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The Second to Fourth Digit Ratio in Patients with Hidradenitis Suppurativa

Hidradenitis Süpürativa Hastalarında İkinci ve Dördüncü Parmakların Birbirine Oranı

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ABSTRACT

Aim: Hidradenitis suppurativa (HS) is a chronic, recurrent, and inflammatory skin disease involving the hair follicles and sweat glands. Based on the link between androgens and the second to fourth digit ratio (2D:4D) and also the connection between sex hormones and HS, it can be stated that there is an association between HS and the 2D:4D ratio. Based on this hypothesis, the present study investigated the relationships between HS, the 2D:4D ratio, and sex hormones.

Materials and methods: Total testosterone and dehidroepiandrosteron-sulfate (DHEA-S) levels were measured in both male and female cases and controls. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH/FSH ratio, estradiol, progesterone, and prolactin levels were analyzed in only female cases and controls. The 2D:4D ratio was calculated by dividing the second finger's length by the fourth finger's length.

Results: One hundred eight patients were diagnosed with HS. Eighty of these patients (39 female) were enrolled and constituted the study group. The control group consisted of 70 healthy participants (35 female). There were significant associations between weight, body mass index, smoking status, duration of smoking, and the length of left 2D and left 4D in both female cases and controls. We also found significant relationships between body mass index, smoking status, duration of smoking, and total testosterone in male cases and controls. In female cases, we determined significant correlations between the length of the DHEA-S and 2D right, 4D right and 2D left. In male patients there were significant associations between age of disease onset and right 2D:4D, age of disease onset and left 2D:4D, disease duration and right 4D length, disease duration and left 2D length, DHEA-S and right 4D length, DHEA-S and left 2D length.

Conclusion: We suggest that our research is a valuable contribution to the literature since it is the first study assessing the relationships between the 2D:4D ratio, HS and circulating hormone levels. However, further prospective studies, including larger patient samples, are required to identify relationships between the 2D:4D ratio and HS.

Keywords: Hidradenitis suppurativa; 2D:4D ratio; hormone

ÖZ

Amaç: Hidradenitis süpürativa (HS), kronik, tekrarlayan ve kıl foliküllerini, ter bezlerini tutan inflamatuar bir deri hastalığıdır. Androjenler ve 2.-4. parmak oranı (2D:4D) arasındaki bağlantıya dayanarak ve ayrıca seks hormonları ve HS arasındaki ilişki gözönünde bulundurulduğunda dolaylı olarak HS ve 2D:4D oranı arasında bir ilişki olabilir hipotezi kurulabilir. Bu çalışmanın amacı HS ve 2D:4D oranı arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Total testosteron ve dehidroepiandrosteron-sülfat (DHEA-S) seviyeleri hem erkek hem de kadın vakalarda ve kontrollerde ölçüldü. Luteinize edici hormon (LH), folikül uyarıcı hormon (FSH), LH/FSH oranı, estradiol, progesteron ve prolaktin seviyeleri sadece kadın olgularda ve kontrollerde analiz edildi. 2D:4D oranı ikinci parmak uzunluğunun dördüncü parmak uzunluğuna bölünmesi ile hesaplandı.

Bulgular: Çalışma süresi boyunca 108 hastaya HS tanısı kondu. Bu hastaların 80'i (39'u kadın) çalışmaya alındı ve çalışma grubunu oluşturdu. Kontrol grubu 70 sağlıklı kişiden (35'i kadın) oluştu. Ağırlık, vücut kitle indeksi, sigara içme durumu, sigara içme süresi ve sol elin 2.-4. parmak uzunluğu arasında anlamlı ilişki hem kadın vakalarda hem de kontrollerde mevcuttu. Aynı anlamlı ilişki erkek cinsiyet ve kontrol gruplarında da mevcuttu. Kadın cinsiyette DHEA-S ile sağ el 2.-4. parmak uzunluğu ve sol el 2. parmak uzunluğu arasında anlamlı ilişki mevcuttu. Erkek cinsiyette Hastalık başlangıcı ile sağ-sol el 2.-4. parmak uzunluğu oranı, hastalık süresi ve sağ el 4. parmak, sol el 2. parmak, DHEA-S ve sağ el 4. parmak- sol el 2. parmak uzunluğu arasında anlamlı ilişki mevcuttu.

Sonuç: Bu çalışmanın HS, dolaşımdaki hormonlar ve 2.-4. parmak uzunluğu arasındaki oranı araştıran ilk çalışma olması nedeni ile önemli olduğu kanısındayız. Daha fazla hastada, ileri dönük çalışmaların yapılmasının yararlı olacağı düşüncesindeyiz.

Anahtar Sözcükler: Hidradenitis süpürativa; 2D:4D oranı; hormon

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Introduction

Hidradenitis suppurativa (HS), also called acne inversa or dissecting terminal hair folliculitis, is a chronic, recurrent, and inflammatory skin disease involving the hair follicles and sweat glands (1,2). The specific lesions are painful, deep-seated inflamed nodules, abscesses, fistulae, or scars in the inframammary, axillary, genital, inguinal, and gluteal areas (3). Pathophysiologically, emergence in the postpubertal period, high prevalence of acne history, gender disparity, exacerbation in the premenstrual period, and healing after menopause support the hypothesis that the sex hormones may be involved in the etiology and progression of HS (4).

The second to fourth digit ratio (2D:4D) is the ratio of the length of the second finger to that of the fourth finger (5). It was previously suggested that this ratio was established during the fetal stage and that a low 2D:4D ratio reflected high prenatal androgen exposure or sensitivity to androgens (6,7). Based on the link between androgens and the 2D:4D ratio and also the connection between sex hormones and HS, it can be stated that there is an association between HS and the 2D:4D ratio (4).

The present study investigated the relationships between HS, the 2D:4D ratio, and sex hormones.

Materials and methods

Study design: This study was designed as a prospective multi-center study and conducted under the ethical principles reported in the Declaration of Helsinki. It was approved by the University of Health Sciences, Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee (2020/7-36-08.06.2020). Patients who presented to the dermatology outpatient clinics of the İzmir Tepecik Training and Research Hospital and İzmir Bozyaka Training and Research Hospital between June 2021- March 2022 and were diagnosed with HS were included in this study along with age-matched healthy controls. Patients and controls were informed about the study, and verbal consent was obtained. Female patients aged between 16 and 40 and male patients aged more than 16 were included. The patients who had finger deformities and those who used androgens, anabolic steroids, corticosteroids, oral contraceptives, or hormone injections were excluded. Also, pregnant patients, patients who had an intrauterine device or implant, those who had any endocrine diseases, or the patients who were breastfeeding were omitted. Data including age, gender, weight, height, body mass index (BMI), smoking status, and duration of smoking were recorded for both patients and controls. Age of onset, disease duration, comorbidities, family history of HS in first-degree relatives, Hurley stage (mild, moderate, or severe disease), previous treatments, and history of adalimumab use (absent/present) were recorded for only patients (i.e., cases).

Additionally, total testosterone and dehydroepiandrosterone-sulfate (DHEA-S) levels were measured in both male and female cases and controls. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH:FSH ratio, estradiol, progesterone, and prolactin levels were analyzed in only female cases and controls. In female patients and controls, total testosterone, DHEA-S, LH, FSH, LH:FSH ratio, estradiol, prolactin, and progesterone levels were measured in blood samples taken in the morning during the luteal phase of the menstrual cycle. Finger length was measured on the palmar side of the hand from the basal metacarpophalangeal crease. The one most proximal to the fingertip was used as a reference in patients with multiple creases. The 2D:4D ratio was calculated by dividing the second finger's length by the fourth finger's length.

Statistical analysis

Statistical analyzes were performed using Statistical Package for Social Sciences(SPSS v.24.0, IBM Corporation, Armonk, New York) software. Descriptive statistics were presented as means±standard deviations (SDs) and ranges (minimum-maximum). The Student`s t test was used to compare continuous data. The chi-square test (Pearson or Fisher) was performed to compare the categorical variables. The analysis of variance (ANOVA) test was used to compare mild, moderate, and severe disease groups, and the homogeneity of variance was tested by the Levene test. The p values were regarded as statistically significant when less than 0.05.

Results

During the study period, 108 patients were diagnosed with HS in the outpatient clinics. After applying the eligibility, inclusion, and exclusion criteria, 80 of these patients (39 females, 41 males) were enrolled and constituted the study group. The control group consisted of 70 healthy participants (35 females, 35 males). The age and height of the patients and controls were compatible with each other in the female and male groups. Eleven male cases had different internal diseases: Gilbert syndrome, hypertension, diabetes mellitus, arthritis, hyperlipidemia, end-stage renal disease, rheumatoid arthritis, and Crohn`s disease. Thirteen female cases and 16 male cases needed adalimumab treatment. Previous treatments given to these patients for treating HS included antibiotics, acitretin, infliximab, isotretinoin, dapsone, and surgery. There were significant associations between weight, BMI, smoking status, duration of smoking, and the length of left 2D and left 4D in both female cases and controls. ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0,02$, $p=0,049$, respectively) (Table 1). We also found significant relationships between BMI, smoking status, duration of smoking, and total testosterone in male cases and controls ($p=0.007$, $p<0.001$, $p<0.001$, $p=0.002$, respectively) (Table 2). Our evaluation regarding the relationships between duration of smoking, age of onset, and Hurley stage in female and male cases revealed significant relationships ($p<0.001$, $p<0.001$, $p<0.001$)

(Table 3). In female cases, we determined significant correlations between DHEA-S and the lenght of the right 2D, right 4D and left 2D (p=0.036, p=0.017, p=0.014)

Table 1. Clinical and laboratory characteristics of female patients and controls

Characteristics	Patients	Controls	p value
Age, mean±SD (years)	27,51±6,34	28,34±7,45	0,61
Weight, mean±SD (kg)	74,67±13,81	61,34±9,1	*<0,001
Height, mean±SD (cm)	165,82±5,04	164,8±4,47	0,35
BMI, mean±SD (kg/m^2)	27,27±5,51	22,64±3,18	*<0,001
Smoking, absent/present (n)	15/24	32/3	*<0,001
Duration of smoking, mean±SD (years)	6,26±6,76	0,57±2,14	*<0,001
Age of onset, mean±SD (years)	20,77±5,98	-	-
Disease duration, mean±SD (years)	6,74±5,31	-	-
Family history, absent/present (n)	28/11	-	-
Hurley stage, 1/2/3 (n)	12/25/2	-	-
Total testosterone, mean±SD, (ng/dL)	55,97±21,49	53,98±20,54	0,68
DHEA-S, mean±SD, (ug/dL)	292,14±168,92	296,46±139,89	0,9
LH, mean±SD, (U/L)	8,24±8,62	6,5±3,47	0,25
FSH, mean±SD (U/L)	5,43±2,98	5,24±1,94	0,74
LH:FSH, mean±SD	1,41±0,7	1,28±0,63	0,41
Estradiol, mean±SD, (ng/L)	108,04±84,36	99,12±70,86	0,62
Prolactin, mean±SD, (U/L)	10,6±5,52	10,93±5,49	0,79
Progesterone, mean±SD (U/L)	3,66±3,73	5,99±6,06	0,055
2D right, mean±SD, cm	7±0,49	6,84±0,37	0,13
4D right, mean±SD, cm	7,02±0,45	6,88±0,36	0,12
2D:4D right, mean±SD, cm	0,99±0,03	0,99±0,03	0,89
2D left, mean±SD, cm	6,98±0,49	6,73±0,38	*0,02
4D left, mean±SD, cm	7,08±0,43	6,9±0,35	*0,049
2D:4D left, mean±SD, cm	0,98±0,03	0,97±0,02	0,19

Table 2. Clinical and laboratory characteristics of male patients and controls

Characteristics	Patients	Controls	p value
Age, mean±SD (years)	39,93±12,88	36,89±6,65	0,19
Weight, mean±SD (kg)	86,66±11,6	79,44±12,1	0,1
Height, mean±SD (cm)	174,85±6,37	173,94±4,71	0,47
BMI, mean±SD (kg/m^2)	28,37±3,55	26,20±3,3	*0,007
Smoking, absent/present (n)	3/38	8/27	*<0,001
Duration of smoking, mean±SD (years)	19,39±13,21	7,72±1,28	*<0,001
Age of onset, mean±SD (years)	31,29±12,89	-	-
Disease duration, mean±SD (years)	8,66±7,45	-	-
Family history, absent/present (n)	36/5	-	-
Hurley stage, 1/2/3 (n)	5/20/16	-	-
Total testosterone, mean±SD, (ng/dL)	444,05±192,25	334,86±102,45	*0,002
DHEA-S, mean±SD, (ug/dL)	379,73±275,7	301,16±82,03	0,08
2D right, mean±SD, cm	7,38±0,48	7,4±0,34	0,85
4D right, mean±SD, cm	7,53±0,51	7,4±0,35	0,51
2D:4D right, mean±SD, cm	0,97±0,025	0,98±0,035	0,09
2D left, mean±SD, cm	7,36±0,48	7,27±0,37	0,38
4D left, mean±SD, cm	7,52±0,5	7,45±0,39	0,53
2D:4D left, mean±SD, cm	0,97±0,033	0,94±0,14	0,25

BMI; body mass index, DHEA-S; dehydroepiandrosterone sulfate, SD: Standard deviation, *p<0.05 was considered significant

,respectively (Table 4). In male patients, there were significant associations between age of disease onset and right 2D:4D (p=0,019), age of disease onset and left 2D:4D (p=0.039), disease duration and right 4D length (p=0,026), disease duration and left 2D length (p=0,021), serum DHEA-S levels and right 4D length (p=0,041), serum DHEA-S levels and left 2D length (p=0,017) (Table 5). There was a significant positive correlation between age of onset and duration of smoking in male cases (p<0,001).

Table 3. Clinical characteristics of female and male patients

Characteristics	**Female patients**	**Male patients**	**p value**
Duration of smoking, mean±SD (years)	6,26±6,76	19,39±13,21	*<0,001
Age of onset, mean±SD (years)	20,77±5,98	31,29±12,89	*<0,001
Disease duration, mean±SD (years)	6,74±5,31	8,66±7,45	0,18
Family history, absent/present (n)	28/11	36/5	0,07
Hurley stage, 1/2/3 (n)	12/25/2	5/20/16	*<0,001

Table 4. Correlation analysis in female patient group

Characteristics	p value; 2D right	p value; 4D right	p value; 2D:4D right	p value; 2D left	p value; 2D left	p value; 2D:4D left
Age of onset, years	0,097	0,27	0,18	0,25	0,27	0,74
Disease duration	0,13	0,26	0,3	0,31	0,2	0,83
Family history	0,61	0,97	0,38	0,44	0,83	0,51
Hurley stage, 1/ 2/ 3	0,12	0,35	0,83	0,81	0,13	0,07
Total testosterone	0,23	0,26	0,74	0,13	0,24	0,3
DHEA-S	*-0,036	*-0,017	0,94	0,12	*-0,014	0,35
LH	0,82	0,83	0,92	0,97	0,78	0,59
FSH	0,34	0,45	0,56	0,39	0,44	0,76
LH: FSH	0,42	0,62	0,55	0,12	0,48	0,83
Estradiol	0,46	0,17	0,42	0,73	0,33	0,38
Prolactin	0,73	0,6	0,62	0,066	0,21	0,16
Progesterone	0,62	0,24	0,31	0,55	0,37	0,83

BMI; body mass index, DHEA-S; dehydroepiandrosterone sulfate, LH; luteinizing hormone, FSH; follicle stimulating hormone, *p<0.05 was considered significant

Table 5. Correlation analysis in male patient group

Characteristics	p value; 2D right	p value; 4D right	p value; 2D:4D right	p value; 2D left	p value; 4D left	p value; 2D:4D left
Age of onset, years	0,91	0,44	*0,019	0,58	0,58	*0,039
Disease duration	0,11	*0,026	0,058	0,11	*0,021	0,096
Family history	0,65	0,62	0,85	0,68	0,52	0,78
Hurley stage, 1/ 2/ 3	0,91	0,62	0,32	0,7	0,66	0,51
Total testosterone	0,55	0,67	0,76	0,43	0,41	0,83
DHEA-S	0,1	*0,041	0,22	0,13	*0,017	0,084

DHEA-S; dehydroepiandrosterone sulfate, *p<0.05 was considered significant

Discussion

Multiple comorbidities, including obesity, are associated with HS (8). Although it was suggested that obesity could exacerbate this disease, there is a debate regarding the correlation between BMI and HS severity. Therefore, further research is needed on this topic. In our research, both female and male cases were overweight; therefore, we suggest that being overweight may cause HS. In addition, BMI correlated with HS severity in female cases but not in male cases (p=0.013) (Tables 1 and 2).

It is known that smoking is associated with HS and the incidence of HS is higher in smokers than in non-smokers (9,10). Our findings revealed that both smoking history and duration of smoking were associated with HS. In our male patient group, the smoking rate was higher and the duration of smoking was longer than in the female patient group. In line with this, the Hurley stages of the male cases were more advanced than the female cases (Table 3).

It was postulated that, in HS, the follicular unit becomes plugged and distended by retained keratin under the effect of exogenous hormones, endogenous reproductive hormones, androgens and their precursors in dairy products, and other dietary factors, especially in the postpubertal and premenopausal periods (8,11). Hence, we investigated the relationships between sex hormones and HS. This investigation revealed that high total testosterone levels, even relatively high levels within normal ranges, could be associated with HS in male patients (Table 2). In agreement with this, it was noted in a case report about two transgender men under testosterone therapy that HS developed, and it was exacerbated in these patients (12).

To the best of our knowledge, our study is the first to assess the relationship between the 2D:4D ratio, HS, and hormone levels. Our female patients' right and left 2D and 4D lengths were more than those of female controls. The cause of this result can be the effect of lower DHEA-S levels on the length of the 2D and 4D right digits but not on the length of left 2D (Table 4). In male cases, DHEA-S levels were significantly positively correlated with the lengths of the 4D right and 4D left (Table 5). Based on these data, we hypothesize that DHEA-S can be used as an indicator for HS both female and male cases, while total testosterone can be used only in male cases. Although some studies suggested that circulating hormone levels and the 2D:4D ratio were not strongly correlated, others reported that male and female subjects with lower 2D:4D ratios had higher testosterone levels than patients of the same gender with higher 2D:4D ratios. In addition, male and female patients with higher 2D:4D ratios had higher LH, estradiol, and prolactin levels than those with lower 2D:4D ratios (13,14). In our study, analysis of the female patients elucidated that the right 2D:4D was similar to controls while the left 2D:4D was higher than controls. Also, female cases had higher LH and estradiol levels and lower prolactin levels than the controls. However, the difference between the groups was not statistically significant. In addition, in male cases, disease duration positively affected the length of the right 4D and left 4D. Also, there was a significantly positive correlation between the age of disease onset and the ratios of right and left 2D:4D.

In addition, there are reports on being overweight and/or obesity in association with the 2D:4D ratio in the literature (15,16). The study of Iljin, A et al. did not confirm the relationship between 2D:4D and body weight but showed that in women with obesity, the right 2D:4D is positively correlated with the thickness of the skin and fat folds in some areas of the body. There is no proven information yet about the relationship between body weight and the 2D:4D ratio. This issue still remains a research topic. In our research, the patient group was overweighted and the control group was of normal weight. In outpatient conditions, HS patients have rarely consulted a doctor, therefore we had to add as many patients as possible, except the obese ones. This situation is a limitation of the study. The sample size is also a limitation.

In summary, higher BMI, smoking history, and longer duration of smoking can be associated with HS in both females and males. Higher testosterone levels in male patients can lead to an exacerbation of HS. Analysis of the DHEA-S levels in female and male patients revealed a significant relationship between DHEA-S levels and the right 2D, right 4D, and left 2D lengths. In addition, there was a significant relationship between the DHEA-S levels and the right and left 4D lengths in male patients. Higher smoking duration is associated with a delayed age of onset for HS and a higher Hurley stage. Therefore, higher disease duration may be associated with an increase in the lengths of the right and left 4D in male cases.

Similarly, the age of disease onset in male patients can be an indicator of increasing the right and left 2D:4D ratios. Although there were no significant differences in 2D:4D ratios between study participants with HS and the control group, there was a significant association between age of onset and the 2D:4D ratio in male patients.

We think that our research is a valuable contribution to the literature since it is the first study assessing the relationships between the 2D:4D ratio, HS, and circulating hormone levels. However, further prospective studies, including larger patient samples, are required to identify relationships between the 2D:4D ratio and HS.

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