Orginal Article

Is There an Association Between Male Alopecia Areata and the Ratio of Second to Fourth Finger Length?

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Abstract

Aim: The ratio between the lengths of the second and fourth fingers (2D to 4D) has been shown to indicate exposure to androgens prenatally. Although an association between alopecia areata (AA) and androgenic hormones has been recently suggested, the 2D to 4D ratio of AA has not yet been investigated. We aimed to investigate the lengths of the 2D to 4D in males with AA, as well as the potential links between 2D to 4D ratios and both AA and disease severity.

Materials and Methods: Male patients with AA and healthy volunteers participated in the study. A digital Vernier caliper was employed to measure the lengths of the fingers. The severity of alopecia tool and AA severity index were used to calculate the severity of AA.

Results: A total of 168 participants were recruited for the study. Compared with healthy controls, the 2D to 4D ratio was significantly lower in both hands of the patients ($P = 0.001$ for the right hand and $P < 0.05$ for the left hand). The right-hand 2D to 4D ratio showed better predictive capacity for AA development than the left hand (area under the curve: 0.952 vs. 0.638). The 2D to 4D ratio of patients and disease severity scores were not significantly correlated ($P > 0.05$).

Conclusion: To our knowledge, this is the first report to investigate the association between the 2D to 4D ratio and AA. The results of our research suggest that the 2D to 4D ratio of fingers is a possible predictor of AA development.

Keywords: Alopecia areata, androgens, fingers, sex hormones

Introduction

Alopecia areata (AA) is a chronic inflammatory disease characterized by non-scarring hair loss. Although the etiopathogenesis is not clearly known, the role of genetic predisposition and T cell-mediated autoimmunity in the development of the disease is emphasized. Emotional stress, psychiatric diseases, autoimmune thyroid diseases, atopy, vaccine use, viral infections, and anemia have been reported to trigger the development of this disease.[1] The prevalence of the disease is reported to be 0.58% and is slightly higher in females than in males.[2]

The ratio between the lengths of the second and fourth fingers (2D to 4D) has been shown to indicate exposure to androgens prenatally.[3,4] Males are known to have a lower 2D to 4D ratio compared to females.[5] 2D to 4D ratio has also been reported to be negatively correlated with testosterone concentration and sperm count in males.[6] There are numerous studies showing a link between the 2D to 4D ratio and many diseases, such as androgenetic alopecia (AGA), seborrheic dermatitis, vitiligo, acne vulgaris, polycystic ovary syndrome (PCOS), psychiatric diseases, and some malignancies.[7-13] The ratio of 2D to 4D in AA has not yet been investigated. Literature exists regarding the link between AA development and androgenic hormones.[14-16] We aimed to investigate the lengths of the 2D to 4D in males with AA, as well as the potential links between 2D to 4D ratios and both AA and disease severity.

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Materials and Methods

This cross-sectional research was approved by the KTO Karatay University Faculty of Medicine Ethics Committee (approval number: 2023/005, date: 26.09.2023). Between June and December 2023, 80 male participants with AA and 88 healthy volunteers were enrolled into this research. Patients were diagnosed based on clinical (patchy areas of hair loss) and dermoscopic findings consistent with AA. Healthy volunteers were selected from patients who presented to dermatology for medical screening and had no previous history of AA. Although the digit ratio is assumed to remain stable after puberty,[17] participants aged 16 years and younger were excluded to eliminate any possible puberty effect related to the digit ratio. We also excluded participants with a history of traumatic injury or disease that caused finger deformity. All participants provided informed consent. The severity of alopecia tool (SALT) was used to calculate the severity of AA with scalp involvement alone, while the alopecia areata severity index (AASI) was used to score the disease involving hairy areas of the head other than the scalp (with or without scalp involvement), such as the beard, eyebrows, and eyelashes. The SALT score was calculated according to the formula [(percent hair loss) right side x18] + [(percent hair loss) left side x18] + [(percent hair loss) top x40] + [(percent hair loss) back x24]. In AASI scoring, the formula [(percentage of hair loss) each eyebrow x15] + [(percentage of hair loss) eyelashes in each eye x10] was used for the upper face, [(percentage of hair loss) each cheek x20] + [(percentage of hair loss) each side of the neck x25] + [(percentage of hair loss) mustache x10] for the beard area.[18]

Second and 4th finger lengths in the palmar area from the intermetacarpophalangeal fold to the fingertip were measured using a digital Vernier caliper. If more than one fold was present at the interbase, the most proximal fold was used. Measurements were taken directly to avoid measurement errors caused by photocopying or scanning. Each measurement was confirmed by a second investigator. The 2D to 4D ratio was obtained by dividing the 2nd finger length by the 4th finger length. The 2D to 4D ratio was recorded for each hand of all participants.

The sample size was determined using the G*Power 3.1.94 software package (Franz Faul, Universität Kiel, Kiel, Germany). According to the t-test comparison of the 2D to 4D ratios of alopecia patients and control group in the study by by Bilgic et al.,[19] it was calculated that a total of 156 patients (78 in each group) should be included in the study for an effect size of 0.453, a margin of error of 0.05, and 80% power.

Statistical analysis

The data obtained from this research were examined using SPSS 22 (SPSS Inc., Chicago, IL, USA) software. The compatibility of the study parameters with normal distributed data was assessed using Kolmogorov-Smirnov test. In addition to descriptive statistical data (mean, frequency, standard deviation), Student's t-test was performed to compare numerical data between two groups for normally distributed variables. Pearson's test was used to assess correlations within normally distributed parameters. The most accurate cut-off point was determined by receiver operating characteristic (ROC) curve analysis. The level of significance was determined as $P < 0.05$.

Results

A total of 168 male participants, including patients (n = 80) aged between 18 and 75 years and healthy controls (n = 88) aged between 18 and 74 years, were recruited for the study. The average age of patients was 35.49±9.80, the average age of healthy controls was 35.86±12.37.

The duration of disease in the patient group ranged between 0.25 months and 48 months, with a mean of 5.40±7.62 months and a median duration of 3 months. SALT scores ranged between 0.2 and 28 with a mean of 5.73±5.64 and a median score of 4.4. AASI scores varied between 1 and 22.9, while the mean was 7.93±6.23 and that of the median was 6.6 (Table 1).

Compared with healthy controls, the 2D to 4D ratio was significantly lower in both hands of the patients ($P = 0.001$ for the right hand and $P < 0.05$ for the left hand) (Table 2, Figure 1).

The ROC curve was generated for the finger ratios of the right hand related to AA, with an area under the curve (AUC) of 0.952 and a standard error of 0.01. The ROC curve area was significantly greater than 0.5 ($P = 0.001$; $P < 0.05$). The cut-off value of the right hand 2D to 4D ratio for AA diagnosis was ≤ 0.99. This value had a sensitivity and specificity of 88.8% and 92.1%, respectively (Table 3, Figure 2a).

Table 1. Descriptive characteristics of variables in the patient group

	n	Minimum	Maximum	Mean ± SD	Median
Disease duration (months)	80	0.25	48	5.40±7.62	3.0
SALT score	56	0.2	28	5.73±5.64	4.4
AASI score	30	1	22.9	7.93±6.23	6.6

SALT: Severity of alopecia tool, AASI: Alopecia areata severity index, SD: Standard deviation

The ROC curve for the 2D to 4D left hand ratio in diagnosing AA was plotted as an AUC of 0.638 with a of 0.04. The ROC curve area was significantly greater than 0.5 ($P = 0.001$; $P < 0.05$). The cut-off value of the left-hand 2D to 4D ratio for AA diagnosis was ≤ 0.96. This value had a sensitivity and specificity of 55% and 63.6%, respectively (Figure 2b).

2D to 4D ratios did not significantly correlate with disease severity scores (SALT and AASI) ($P > 0.05$) (Table 4).

Discussion

We revealed a significantly reduced 2D to 4D ratio of both hands in male AA participants compared with healthy controls. The ROC analysis suggested that patients with a right hand 2D to 4D ratio smaller than 0.99 and left hand ratio smaller than 0.96 may have a relatively higher risk of developing AA.

2D to 4D ratio has been shown to indicate exposure to androgens prenatally.[3,20,21] Females affected by congenital adrenal hyperplasia have elevated levels of androgens as well as a lower 2D to 4D ratio than healthy females. Furthermore, because of the brain virilization effect of prenatal androgenic exposure, these patients are at risk of future gender confusion.[22,23] The Digit ratio is lower in many diseases thought to be related to androgens, suggesting a link between these diseases and prenatal androgen exposure.[7-13] For example, in a study investigating finger ratios in AGA, an androgen-dependent disease, the right hand 2D to 4D ratio revealed lower values than controls. Furthermore, in the patient group, the 2D to 4D ratio of the right hand had an inverse association with AGA grade.[12] In another study conducted in AGA, the

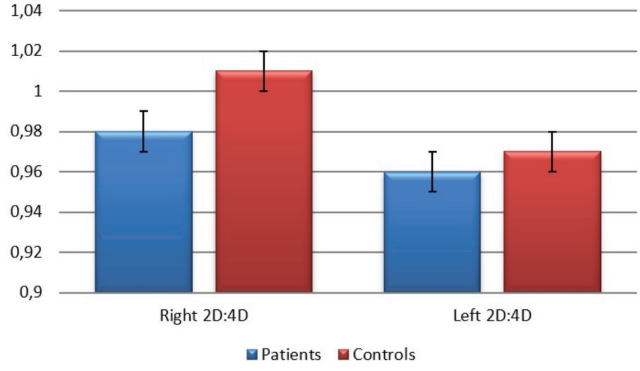

Figure 1: Comparison of right- and left-hand 2D to 4D ratios of the groups

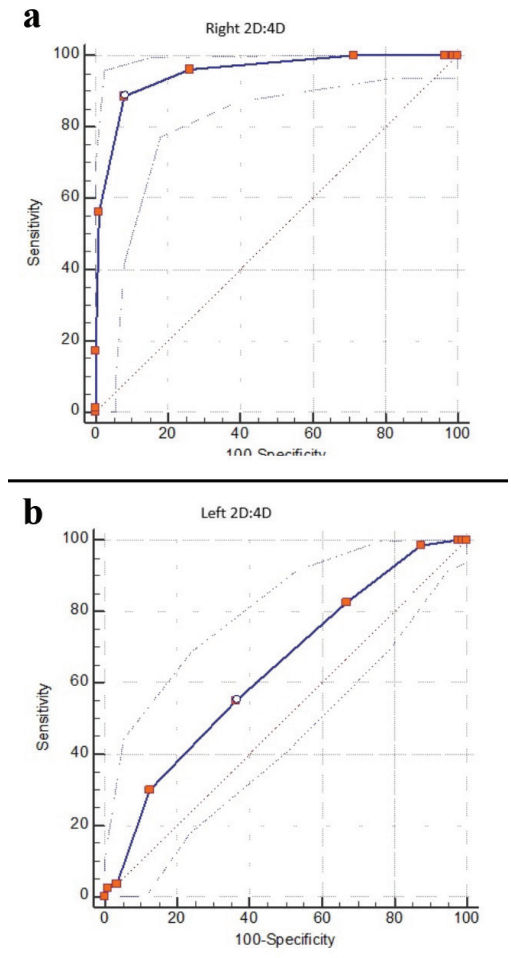

Figure 2. Receiver operating characteristic curves for right- and left-hand 2D to 4D ratios in the prediction of alopecia areata development

Table 2. Comparison of right- and left-hand 2D to 4D ratios among the groups

	Patients	Controls	*P* value
	Mean ± SD	Mean ± SD	
Right 2D to 4D	0.98±0.01	1.01±0.01	0.001*
Left 2D to 4D	0.96±0.01	0.97±0.01	0.001*

Student's t-test, *$P < 0.05$, SD: Standard deviation

Table 3. ROC analysis results for right and left-hand 2D to 4D ratios

	AUC	S.E.	95% CI	*P* value	Cut-off point	Sensitivity	Specificity
Right 2D to 4D	0.952	0.01	0.908-0.979	0.001*	≤ 0.99	88.8	92.1
Left 2D to 4D	0.638	0.04	0.561-0.711	0.001*	≤ 0.96	55.0	63.6

AUC: Area under the curve, CI: Confidence interval, S.E.: Standard error

Table 4. Correlation of SALT and AASI scores with right- and left-hand 2D to 4D ratios in the patient group

Patients		SALT score	AASI score
Right 2D to 4D	r	-0.172	0.087
	p	0.204	0.648
Left 2D to 4D	r	-0.070	0.057
	p	0.610	0.765

Pearson's correlation analysis. SALT: Severity of alopecia tool, AASI: Alopecia areata severity index

left-hand 2D to 4D ratio was reported to be lower than the control group. However, compared with controls, the 2D and 4D patterns of the right hand did not differ significantly among patients. There was no correlation between disease severity and left hand finger ratios.[24] According to a study by Bilgiç et al.[10] involving female patients diagnosed with acne vulgaris, 2D to 4D ratios were markedly decreased in both hands in comparison with the controls, whereas male patients showed no difference across the groups. In another study investigating the 2D to 4D ratios for seborrheic dermatitis, the finger ratio of the right hand was markedly reduced compared with that of the controls. Furthermore, the 2D to 4D ratio of the right hand had a negative association with the severity of the disease.[11] Demirbaş and Eker[9] found a significantly decreased right hand 2D to 4D ratio in patients with vitiligo compared with controls; however, they did not report an association with disease severity or finger ratios.

Hair follicles are protected from host immune defense mechanisms in the absence of MHC molecules and immune inhibitory secretions of membranous glycoproteins, perifollicular mast cells, and Treg cells. This is called the immune privilege. The main mechanism underlying the pathogenesis of AA is the disruption of the immune privilege area of hair follicles, resulting in cytotoxic T cell-mediated autoimmunity targeting the hair follicles leading to the recognition of hair follicle autoantigen by lymphocytes.[25] Androgenic hormones play an important role in terminal hair development through a complex mechanism via androgen receptors, androgen receptor coactivator, and 5-alpha reductase enzymes in hair follicles.[26] It has been suggested that androgen excess may disrupt the microenvironment of hair follicles consisting of dihydrotestosterone, growth factors, corticotropin-releasing hormone, cytokines, insulin, and vitamins.[16] There are several studies on the relationship between AA and sex hormone imbalance. In a study of female AA patients by Ranasinghe et al.,[16] it was reported that hyperandrogenism and clinical findings of hyperandrogenism, such as PCOS, adult acne and hirsutism were significantly increased compared with the normal population. It has been suggested that anti-androgen treatment agents should be investigated in the treatment of AA.[16] In another study by Hussein et al.,[15] compared to healthy controls, male participants with AA demonstrated a marked elevation in testosterone levels. Female AA patients did not have a marked difference in estrogen levels compared with controls. The previous study emphasized the possible role of hyperandrogenism in the pathogenesis of AA.[15] These findings may suggest a link between prenatal androgen exposure and AA, which is also thought to be related to androgens. The decreased 2D to 4D ratio in AA patients compared to the controls in this study revealed the potential involvement of androgenic exposure in the pathogenesis of the disease. The lack of correlation between AA severity scores (SALT and AASI) and digit ratios were not correlated may have been due to the small number of patients. It has been reported with a higher sensitivity of the 2D to 4D ratio of the right hand to prenatal androgen exposure compared with the 2D to 4D ratio of the left hand.[27] Features that differ between the sexes are most pronounced on the right part of the body in men. It has been reported that the finger ratios of the right hand are more sensitive to the effects of testosterone than the left hand.[28] Our study's 2D to 4D ratio cut-offs for both hands may be predictive factors for the development of AA. However, finger ratios were more sensitive and specific for AA development in the right hand than in the left hand. These findings suggest the potential prenatal involvement of androgen exposure in AA.

Study limitations

The results obtained from the present study should be interpreted within its limitations. The small number of participants is one of the limitations of the current study. This prevented us from making conclusive findings on the digit ratio and AA. Another limitation of this study is that it was a single-center study.

Conclusion

The current study is, to our knowledge, the first report to investigate the association between the 2D to 4D ratio and AA. According to our study, we have revealed two new points related to this issue. First, the 2D to 4D ratio is lower in male AA patients, and therefore, a low 2D to 4D ratio (cut-offs: smaller than 0.99 and 0.96 for right and left hand, respectively) may predict whether an individual will develop AA in the future because the finger ratio remains constant after birth. Second, the 2D to 4D ratio had higher sensitivity and specificity for the right hand with respect to the left hand as a predictor of AA development. Finally, the results of this study suggest that androgenic hormones may be associated with AA prenatally. To establish the role of androgenic exposure in AA development, larger patient populations are needed to be included in further studies.

Ethics

Ethics Committee Approval: This cross-sectional research was approved by the KTO Karatay University Faculty of Medicine Ethics Committee (approval number: 2023/005, date: 26.09.2023).

Informed Consent: All participants provided informed consent.

Authorship Contributions

Surgical and Medical Practices: M.Ö., Concept: M.Ö., T.A., Design: T.A., Data Collection or Processing: M.Ö., Analysis or Interpretation: M.Ö., Literature Search: M.Ö., T.A., Writing: M.Ö., T.A.

Conflict of Interest: The authors declared that they have no conflict of interest.

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