There were 680 patients in the postadolescent acne group and 545 in the control group. In the postadolescent group, incidence of metabolic disease was lower than the control group ($P = 0.003$). In the postadolescent group, premenstrual syndrome ($P < 0.001$) and PCOS ($P = 0.007$) were more common than the control group.

Conclusions In this study, we observed that acne vulgaris does not cause systemic comorbidities. There is also a need for new studies involving a large number of patients to illuminate systemic diseases accompanying acne vulgaris.

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Introduction

Acne vulgaris is a chronic inflammatory skin disease.[1–5] The main recognized mechanism is follicular hyperkeratinization, androgen hypersensitivity, excessive sebum secretion, *P. acnes*, colonization of bacteria, such as *S. epidermis*, and inflammation.[1–6] In recent years, some publications on acne and *P. acnes* and their related diseases have been reported. *P. acnes* was claimed to be responsible for the pathogenesis of endophthalmitis.[7,8] It was also identified as a pathogen in infective endocarditis, meningitis, and sarcoidosis.[9–13] Recently, it has been reported that there is a relationship between acne and insulin resistance, sinus infection, asthma, non-asthma lung disease, reflux, abdominal pain, nausea and food allergy, depression, anxiety, attention deficit hyperactivity disorder, and increased insomnia.[4,14–16]

The number of studies related to acne and comorbidities is very limited, and there is no data belonging to our country. The present study aimed to determine what systemic comorbidities accompany acne vulgaris (primary objective) and to determine the relationship between the severity and the presence of any type of systemic comorbidities (secondary objective).

Materials and methods

Study design

The study was conducted by the Turkish Dermatology Association Acne Study Group. The study was designed by the first two authors, and 12 dermatology clinics and 14 clinicians participated in the study. The study protocol was approved by the Istanbul Medeniyet University Ethics Committee (0107/2017). All the participants provided written informed consent, and the study was performed according to the principles of the Declaration of Helsinki.

Study population

The diagnostic criteria for acne vulgaris are having comedone, inflammatory papules, and pustules. Nodules and cysts are also included if comedone is present. Acne vulgaris patients are divided into two groups as adolescent and postadolescent and control group selected. Group members consisted of male and female patients aged 12–55 years. The demographic and clinical features of the patients were recorded. Height, weight, and body mass index (BMI) were calculated. Whether there were any additional diseases, the medications used, smoking, and the use of alcohol were questioned by the specialist. Acne severity was calculated according to the scoring system recommended by the Food and Drug Administration (FDA).[17]

Parental consent was obtained for patients under 18 years of age.

The control group was selected from other patients and hospital staff who were suitable for the patients in terms of age and sex, with no acne or acneiform eruption, who applied to the outpatient clinic for cosmetic purposes or other reasons, and their information was recorded using the same form.

Exclusion criteria

Patients with disabilities, who have no authority to sign, or who are nursing, pregnant, or planning to become pregnant were excluded from the study. Acne cosmetica, acne excoriée, rosacea, and acneiform eruptions such as drug-induced acne patients were not included in the study.

Height and weight measurement

Anthropometric measurements including height and weight and BMI were calculated as weight/height^2. Those with a BMI of less than 18.5 were evaluated as underweight, those between 18.5 and 23 as normal weight, and with more than 23 as overweight.

Alcohol consumption and smoking

Smoking was evaluated as "presmokers", "current smokers", and "nonsmokers". Those who have stopped smoking at least 6 months ago were considered as “presmokers”. How many packs of cigarettes per day was recorded for current smokers.

Alcohol consumption for “those who use it in any amount for 3 times a week regularly” was recorded as “using”, for “those who do not use it” and “social drinkers occasionally” was recorded as “not using”.

Systemic comorbidity inquiry

Systemic comorbidities (lifetime) were self-reported and confirmed by medication use or when possible by medical records. Systemic comorbidities were categorized as allergies, respiratory tract diseases, gastrointestinal system diseases, metabolic disorders, cardiovascular diseases, urogenital disorders, neurological disorders, musculoskeletal system disorders, hepatobiliary system disorders, thyroid disorders, cancer, psychiatric disorders, female hormonal diseases, and male hormonal diseases.[18]

Statistical analysis

Whether the distributions of continuous variables were normal or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Descriptive statistics for continuous variables were shown as mean $\pm$ SD. Number of cases and percentage were used for categorical data. Each participating study center was requested to recruit $\geq$250 acne vulgaris patients and gender- and age-matched controls with at least one-fourth enrollment ratio.

Mean differences between groups were compared by Student’s *t*-test; contrarily, one-way ANOVA was performed to make comparisons among more than two independent groups. When the *P*-value from one-way ANOVA was statistically significant, post hoc Tukey HSD test was used to know which group differs from which others. To compare categorical

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variables, in 2 × 2 contingency tables, the Continuity Corrected Chi-square test was used when one or more of the cells have an expected frequency of 5–25, and the Fisher's exact test was used when one or more of the cells have an expected frequency of 5 or less. However, the likelihood ratio test was performed in R × C contingency tables, when one or more of the cells have an expected frequency of 5 or less. Otherwise, Pearson's Chi-square test was applied for categorical data analyses. Determining the best predictor(s) which affect on the existence of acne were evaluated by multiple logistic regression analyses. Any variable whose univariable test had a p-value less than 0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratios, 95% confidence intervals, and Wald statistics for each independent variable were also calculated.

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

In the adolescent acne group, there were 3022 patients, and in the control group, there were 897 patients.

Among the patients under 25 years of age, the rate of females was higher in the acne group, and the rate of males was lower than the control group ($P < 0.001$). The prevalence of alcohol history ($P < 0.001$), smoking history ($P = 0.011$), and gastrointestinal disease ($P < 0.001$) was statistically significantly lower in the acne group compared to the control group. Family history ($P < 0.001$) and frequency of neurological diseases ($P = 0.043$) were significantly higher in the acne group compared to the control group. The average BMI of the acne group was statistically significantly lower than the control group ($P < 0.001$). The clinical and demographic findings of the patients are given in Table 1.

In the postadolescent acne group, there were 680 patients, and in the control group, there were 545 patients.

The rate of females was higher in the acne group, and the rate of males was lower in the patients aged 25 and over compared to the control group ($P < 0.001$). Compared to the control group, the rate of having metabolic diseases was statistically significantly lower in the acne group ($P = 0.003$). The frequency of family history ($P < 0.001$), smoking history ($P = 0.045$), and female hormonal diseases ($P < 0.001$) was statistically significantly higher in the acne group compared to the control group. The average BMI of the acne group was statistically significantly lower than the control group ($P < 0.001$). The clinical and demographic findings of the patients are given in Table 2.

In the multivariate logistic regression analysis, the most determinant factors in distinguishing between acne and control groups were as follows: age, family history, gender, history of alcohol, smoking history, and BMI. When the correction was made according to other possible risk factors, low age, family history of acne, female gender, no alcohol history, smoking history, and low BMI statistically significantly increased the probability of having acne ($P < 0.05$) (Table 3).

Table 1 Clinical, demographic features, and different accompanying diseases between control and patient groups in <25 years old (adolescent)

	Control (n = 897)	Acne (n = 3022)	*P*-value
Gender			**<0.001**†
Female	551 (61.4%)	2081 (68.9%)	
Male	346 (38.6%)	941 (31.1%)	
BMI (kg/m^2)	22.28 ± 3.24	21.76 ± 3.23	**<0.001**‡
Smoking history	155 (17.3%)	419 (13.9%)	**0.011**†
Alcohol history	53 (5.9%)	65 (2.2%)	**<0.001**†
Family history	185 (23.6%)	1478 (48.9%)	**<0.001**†
Accompanying diseases	386 (43.0%)	1244 (41.2%)	0.319†
Allergies	103 (11.5%)	283 (9.4%)	0.062†
Respiratory tract diseases	73 (8.1%)	282 (9.3%)	0.274†
Gastrointestinal system diseases	101 (11.3%)	233 (7.7%)	**<0.001**†
Metabolic diseases	18 (2.0%)	58 (1.9%)	0.977¶
Cardiovascular system diseases	2 (0.2%)	5 (0.2%)	0.663$
Urogenital system diseases	16 (1.8%)	73 (2.4%)	0.323¶
Neurological diseases	66 (7.4%)	289 (9.6%)	**0.043**†
Musculoskeletal system diseases	32 (3.6%)	114 (3.8%)	0.776†
Hepatobiliary system diseases	3 (0.3%)	9 (0.3%)	0.743$
Thyroid diseases	25 (2.8%)	67 (2.2%)	0.387¶
Malignant tumors	0 (0.0%)	3 (0.1%)	>0.999$
Psychiatric diseases	59 (6.6%)	212 (7.0%)	0.650†
Female hormonal diseases	92 (16.7%)	349 (16.8%)	0.967†
Male hormonal diseases	0 (0.0%)	3 (0.3%)	0.568$

P-values are bolded when statistically significant difference is detected.
† Pearson's Chi-square test.
‡ Student's *t* test.
¶ Continuity Corrected Chi-square test.
$ Fisher's exact test.

Discussion

Many factors are blamed for the etiopathogenesis of acne. Genetic susceptibility, androgen hyperactivity, increased proinflammatory lipids targeting sebocytes, toll-like receptor 2 (Toll 2), IL-1, IL-2, IL-6, IL-8, IL-4, IL-17, TNF, chemokines, neuroendocrine system fluctuations, the consumption of high glycemic indexed foods, and increased insulin/IGF-1 signaling are suggested to be the cause of acne formation.[1–6] In recent years, it has been accepted that acne vulgaris is a metabolic disease of sebaceous glands.[4,19] It is known that insulin resistance, obesity, type 2 diabetes, cancer, and Alzheimer's disease develop

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Table 2 Clinical, demographic features, and difference accompanying diseases between control and patient groups in ≥25 years old (postadolescent)

	Control (n = 545)	Acne (n = 680)	P-value
Gender			**<0.001**[†]
Female	365 (67.0%)	555 (81.6%)	
Male	180 (33.0%)	125 (18.4%)	
BMI (kg/m^2)	24.44 ± 4.06	23.49 ± 3.60	**<0.001**[‡]
Smoking history	143 (26.2%)	214 (31.5%)	**0.045**[†]
Alcohol history	41 (7.5%)	43 (6.3%)	0.409[†]
Family history	124 (23.2%)	287 (42.2%)	**<0.001**[†]
Accompanying diseases	297 (54.5%)	388 (57.1%)	0.369[†]
Allergies	67 (12.3%)	74 (10.9%)	0.447[†]
Respiratory tract diseases	39 (7.2%)	48 (7.1%)	0.948[†]
Gastrointestinal system diseases	94 (17.2%)	109 (16.0%)	0.569[†]
Metabolic diseases	53 (9.7%)	36 (5.3%)	**0.003**[†]
Cardiovascular system diseases	4 (0.7%)	8 (1.2%)	0.627[¶]
Urogenital system diseases	13 (2.4%)	31 (4.6%)	0.061[¶]
Neurological diseases	85 (15.6%)	120 (17.6%)	0.339[†]
Musculoskeletal system diseases	44 (8.1%)	64 (9.4%)	0.412[†]
Hepatobiliary system diseases	5 (0.9%)	6 (0.9%)	>0.999[$]
Thyroid diseases	28 (5.1%)	48 (7.1%)	0.166[†]
Malignant tumors	2 (0.4%)	1 (0.1%)	0.588[$]
Psychiatric diseases	62 (11.4%)	99 (14.6%)	0.104[†]
Female hormonal diseases	56 (15.3%)	149 (26.8%)	**<0.001**[†]
Male hormonal diseases	1 (0.6%)	0 (0.0%)	>0.999[$]

P-values are bolded when statistically significant difference is detected.
[†] Pearson's Chi-square test.
[‡] Student's t-test.
[¶] Continuity Corrected Chi-square test.
[$] Fisher's exact test.

Table 3 The most determinant factors in distinguishing between acne and control groups (according to the multivariate logistic regression analysis)

		95% CI		
	Ratio of odds	Lower limit	Upper limit	Wald value
Adolescent group				
Female	1.394	1.171	1.659	13.954
BMI (kg/m^2)	0.967	0.943	0.992	6.777
Smoking history	0.918	0.729	1.156	0.530
Alcohol history	0.429	0.284	0.648	16.176
Accompanying disease	0.854	0.723	1.010	3.414
Family history	3.074	2.564	3.686	147.116
Postadolescent group				
Female	2.184	1.626	2.932	26.977
BMI (kg/m^2)	0.944	0.915	0.975	12.336
Smoking history	1.628	1.230	2.156	11.585
Alcohol history	0.974	0.596	1.592	0.011
Accompanying disease	0.951	0.742	1.217	0.161
Family history	2.324	1.794	3.011	40.726

through the pathway of a kinase termed mammalian target of rapamycin complex 1 (mTORC1). Acne vulgaris is also suggested to occur through the same pathway.[19–21]

Sinopulmonary diseases

Silverberg *et al.* reported that the prevalence of sinus infection, asthma, and non-asthma lung disease, reflux, abdominal pain, nausea/vomiting, and food allergy was found to be more frequent in severe acne than in nonacne patients.[4] Depression, anxiety, insomnia, and attention-deficit hyperactivity syndrome were also stated to be more common in these individuals.[4] In another study, it was found that severe acne and sinopulmonary diseases, sinusitis, asthma, and other lung diseases were found to be more frequent in severe acne. In 48 patients with chronic maxillary sinusitis, colonization of *P. acnes* and other anaerobes was shown.[20] The reason for the frequency of acute or chronic sinusitis in acne may be *P. acnes* colonization. Another hypothesis is that systemic antibiotic therapies used for acne disrupt the normal flora and localization of pathogenic strains. In our study, the incidence of sinopulmonary diseases did not statistically differ in the adolescent acne group (P = 0.274) and the postadolescent group (P = 0.948) than their own control groups. Also allergy incidence did not differ in two groups (Tables 1 and 2). There were no differences between acne severity and history of having any sinopulmonary disease (P > 0.05).

Metabolic condition

In Nagpal *et al.*'s study, insulin resistance in the acne group was reported to be more common compared to the control group. In this study, the incidence frequency of insulin resistance and metabolic syndrome did not vary according to the severity of acne. In another study, it was reported that insulin resistance is more common in male patients aged 25 years and older (postadolescent acne), and it was emphasized that these patients may develop type 2 diabetes in the future.[15,21] In societies adopting a nutrition type suitable to Palaeolithic diet, which is poor in high glycemic carbohydrates, milk, and dairy products, the incidence rate of acne is very low. Excessive consumption of Western-style diet, milk, and milk proteins stimulates mTORC1, which may cause insulin resistance, obesity, type 2 diabetes, cancer, and neurodegenerative diseases such as Alzheimer's disease. In one study, some of the patients with acne were given low glycemic index diets, and after 2 weeks, their IGF-1 levels decreased and positive effects were found in treatment compared to the control group.[22,23] In our study, history of hypertension, diabetes mellitus, and hyperlipidemia was not different between adolescent acne groups (P = 0.977) when compared to the control group. In the

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Table 4 Frequency distribution of patients over 25 years of age in terms of metabolic and gynecological diseases according to control and acne groups

	Control (n = 545)	Acne (n = 680)	P-value
Obesity	33 (6.1%)	16 (2.4%)	**0.002**†
Chronic urinary tract infection	3 (0.56%)	11 (1.7%)	<0.05
	Control (n = 365)	**Acne (n = 555)**	**P-value**
Premenstrual syndrome	30 (8.2%)	92 (16.6%)	**<0.001**¶
PCOS	14 (3.8%)	48 (8.6%)	**0.007**†

P-values are bolded when statistically significant difference is detected.
† Continuity Corrected Chi-square test.
‡ Fisher's exact test of probability.
¶ Pearson's Chi-square test.

Table 5 Frequency distribution of cases under 25 years of age in terms of accompanying comorbid diseases according to control and acne groups

	Control (n = 897)	Acne (n = 3022)	P-value
Gastritis	62 (6.9%)	115 (3.8%)	**<0.001**†
Reflux	38 (4.2%)	83 (2.7%)	**0.024**†
Nausea, vomiting	6 (0.7%)	16 (0.5%)	0.813‡
Duodenal ulcer	0 (0.0%)	18 (0.6%)	**0.020**¶
Malabsorption	3 (0.3%)	1 (0.03%)	**0.040**¶
Celiac	0 (0.0%)	3 (0.1%)	>0.999¶
Inflammatory bowel diseases	5 (0.6%)	12 (0.4%)	0.562¶
Migraine	27 (3.0%)	87 (2.9%)	0.837†
Other headache	35 (3.9%)	179 (5.9%)	**0.019**†
Epilepsy	2 (0.2%)	15 (0.5%)	0.390¶
Neuropathy	1 (0.1%)	2 (0.1%)	0.542¶
Degenerative disc diseases	1 (0.1%)	5 (0.2%)	>0.999¶
Brain tumors	0 (0.0%)	4 (0.1%)	0.580¶

P-values are bolded when statistically significant difference is detected.
† Pearson's Chi-Square test.
‡ Continuity Corrected Chi-Square Test.
¶ Fisher's exact test of probability.

postadolescent group, incidence of metabolic disease was lower than the control group ($P = 0.003$) (see Table 4). We think that it can be owing to lower BMI in the postadolescent acne group than the control group ($P < 0.001$), and it may be because of the fact that in the postadolescent acne group, the rate of alcohol consumption ($P = 0.409$) was lower than the control group.

Different results have been reported in studies on the relationship between BMI and acne vulgaris. In some studies, increased BMI has been reported to trigger acne vulgaris formation, whereas in some studies, no positive relationship was found.[19,23–25] In our study, the mean BMI of the adolescent acne group (21.76 ± 3.23) was lower than the control group (22.28 ± 3.24) ($P < 0.001$). The mean BMI of the postadolescent acne group (23.49 ± 3.60) was also lower than the control group (24.44 ± 4.06) ($P < 0.001$) (see Tables 1 and 2).

As a result of multivariate logistic regression analysis, the fact that having low BMI values statistically significantly increased the likelihood of acne ($P < 0.05$). No significant difference was found in mean BMI according to acne severity in acne groups ($P < 0.05$).

Gastrointestinal system

In light of recent studies, it is argued that *P. acnes* may be a factor in the head, neck, and gastrointestinal system diseases due to colonization in these regions. A study with 13,215 acne adolescents in China showed that acne is associated with gastric reflux, abdominal bloating, and constipation. It was discussed whether these symptoms are due to drug side effects or *P. acnes*.[26] In the adolescent acne group, the incidence of gastritis ($P < 0.001$), reflux ($P = 0.024$), and malabsorption ($P = 0.040$) rate was low, and the difference was statistically significant (see Table 5). It may be due to the lower BMI index in the acne group. Incidence of duodenal ulcer ($P = 0.020$) rate is higher. There was no difference between the postadolescent groups ($P = 0.569$).

Smoking

Nicotine triggers follicular hyperkeratinization, causes epithelial hyperplasia, and triggers acne formation. However, different results have been obtained in studies investigating the relationship between smoking and acne. In Capitanio *et al.*'s study, cigarette smoking was found in 66% of patients with postadolescent acne. In Yang *et al.*'s study, the relationship between smoking and postadolescent acne was investigated, and it was suggested that smoking may cause acne formation by increasing oxidative stress.[3,27–29] In our study, it was found that smoking was not a determinant factor in disease formation in the adolescent acne group ($P = 0.466$), but acne was more common in smokers with postadolescent acne ($P = 0.045$) (Table 2). This finding is the same as Capitanio *et al.*'s study.

Cardiovascular system

In a 20 -year long cohort study in male university students, BMI, blood pressure, and coronary artery risk factors were compared between the individuals with acne and the control group, and the risk of coronary artery disease was reported to be less in individuals with acne. However, in this study, the group of acne is in a low socioeconomic level and has a low smoking level.[16] In our study, history of coronary artery disease, heart attack, peripheral arterial disease, and cerebrovascular history did not differ between acne groups and control groups (see Tables 1 and 2).

Thyroid diseases

In Vergou *et al.*'s study, there was no significant difference between thyroid hormone and thyroid autoantibody values

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Table 6 Demographic and clinical characteristics of the cases according to the severity of the disease within the acne groups

	Mild (n = 1303)	Moderate (n = 1636)	Severe (n = 763)	P-value
Age <25 years	21.5 ± 5.6[a]	21.1 ± 5.6[b]	20.2 ± 5.2[a,b]	**<0.001**[†]
Age ≥25 years	260 (20.0%)[a]	309 (18.9%)[b]	111 (14.5%)[a,b]	**0.007**[‡]
Female factors	1011 (77.6%)[a,c]	1204 (73.6%)[b,c]	421 (55.2%)[a,b]	**<0.001**[‡]
BMI (kg/m^2)	22.0 ± 3.4	22.1 ± 3.4	22.3 ± 3.2	0.252[†]
Smoking history	220 (16.9%)	263 (16.1%)	150 (19.7%)	0.092[‡]
Alcohol history	32 (2.5%)[a]	39 (2.4%)[b]	37 (4.8%)[a,b]	**0.002**[‡]
Family history	554 (42.5%)[a,c]	790 (48.3%)[b,c]	421 (55.2%)[a,b]	**<0.001**[‡]
Accompanying diseases	627 (48.1%)[a]	768 (46.9%)[b]	237 (31.1%)[a,b]	**<0.001**[‡]
Allergies	136 (10.4%)[a]	168 (10.3%)[b]	53 (6.9%)[a,b]	**0.018**[‡]
Respiratory disease	129 (9.9%)[a]	155 (9.5%)[b]	46 (6.0%)[a,b]	**0.007**[‡]
Gastrointestinal disease	125 (9.6%)[a]	177 (10.8%)[b]	40 (5.2%)[a,b]	**<0.001**[‡]
Metabolic diseases	32 (2.5%)	35 (2.1%)	27 (3.5%)	0.124[‡]
Cardiovascular system disease	3 (0.2%)	9 (0.6%)	1 (0.1%)	0.166[¶]
Urogenital system disease	50 (3.8%)[a,c]	40 (2.4%)[c]	14 (1.8%)[a]	**0.014**[‡]
Neurological disease	162 (12.4%)[a]	202 (12.3%)[b]	45 (5.9%)[a,b]	**<0.001**[‡]
Musculoskeletal diseases	68 (5.2%)	86 (5.3%)	24 (3.1%)	0.055[‡]
Hepatobiliary system	7 (0.5%)	6 (0.4%)	2 (0.3%)	0.604[‡]
Thyroid diseases	47 (3.6%)	52 (3.2%)	16 (2.1%)	0.158[‡]
Malignant tumors	4 (0.3%)[c]	0 (0.0%)[c]	0 (0.0%)	**0.015**[¶]
Psychiatric disease	119 (9.1%)[a]	147 (9.0%)[b]	45 (5.9%)[a,b]	**0.020**[‡]
Female hormonal diseases	226 (22.4%)[a,c]	216 (17.9%)[b,c]	56 (13.3%)[a,b]	**<0.001**[‡]
Male hormonal diseases	0 (0.0%)	2 (0.5%)	1 (0.3%)	0.355[¶]

P-values are bolded when statistically significant difference is detected.
[†] One-way analysis of variance (ANOVA).
[‡] Pearson's Chi-square test.
[¶] Likelihood ratio test, a: The difference between mild acne group and severe acne group is statistically significant ($P < 0.05$), b: Moderate, The difference between acne group and severe acne group is statistically significant ($P < 0.05$), c: The difference between mild acne group and moderate acne group is statistically significant ($P < 0.05$).

between the acne group and the control group, whereas anti-TG autoantibodies were higher in the acne group and especially in postadolescent acne. It has been suggested that thyroid autoimmunity may be seen more in individuals with acne, and if there is acne in adult women, it is recommended to look for thyroid autoantibody in these patients.[30] In our study, the incidence of thyroid disorders did not differ in two acne groups than the control groups (see Tables 1 and 2). Drug use due to these diseases did not vary between groups ($P > 0.05$).

Neurological system

The incidence of nonmigraine headache in adolescents with acne was significantly higher than in the nonacne group ($P = 0.019$) (Table 5). In one study, *P. acnes* was isolated in meningitis patients.[12,13] We think that settling of *P. acnes* in this region in patients with acne and inflammation in acne exacerbation period may be the cause of pain. It is also known that depression and anxiety are more common in acne patients compared to a similar age group without acne.[31] The frequency of nonmigraine headaches may be related to this condition.

Musculoskeletal system

Yazmalar *et al.*, reported that fibromyalgia-related pain, fibromyalgia syndrome, sleep disturbance, menstrual disorder, and anxiety were more common in the acne group.[32] However, in our study, the incidence of fibromyalgia and other musculoskeletal conditions did not differ between acne and the control groups ($P > 0.05$).

Female hormonal diseases

Xie *et al.* investigated the relationship between acne and endometriosis in 4382 endometriosis patients. In this study, it was determined that the risk of developing endometriosis in women with a history of severe acne increased by 20% compared to those with no history of acne or mild acne. It was also shown that this difference was not due to the use of tetracycline or oral isotretinoin (HR = 1.20, 95% CI: 1.08–1.32).[33] The incidence of female hormonal diseases and drug use was not different between the adolescent acne and control groups in our study ($P = 0.967$). In the postadolescent group, premenstrual syndrome ($P < 0.001$) and PCOS ($P = 0.007$) were more common (see Table 4).

Urogenital system diseases

Chronic urinary tract infection was more common in the postadolescent acne group than the control group in our study ($P < 0.05$) (Table 4). The cause of the prevalence of chronic urinary tract infection may be *P. acnes* colonization[2,4] or may be the side effect of frequently used antibiotics.

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Evaluations based on acne severity

Severe acne was more common in men than women ($P < 0.001$). The average age of patients with severe acne was lower than those with mild to moderate acne severity ($P < 0.001$). In the acne group, the frequency of history of a systemic disease decreased as the severity of acne increased ($P < 0.05$). There was no statistically significant difference in mean BMI according to acne severity in the acne group ($P = 0.252$) (see Table 6).

This may be because of the fact that severe acne is usually treated with oral antibiotics or other systemic drugs such as isotretinoin and then mTOR pathway inactivated with treatment. Brüning and colleagues suggested that long-term tetracycline incubation also caused inhibition of the mTOR complex, a central regulator of cell metabolism, further contributing to the observed cell-cycle arrest and autophagy in doxycycline- and minocycline-treated cell lines.[34] Bergström and colleagues write that azithromycin is a bacteriostatic macrolide with mTOR inhibitory activity that has been shown to exert immunomodulatory effects on several types of immune cells.[35] *In vitro* studies have shown that retinoids influence T-cell differentiation. Karadag and colleagues' study showed that isotretinoin treatment significantly decreases TNF, IL-4, IL-17, and IFN-γ levels in patients with acne.[6] We think that isotretinoin-mediated downregulation of mTORC1 may attenuate the expression of mTORC1-induced production of IL-17, a proinflammatory signature cytokine overexpressed in acne lesions. With the treatment of acne vulgaris, the mTOR pathway is suppressed, and therefore we think that the development of metabolic disease may be prevented.

Conclusion

The incidence of nonmigraine headache in adolescents with acne was significantly higher than in the nonacne group ($P = 0.019$). In the adolescent acne group, the incidence of gastritis ($P < 0.001$), reflux ($P = 0.024$), and malabsorption ($P = 0.040$) rate was low, and the difference was statistically significant (see Table 5). The incidence of duodenal ulcer ($P = 0.020$) rate was higher than control group. In the postadolescent group, incidence of metabolic disease was lower than the control group ($P = 0.003$). We think that it can be owing to lower BMI in postadolescent acne group rather than the control group ($P < 0.001$), and it may be because of the fact that in postadolescent acne group, the rate of alcohol consumption ($P < 0.001$) was lower than control group.

Chronic urinary tract infection was more common in the postadolescent acne group than the control group in our study ($P < 0.05$).

Our study results show that patients with acne are thinner and they smoke less. Unlike the recent theories on acne, no association between acne severity and hyperglycemia and metabolic syndrome was found. The postadolescent acne group is again observed to be thin, but smoking is observed to be more in this group. Again, there was no relationship between postadolescent acne and metabolic syndrome. Among the chronic diseases investigated, the risk of chronic urinary tract infection and migraine was found to be increased, and no increased association with other diseases was found. In this case, it is unclear whether comorbidities with acne vulgaris are associated with *P. acnes* colonization and frequent antibiotic use. Our study results suggest that acne vulgaris is not a disease leading to comorbidity as much as psoriasis, rosacea, and hidradenitis suppurativa.[18] In addition, the nonpresence of comorbidities such as obesity, hypertension, and hepatitis suggests that this may be due to the fact that the age group where acne vulgaris is seen is pretty young. Long-term advanced research is needed to detect systemic inflammatory diseases caused by mediators causing acne vulgaris.

Limitations

The study's limitations include unequivocal 1 : 2 enrollment of controls, increased number of women in acne groups according to control groups, lack of inclusion of any laboratory data, recall and response bias, and lack of control for the presence of potential confounders. Patients using topical and systemic drugs with the diagnosis of acne vulgaris were also included in the study. However, no classification was made according to treatments. The type and frequency of treatments given to the patients not being specified in the study is a limitation of the study.

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