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Is Prenatal Sex Hormone Balance a Risk Factor for the Development of Hidradenitis Suppurativa?

Prenatal Sex Hormon Balansı Hidradenitis Suppurativa Gelişimi için Bir Risk Faktörü müdür?

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ÖZET

Amaç: Hidradenitis suppurativa (HS), hormonal etkilerin de rol oynadığı karmaşık ve çok faktörlü bir patogeneze sahip, kronik, inflamatuvar özellik gösteren bir deri hastalığıdır. İkinci ve dördüncü parmak uzunluğu oranı (2D:4D), doğum öncesi androjen etkisinin güvenilir bir biyobelirteci olarak kabul edilmekte olup, HS gelişimine yakınlıkta etkili olabilir. Bu çalışmada, HS hastalarında 2D:4D oranı ile hastalık varlığı ve klinik şiddeti arasındaki olası ilişki araştırılmıştır.

Gereç ve Yöntemler: Yaş ve cinsiyet açısından eşleştirilmiş 140 HS hastası ile 140 sağlıklı kontrolün dahil edildiği kesitsel bir çalışma yürütüldü. Klinik hastalık şiddeti Hurley evrelemesi, Modifiye Sartorius Skoru (MSS) ve Klinik Genel Değerlendirme (PGA) kullanılarak değerlendirildi. Parmak uzunlukları dijital kumpas aracılığıyla standartize şekilde ölçülerek her iki el için ayrı ayrı 2D:4D oranları hesaplandı.

Bulgular: HS hastalarının her iki el 2D:4D oranı, kontrol grubuna kıyasla anlamlı olarak daha düşüktü ($p < 0.001$). Kadınlarda hem sol hem de sağ el oranları daha düşüktü ($p < 0.001$), erkeklerde ise yalnızca sol el oranı farklıydı ($p = 0.038$). Kadın hastalarda sol el oranı ile Hurley evresi, Modifiye Sartorius Skoru ve PGA arasında anlamlı ilişkiler saptandı (tüm $p < 0.05$).

Sonuç: Özellikle kadın HS hastalarında görülen düşük 2D:4D oranları, doğum öncesi artmış androjen maruziyetini yansıtabilir ve hastalık şiddeti ile ilişkili olabilir. Bulgular, HS patogenezinde hormonal etkilerin rolünü desteklemektedir; ancak bu ilişkinin doğrulanması için doğrudan hormonal ölçümleri içeren ileriye dönük çalışmalara ihtiyaç vardır. Bulguların yorumu, çalışmanın kesitsel tasarımı ile sınırlıdır. Ayrıca, tek merkezli tasarım ve biyokimyasal hormon düzeylerinin ölçülmemiş olması, sonuçların genellenebilirliğini ve hastalık mekanizmasına yönelik yorumların gücünü kısmen kısıtlayabilir.

Anahtar Kelimeler: Hidradenitis suppurativa, parmak uzunluğu oranı, testosteron, östrojen, hastalık şiddeti

ABSTRACT

Objective: Hidradenitis Suppurativa (HS) is a chronic skin condition marked by inflammation and driven by diverse underlying mechanisms, including hormonal involvement. The second-to-fourth digit ratio (2D:4D) is an established marker of prenatal androgen exposure, which may contribute to HS susceptibility. The objective of this study was to explore the potential link between 2D:4D digit ratios and hidradenitis suppurativa, along with their correlation to disease severity.

Materials and Methods: A total of 140 HS cases and 140 healthy subjects matched by age and gender were enrolled in this cross-sectional investigation. Clinical severity was assessed using Hurley staging, the Modified Sartorius Score, and the Physician Global Assessment (PGA). Finger lengths were measured using a digital caliper, and 2D:4D ratios were calculated separately for each hand.

Results: HS patients had significantly lower 2D:4D ratios in both hands compared with controls ($p < 0.001$). In females, both left- and right-hand ratios were lower ($p < 0.001$), while in males only the left-hand ratio differed ($p = 0.038$). In female patients, the left-hand ratio correlated with disease severity measures, including Hurley stage, Modified Sartorius Score, and PGA (all $p < 0.05$).

Conclusion: Lower 2D:4D ratios, particularly in female HS patients, may reflect higher prenatal androgen exposure and be linked to greater disease severity. These findings support a possible hormonal contribution to HS pathogenesis, though confirmation in prospective studies with direct hormonal assessment is warranted. Interpretation is limited by the cross-sectional design. Additionally, the single-center setting and absence of biochemical hormone measurements may partly limit generalizability and the strength of disease mechanism-related interpretations.

Keywords: Hidradenitis suppurativa, finger length ratio, testosterone, estrogen, disease severity

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the follicular units, most often affecting apocrine-bearing flexural regions such as the axillae, groin, and perianal area. The disease typically develops after puberty, with a reported prevalence between 1% and 4% (1). Its etiopathogenesis is multifactorial, involving hormonal factors, immune dysregulation, genetic predisposition, mechanical stress, smoking, and other environmental triggers (2,3). Hormonal influences are supported by the higher prevalence of HS in women and by symptom fluctuations linked to hormonal changes, such as exacerbations during the luteal phase and improvement during pregnancy, possibly due to the protective effects of elevated estrogen (4). HS also shares pathogenic features with acne vulgaris, including androgen-dependent follicular keratinization, suggesting a role for androgens in disease development (5-10).

The second-to-fourth digit ratio (2D:4D), calculated as the length of the second finger divided by the fourth, is an established indirect marker of prenatal androgen exposure and demonstrates sexual dimorphism (11). Lower 2D:4D ratios are associated with higher prenatal androgen and lower estrogen exposure, whereas higher ratios correspond to the opposite hormonal profile (11-14). Previous studies have reported significantly lower 2D:4D ratios in patients with androgen-dependent dermatological disorders such as androgenetic alopecia, seborrheic dermatitis, and acne vulgaris compared to healthy controls, reinforcing the hormonal connection in these conditions (15-17). Despite the recognized role of androgens in HS, the relationship between prenatal androgen exposure, as indicated by the 2D:4D digit ratio, and HS has not been systematically evaluated. This study aimed to investigate the potential association between 2D:4D ratios and HS, as well as their relationship with disease severity, to clarify the contribution of prenatal hormonal factors to HS pathogenesis.

MATERIALS AND METHODS

This cross-sectional study included 140 patients aged 18 years or older diagnosed with hidradenitis suppurativa (HS) based on clinical criteria, and 140 age- and gender-matched healthy controls, recruited from the Dermatology Clinic of a tertiary hospital between May 2024 and March 2025. Controls were healthy individuals without dermatological diseases or significant chronic illnesses. Demographic data (age, gender, BMI, waist circumference), disease duration, Hurley stage, modified Sartorius score, Physician Global Assessment (PGA), presence of comorbidities, and family history were obtained by anamnesis and clinical examination. PGA severity was classified into four categories (mild, moderate, severe, and very severe) based on lesion counts and characteristics.

Finger measurements were taken from both hands. The lengths of the second (index) and fourth (ring) fingers were measured on the palmar surface from the proximal palmar crease to the fingertip, using a digital Vernier caliper with 0.01 mm precision. All measurements were performed directly on the skin (not via photographs) by the same investigator to

minimize inter-observer variability. Intra- and inter-observer reliability testing for finger length measurements was not conducted. The second-to-fourth digit length ratio (2D:4D) was calculated separately for the left and right hands. Blood samples for inflammatory markers (CRP, ESR), metabolic parameters (fasting blood glucose, LDL, triglycerides), and biochemical markers (ALT, creatinine) were collected from venous blood into vacuum tubes containing ethylenediaminetetraacetic acid (Vacutainer, Becton Dickinson, Marseille, France). ABO and Rh blood types were determined using standard tube and gel methods.

Psychological parameters (stress, depression, sleep quality) were evaluated using validated scales: Perceived Stress Scale (PSS), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index (PSQI).

Statistical analysis

The analysis was performed using SPSS version 25.0 (IBM Corp.). To determine data normality, the Kolmogorov-Smirnov test was used. As the data were non-normally distributed, outcomes were presented as median and interquartile range. Group comparisons for continuous variables were performed using the Mann-Whitney U test, while categorical variables were compared using the Chi-square test. Values of $p < 0.05$ were deemed statistically significant.

Ethics Approval

In accordance with the Declaration of Helsinki, the study was ethically approved by the institutional review board (Decision No: 2024/187).

RESULTS

A total of 140 patients with hidradenitis suppurativa (HS) and 140 healthy controls were enrolled in the study. Median age was similar between groups (patients: 36.00 years; controls: 35.00 years, $p=0.781$), and the proportion of females was comparable between patients (60.71%) and controls (55.00%; $p=0.334$). Median disease duration was 10.00 years (IQR: 8.00–14.00), and according to Hurley staging, 55.71% had stage 1, 34.29% had stage 2, and 10.00% had stage 3 disease. Inflammatory markers (CRP, ESR), metabolic parameters (blood glucose, LDL cholesterol, triglycerides), and liver enzyme (ALT) were significantly higher among patients compared to controls ($p<0.001$). Psychological and quality-of-life scores, including Perceived Stress Scale (PSS, 18.83 vs. 13.18), Beck Depression Inventory (BDI, 33.89 vs. 23.72), and sleep quality scores (9.62 vs. 6.73), were significantly worse in patients than controls ($p<0.001$; Table 1).

Digit length measurements and their ratios showed significant differences between hidradenitis suppurativa (HS) patients and controls. HS patients had significantly shorter left-hand 2nd finger (67.40 mm vs. 70.00 mm, $p<0.001$) and right-hand 2nd finger lengths (68.30 mm vs. 71.85 mm, $p<0.001$). The left (0.94 vs. 0.99) and right (0.95 vs. 0.99) hand 2D:4D ratios were also significantly lower in patients compared to controls ($p<0.001$ for both; Table 2). Gender-based subgroup analyses showed that female HS patients had significantly shorter left-hand 2nd finger lengths compared to female controls

Table 1. Clinical and Demographic Characteristics of Patient and Control Groups

Variables	Control (n=140)	Patient (n=140)	p-value
Age, years (median [IQR])	35.00 [32.00–38.00]	36.00 [30.00–38.00]	0.781 ^a
Gender, female, n (%)	77 (55.00%)	85 (60.71%)	0.334 ^b
BMI, kg/m ² (median [IQR])	27.77 [26.57–29.05]	27.99 [26.52–28.63]	0.344 ^a
Waist circumference, cm (median [IQR])	94.00 [85.00–106.75]	95.00 [82.50–106.00]	0.832 ^a
Disease duration, years (median [IQR])	—	10.00 [8.00–14.00]	—
Hurley staging, n (%)	—	Stage 1: 78 (55.71%) Stage 2: 48 (34.29%) Stage 3: 14 (10.00%)	—
Modified Sartorius score (median [IQR])	—	13.00 [8.00–24.00]	—
Physician global assessment, n (%)	—	Mild: 78 (55.71%) Moderate: 48 (34.29%) Severe: 7 (5.00%) Very severe: 7 (5.00%)	—
Comorbidities, n (%)	—	None: 55 (39.29%) Severe Acne: 63 (45.00%) Pilonidal Sinus: 22 (15.71%)	—
Family history, n (%)	—	Yes: 38 (27.14%) No: 102 (72.86%)	—
Smoking, n (%)	65 (46.43%)	77 (55.00%)	0.152 ^b
Alcohol consumption, n (%)	57 (40.71%)	67 (47.86%)	0.230 ^b
CRP, mg/L (median [IQR])	17.08 [8.95–24.20]	24.40 [12.86–34.43]	<0.001 ^a
ESR, mm/h (median [IQR])	12.16 [5.22–20.80]	17.38 [7.46–29.66]	<0.001 ^a
Blood glucose, mg/dL (median [IQR])	108.51 [77.62–126.84]	155.01 [110.91–181.20]	<0.001 ^a
HDL, mg/dL (median [IQR])	62.50 [45.71–79.01]	52.09 [38.09–65.83]	<0.001 ^a
LDL, mg/dL (median [IQR])	92.92 [73.95–107.55]	132.75 [105.64–153.56]	<0.001 ^a
Triglyceride, mg/dL (median [IQR])	129.60 [80.79–180.06]	185.14 [115.95–254.91]	<0.001 ^a
ALT, U/L (median [IQR])	28.54 [21.62–34.57]	40.77 [30.89–49.33]	<0.001 ^a
Creatinine, mg/dL (median [IQR])	0.71 [0.50–0.86]	1.02 [0.72–1.23]	<0.001 ^a
PSS score (median [IQR])	13.18 [5.95–20.67]	18.83 [8.88–29.49]	<0.001 ^a
BDI score (median [IQR])	23.72 [11.45–35.56]	33.89 [16.35–50.80]	<0.001 ^a
Sleep quality score (median [IQR])	6.73 [3.54–10.84]	9.62 [5.06–15.45]	<0.001 ^a

BMI: Body Mass Index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; PSS: Perceived Stress Scale; BDI: Beck Depression Inventory; 2D:4D ratio: 2nd to 4th digit length ratio; ^aMann-Whitney U test, ^bChi-square test.

Table 2. Comparison of Digit Length Measurements and 2D:4D Ratios between Patient and Control Groups

Variables	Control (n=140)	Patient (n=140)	p-value
Left hand 2nd finger length, mm (median [IQR])	70.00 [67.00–73.73]	67.40 [63.60–71.85]	<0.001 ^a
Left hand 4th finger length, mm (median [IQR])	71.10 [68.60–75.60]	72.23 [69.10–75.30]	0.244 ^a
Left hand 2D:4D ratio (median [IQR])	0.99 [0.94–1.01]	0.94 [0.88–0.99]	<0.001 ^a
Right hand 2nd finger length, mm (median [IQR])	71.85 [68.60–75.30]	68.30 [64.13–73.30]	<0.001 ^a
Right hand 4th finger length, mm (median [IQR])	71.60 [68.40–76.20]	72.45 [69.80–75.40]	0.437 ^a
Right hand 2D:4D ratio (median [IQR])	0.99 [0.98–1.01]	0.95 [0.90–0.98]	<0.001 ^a

^a Mann-Whitney U test, IQR: Interquartile range, 2D:4D ratios: Second-to-fourth digit length ratios

(median: 67.04 vs. 69.80 mm; $p < 0.001$). Similarly, female HS patients exhibited significantly lower 2D:4D ratios for both left (0.91 vs. 0.96; $p < 0.001$) and right hands (0.92 vs. 0.97; $p < 0.001$). Among male participants, only the left-hand 2D:4D ratio was significantly different between patients and controls (patients: 0.97, controls: 0.97; $p = 0.038$), whereas other digit length measurements and right-hand 2D:4D ratio showed no significant differences (Table 3).

Gender subgroup analyses among clinical parameters showed that male HS patients had a significantly higher BMI than female patients (28.20 vs. 27.64 kg/m², $p = 0.028$). Disease severity was also greater in males, with a higher proportion classified as Hurley stage 3 (18.18% vs. 4.71%, $p = 0.034$)

and more severe disease according to the Physician Global Assessment (PGA) ($p = 0.047$). There was no significant difference between males and females in disease duration (10.00 vs. 9.00 years, $p = 0.928$), Modified Sartorius Scores ($p = 0.416$), or family history of HS (30.91% vs. 24.71%, $p = 0.420$) (Table 4).

Analysis of the relationship between 2D:4D ratios and clinical parameters in HS patients revealed significant correlations in females but not in males. In female patients, left-hand 2D:4D ratio showed a positive correlation with Hurley staging ($p = 0.236$, $p = 0.029$), Modified Sartorius Score ($p = 0.255$, $p = 0.019$), and Physician Global Assessment ($p = 0.236$, $p = 0.029$). Additionally, right-hand 2D:4D ratio was negatively correlated with family history ($p = -0.234$, $p = 0.031$) (Table 5).

Table 3. Gender subgroup comparison of digit lengths and 2D:4D ratios in patients and controls

Variables	Females (Median, IQR)			Males (Median, IQR)		
	Controls (n=77)	Patients (n=85)	P-value ^a	Controls (n=63)	Patients (n=55)	P-value ^a
Left-hand 2D	69.80 [67.00–72.65]	66.40 [62.40–70.40]	<0.001	68.90 [66.04–72.43]	68.90 [66.05–72.85]	0.573
Left-hand 4D	71.90 [68.85–75.60]	72.70 [69.20–75.60]	0.061	72.35 [69.10–75.40]	72.10 [68.50–75.60]	0.882
Left-hand 2D:4D ratios	0.96 [0.89–1.01]	0.91 [0.87–0.96]	<0.001	0.97 [0.93–0.99]	0.97 [0.94–1.00]	0.038
Right-hand 2D	68.90 [66.43–73.55]	66.90 [63.60–71.40]	<0.001	71.70 [67.85–74.60]	71.70 [67.90–74.30]	0.895
Right-hand 4D	72.20 [69.80–75.45]	73.20 [70.20–75.40]	0.163	72.75 [68.40–76.80]	72.20 [68.70–75.90]	0.846
Right-hand 2D:4D ratios	0.97 [0.92–1.01]	0.92 [0.88–0.96]	<0.001	0.98 [0.96–1.00]	0.98 [0.95–1.00]	0.452

^a Mann-Whitney U test, IQR: Interquartile range, 2D:4D ratios: Second-to-fourth digit length ratios

Table 4. Clinical Characteristics of Female and Male Patients with HS

Variables	Females	Males	p-value
BMI (kg/m ²) (Median [IQR])	27.64 [26.26–28.60]	28.20 [26.96–29.30]	0.028 ^a
Disease duration (years) (Median [IQR])	9.00 [8.00–14.00]	10.00 [7.00–14.00]	0.928 ^a
Hurley staging 1/2/3 (n, %)	50 (58.82%)/ 31 (36.47%)/ 4 (4.71%)	28 (50.91%)/ 17 (30.91%)/ 10 (18.18%)	0.034 ^b
Modified Sartorius Score (Median [IQR])	13.00 [8.00–23.00]	16.00 [8.00–26.00]	0.416 ^a
Physician Global Assessment Mild/ Modarete/Severe/Very Severe (n, %)	50 (58.82%)/ 31 (36.47%)/ 1 (1.18%)/ 3 (3.53%)	28 (50.91%)/ 17 (30.91%)/ 6 (10.91%)/ 4 (7.27%)	0.047 ^b
Family History (Yes, n [%])	21 (24.71%)	17 (30.91%)	0.420 ^b

^a Mann-Whitney U test, ^b Chi-Square test, IQR: Interquartile range

Table 5. Relationship Between 2D:4D Ratios and Disease Parameters in HS Patients

Variables	Females		Males	
	Left-hand 2D:4D	Right-hand 2D:4D	Left-hand 2D:4D	Right-hand 2D:4D
BMI (kg/m ²)	-0.056	0.041	-0.240	-0.163
Disease duration (years)	0.070	-0.069	0.045	-0.258
Hurley staging	0.236*	-0.012	0.116	-0.034
Modified Sartorius Score	0.255*	-0.094	0.114	-0.105
Physician Global Assessment	0.236*	-0.011	0.103	-0.119
Family History	-0.165	-0.234*	0.159	-0.102

Spearman's correlation coefficients (p) are shown. *Statistically significant correlations at p < 0.05.

DISCUSSION

In this study, we explored the association between second-to-fourth digit length ratios (2D:4D), an indirect marker of prenatal androgen exposure, and hidradenitis suppurativa (HS). HS is known to predominantly affect women, often emerging after puberty, which suggests a hormonal influence on disease expression (2). The majority of our HS patients were female (60.71%), and overall, patients had a similar median age (36 years) and BMI (27.99 kg/m²) compared to controls. However, gender subgroup analysis in patients revealed that male HS patients exhibited significantly higher BMI and greater

disease severity, with a higher proportion classified as Hurley stage 3 and more severe disease according to PGA, consistent with previous studies indicating that male HS patients are more likely to present with severe disease (3).

The exact hormonal mechanisms underlying HS are not fully understood, but clinical observations suggest significant hormonal influences, as disease flares often occur during low-estrogen, high-androgen menstrual phases, whereas clinical improvements are noted during pregnancy when estrogen levels rise (4). Furthermore, androgen-mediated follicular hyperkeratinization, a key feature shared with acne vulgaris,

may contribute to follicular occlusion and inflammation in HS patients (5-10). Supporting the androgen connection, previous studies have demonstrated beneficial effects of antiandrogen therapy in some HS cases, reinforcing androgen involvement in HS pathogenesis (18-23).

Recent studies have identified an association between 2D:4D ratios and various androgen-affected dermatological conditions. Research on androgenetic alopecia (AGA) has shown significantly lower right-hand 2D:4D ratios in affected individuals compared to healthy controls, though no correlation was found with disease severity (24). Another study reported a significant reduction in the left-hand 2D:4D ratio in AGA patients, while no change was observed in the right hand (15). Similarly, studies on acne vulgaris have reported lower 2D:4D ratios in female patients, with an observed link between increased sebaceous secretion and lower digit ratios in acne-prone women (17,21). However, conflicting findings exist, as some studies found no significant differences in 2D:4D ratios between acne patients and controls or correlations with reproductive hormones (26). Additionally, it has been suggested that right-hand 2D:4D ratios may serve as a stronger indicator of prenatal androgen exposure than left-hand ratios, although other research highlights a greater genetic influence on left-hand digit ratios (27).

Our findings revealed significantly lower left- and right-hand 2D:4D ratios in HS patients compared to controls, suggesting higher prenatal androgen exposure as a potential risk factor for HS. Gender subgroup analyses further demonstrated significantly lower 2D:4D ratios in female HS patients compared to female controls, consistent with similar observations in other androgen-sensitive dermatological diseases such as acne vulgaris and androgenetic alopecia (15-17,24,25). These previous studies indicated that lower 2D:4D ratios were associated with increased androgen sensitivity and disease severity in female patients (24,25). Interestingly, in our male subgroup, only the left-hand 2D:4D ratio showed a statistically significant difference between patients and controls. The relatively weaker associations observed in male patients could be related to inherently higher androgen levels in males, which might mask subtle variations in digit ratios linked to prenatal exposure. Further analysis of the relationship between 2D:4D ratios and clinical parameters in HS patients revealed significant correlations in females but not in males. The left-hand 2D:4D ratio was positively correlated with Hurley staging, Modified Sartorius Score, and Physician Global Assessment, suggesting a link between prenatal androgen exposure and disease severity in female patients. Additionally, a negative correlation was observed between the right-hand 2D:4D ratio and family history, indicating individuals with a family history of HS might have been exposed to higher prenatal androgen levels, which could play a role in disease susceptibility.

In addition, our study emphasized systemic involvement in HS patients, who demonstrated significantly elevated inflammatory markers (CRP, ESR), metabolic disturbances (higher LDL cholesterol, triglycerides, and fasting glucose),

and increased liver enzyme levels (ALT). These findings are consistent with previous studies showing systemic inflammatory and metabolic implications of HS (8,9). Moreover, psychological and sleep quality assessments (PSS, BDI, sleep quality scores) were significantly worse among HS patients, highlighting the substantial psychosocial burden and impaired quality of life associated with HS. This study is among the first to investigate the role of prenatal androgen exposure in HS pathogenesis using digit ratios. A recently published study in 2023, which included 80 HS patients and 70 controls, found no significant difference in 2D:4D ratios between HS patients and controls. Additionally, in male HS patients, both right- and left-hand 2D:4D ratios were correlated with age of disease onset, while in female patients, individual right 2D and 4D finger lengths, not the ratio, were correlated with DHEA-S levels (28). However, our larger sample size enabled subgroup analyses by gender, providing additional insights into the relationship between 2D:4D ratios and HS.

Our study has some limitations. The cross-sectional design limits causal interpretations of our results. Furthermore, direct hormonal levels were not assessed, preventing confirmation of current hormonal status associations. Intra- and inter-observer reliability testing for finger length measurements was not conducted, which may introduce potential measurement variability. Future prospective studies with larger sample sizes, comprehensive hormonal profiling, and advanced analytical models such as factorial ANOVA, multiple linear regression, and interaction modeling are needed to validate and expand upon these findings.

CONCLUSION

In conclusion, our findings suggest that lower 2D:4D ratios, particularly in female HS patients, may indicate higher prenatal androgen exposure, potentially contributing to disease susceptibility and severity. Additionally, the left-hand 2D:4D ratio correlated with disease severity in females, while a negative correlation between the right-hand 2D:4D ratio and family history suggests a possible genetic influence on hormonal factors in HS. Further research should focus on prospective hormonal profiling alongside digit ratios to clarify their predictive role and to better understand HS pathogenesis.

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