Quantitative measurement and practical application of hair diameter diversity as a diagnostic indicator of androgenetic alopecia

Hee Ung Park

The Graduate School
Yonsei University
Department of Medicine

Quantitative measurement and practical application of hair diameter diversity as a diagnostic indicator of androgenetic alopecia

Hee Ung Park

The Graduate School
Yonsei University
Department of Medicine

Quantitative measurement and practical application of hair diameter diversity as a diagnostic indicator of androgenetic alopecia

A Master's Thesis submitted
to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master’s of Medical science

Hee Ung Park

June 2024

This certifies that the Master's Thesis
of Hee Ung Park is approved.

Thesis Supervisor	Do-Young Kim
Thesis Committee Chair	Chang Ook Park
Thesis Committee Member	Byung Cheol Park

The Graduate School
Yonsei University
June 2024

ACKNOWLEDGEMENTS

I am immensely grateful to Professor Do Young Kim, my mentor and advisor, for his unwavering guidance, support, and insightful criticisms throughout the course of this study. His expertise and dedication have been pivotal to the success of this study.

I owe my profound gratitude to Professor Chang Ook Park for his insightful critiques and direction, and to Professor Byung Cheol Park for his valuable feedback and support. I am also grateful to Professor Sun Kook Yoo for his meaningful contributions and advice.

I extend my appreciation to Dr. Chung Kyung Bae and Clinical Research Nurse Eunji Kang for their invaluable assistance and collaboration in the study process.

Gratitude is also due to the patients who provided their hair data, a fundamental element of our study. Their willingness to participate has been greatly appreciated.

I would like to express my special thanks to Professor Han Kyung Cho for his guidance and support. Additionally, I acknowledge the unwavering support and encouragement from my colleagues in dermatology residency and the entire dermatology department, which have been instrumental throughout my academic journey.

This acknowledgment reflects my gratitude towards those who have played a significant role in my study, offering a balanced appreciation of each contribution.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Quantitative measurement and practical application of hair diameter diversity as a diagnostic indicator of androgenetic alopecia

Androgenetic alopecia (AGA), a common form of pattern hair loss, is traditionally diagnosed using subjective methods like the Norwood-Hamilton and Ludwig's classifications. While hair diameter diversity (HDD) serves as an objective indicator within AGA diagnostic processes, reflecting the variation in hair diameter, its quantitative definition remains ambiguous. This study introduces and evaluates two quantitative definitions of HDD, employing a robust methodology on a cohort of 240 Korean male AGA patients. In Part 1, we explore HDD through the 'thin hair ratio' at the vertex, considering diverse diameter thresholds beyond the initial 40 μm to define thin hairs. This approach investigates how varying thresholds impact the correlation between thin hair ratio and AGA progression, aiming to identify the most effective diameter threshold for the Korean male. Part 2 explore a distribution-based definition of HDD, analyzing the 'change point in hair diameter distribution' at both the vertex and occiput. This method assesses the shift in hair diameter percentile, seeking to understand how these changes in distribution patterns correspond to AGA's severity.

In Part 1, the application of various thresholds revealed that a 45 μm threshold for defining thin hair, alongside a 21.65% cutoff for the thin hair ratio, provides optimal diagnostic accuracy for Korean males. In Part 2, the analysis indicated that the change point in hair diameter distribution aligns with AGA progression, demonstrating that change points within the 20-30% range are significantly related to AGA diagnosis. Comparing the change points between the vertex and occiput suggests potential diagnostic benefits for early AGA diagnosis. Additionally, this analysis reveals individual differences in hair diameter irrespective of AGA stage, highlighting the importance of personalized assessment.

In conclusion, our study reinforced the validity of the traditional HDD 20% threshold, suggesting that it remains a reliable indicator of AGA. We found that employing a 45 μm threshold for defining thin hair provides optimal diagnostic accuracy. Furthermore, change point analysis in hair diameter

distribution underscores their correlation with AGA progression, suggesting potential diagnostic benefits for early AGA diagnosis.

Key words : androgenetic alopecia, hair diameter diversity, korean male, quantitative measurement

1. INTRODUCTION

Androgenetic alopecia (AGA), commonly known as pattern hair loss, predominantly leads to the thinning of hair in affected individuals.[1–5]. Traditionally, the diagnosis of AGA has been largely subjective, utilizing classification systems like Norwood-Hamilton, Ludwig's, or the Basic and Specific (BASP) classification to assess severity[2]. The concept of increased variation in hair diameter, known as hair diameter diversity (HDD), was first presented in 2001 and has since been acknowledged as a crucial clinical marker for diagnosing AGA[6]. Hair follicle miniaturization is a key aspect of AGA, making HDD an essential and easily understandable sign of this condition[6]. Referred to as anisotrichosis as well, HDD is currently viewed as a precise marker for AGA in literature, especially if the diversity surpasses a 20% threshold[7–12]. HDD implies an increase in the diversity of hair thickness, which is intuitively understandable, yet even the study that first introduced it does not provide a clear definition of its criteria[6]. Moreover, the specific methodology for quantitatively measuring the diversity of hair thickness has not been defined, making the 20% threshold criterion for HDD challenging to use as an objective indicator[6]. Consequently, we have speculated on two possible quantitative definitions for this ambiguous concept. Firstly, we hypothesized that HDD could be considered as 'an increase in the ratio of thin hairs in the vertex' corresponding to the progression of AGA. This approach is utilized in various studies citing HDD, and the threshold for thin hairs is assumed to be 40 μm, based on the paper that initially proposed HDD[6,9,13]. Secondly, we hypothesized that the increase in HDD, attributable to a diversity of hair thickness, could be interpreted as 'a change in the distribution pattern of hair diameter'. To further investigate this hypothesis, we conducted a comparative analysis of HDD patterns in the vertex and occiput areas, noting that the occiput is relatively less influenced by AGA, to elucidate the differences in HDD between these two areas[3,14]. In conclusion, through quantitative measurement of hair diameter, we have analyzed two potential quantitative definitions of HDD. This endeavor not only advances our understanding of HDD but also

contributes to a more objective and precise diagnostic framework for AGA.

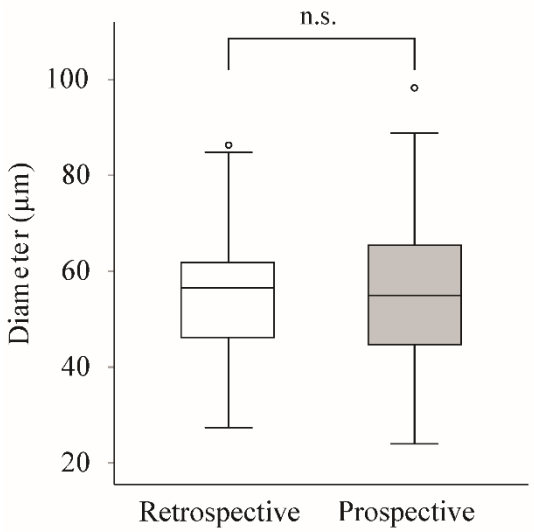
2. MATERIALS AND METHODS

2.1. Participant selection

This study included 240 Korean male patients with AGA who visited the Dermatology Department at Severance Hospital in Seoul, South Korea, between January 2020 and August 2023. The study only included AGA patients aged 18 and above without significant systemic diseases. Those with other specific hair conditions (e.g., telogen effluvium, alopecia areata, scarring alopecia and psoriasis) or scalp abnormalities (e.g., burns or inflammation) were excluded. This study followed the principles of the Declaration of Helsinki and received approval from the Institutional Review Board at Severance Hospital (approval # 4-2022-1003). All procedures and methodologies were conducted in accordance with the relevant guidelines and regulations.

2.2. Sample size determination and cohort selection

To achieve a sample size with 90% power and account for a Type I error of 0.05 and a Type II error of 0.10, based on the anticipated area under cover (AUC) of 0.7 for HDD, 124 patients were prospectively enrolled considering an approximate 10% dropout rate, and 116 were retrospectively included to form a replication cohort. The selection was based on the prevalent clinical application and reasonable diagnostic efficacy of HDD, even though there is limited literature on its precise diagnostic accuracy. The use of both a prospective cohort and a retrospective cohort aimed to enhance the study's statistical significance and confirm the consistency of HDD's diagnostic performance in actual clinical environments **(Figure 1)**.



	Average diameter (μm)
Retrospective (n=116)	55.3±12.6
Prospective (n=124)	56.1±14.5

Figure 1. Comparison of hair diameter between retrospective and prospective cohorts. The comparison between the retrospective (n=116, 55.3±12.6 μm) and prospective (n=124, 56.1±14.5 μm) cohorts shows no significant difference (n.s.) in overall hair diameter measurements.

2.3. Clinical assessment and photography

Each participant in the prospective cohort provided informed consent, followed by a comprehensive history review and clinical evaluation. For the retrospective cohort, the study utilized standardized global photography and analyzed existing medical records of the patients. The photography protocol was uniform for all subjects, employing headrest and headband to maintain consistent head positioning and ensuring image clarity. A headband was used to expose the frontal hairline, and photographs of the frontal area were taken. In this position, photographs were taken of the temporal areas, and then, upon removing the headband, additional photographs of the vertex area were taken **(Figure 2)**. Two board-certified dermatologists classified the clinical photos using the BASP classification to accurately determine the extent of hair loss. Subsequently, patients were grouped according to the V stages of the BASP classification, with V0 designated as the

control group, representing individuals without AGA in the vertex region.

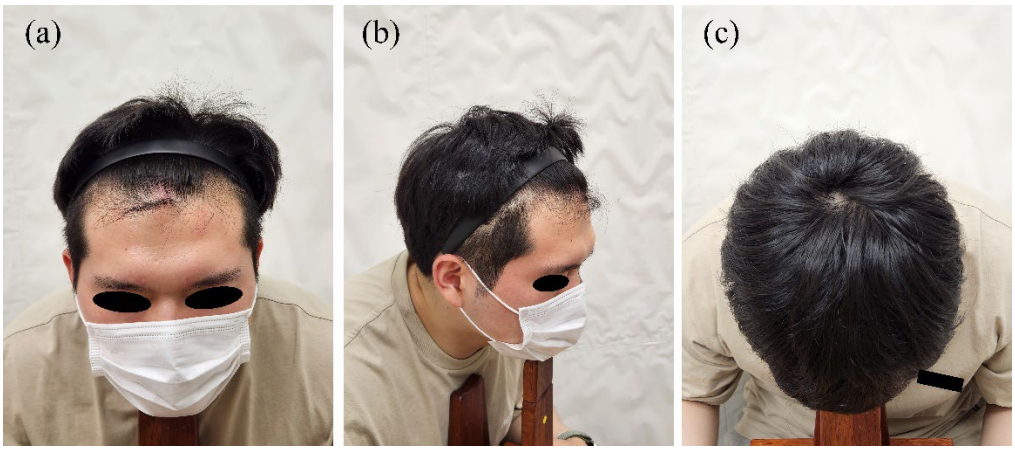


Figure 2. Standardized photographic assessment of AGA. (a) is a frontal view with a headband exposing the frontal hairline; (b) is a lateral view showing the temporal areas; (c) is a vertex view taken without the headband. *Abbreviations: AGA*; androgenetic alopecia

2.4. Phototrichogram technique for magnified hair imaging

A phototrichogram (Folliscope® 5.0; Lead M, Seoul, Republic of Korea) was utilized to capture magnified images of hair at the vertex and occiput, using magnifications between 50x and 85x. The focus was on two specific points: V point at the vertex and the P point at the occiput **(Figure 3)**[15,16]. To ensure the hair maintained a uniform direction and arrangement, combing was performed from side to side, centering on the V and P points. For accuracy of the analysis, between 2 to 4 photographs were captured at each location, with the selection of the clearest image that showed the minimum hair overlap for further analysis.

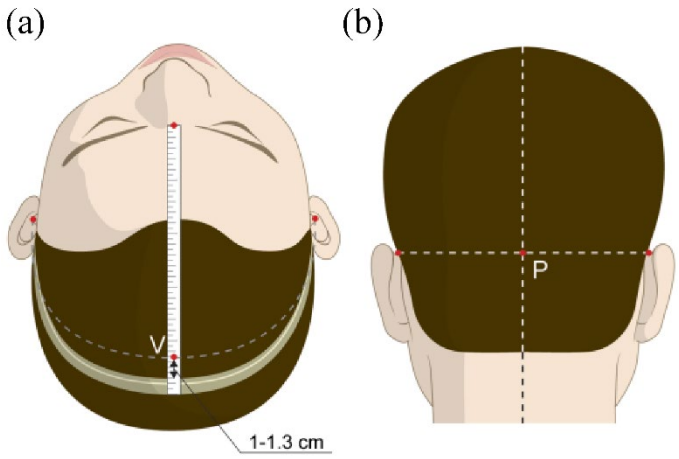


Figure 3. Anatomical reference points for hair imaging in AGA. (a) shows the 'V point' marked at the intersection of the mid-sagittal and coronal lines above the headband; (b) indicates the 'P point' at the junction of the posterior mid-sagittal line and the horizontal line across the top of the ears. Adapted from Lee EH et al., Dermatol Surg. 2010;37(8):1150-1152[16]. *Abbreviations: AGA*; androgenetic alopecia

2.5. Hair diameter measurement using Image J software

While the Folliscope® 5.0 was utilized to measure hair diameter, its precision did not meet the necessary standards for this study. To enhance accuracy, the clearest images obtained from the Folliscope® 5.0 were analyzed using Image J software (Rasband, W.S., Image J, U. S. National Institutes of Health, Bethesda, Maryland, USA, Version 1.53e). This analysis involved precise hair diameter measurements, with calibration based on a 1 mm reference scale from the Folliscope® 5.0. The images were zoomed to pixel-level detail to allow for precise measurement of each hair's diameter. All visible hairs were measured, except for those significantly overlapped or located at the image's edges where measurement accuracy could be compromised **(Figure 4)**. To account for the natural increase in hair diameter closer to the follicle, measurements were consistently taken 350-450 μm above the scalp's surface **(Figure 5)**. For each subject, 10 to 72 hairs were measured, calculating hair density per square centimeter, and 73% of the patients had

more than 20 hairs measured. The researchers measuring the hair were blinded to the clinical and reference standards.

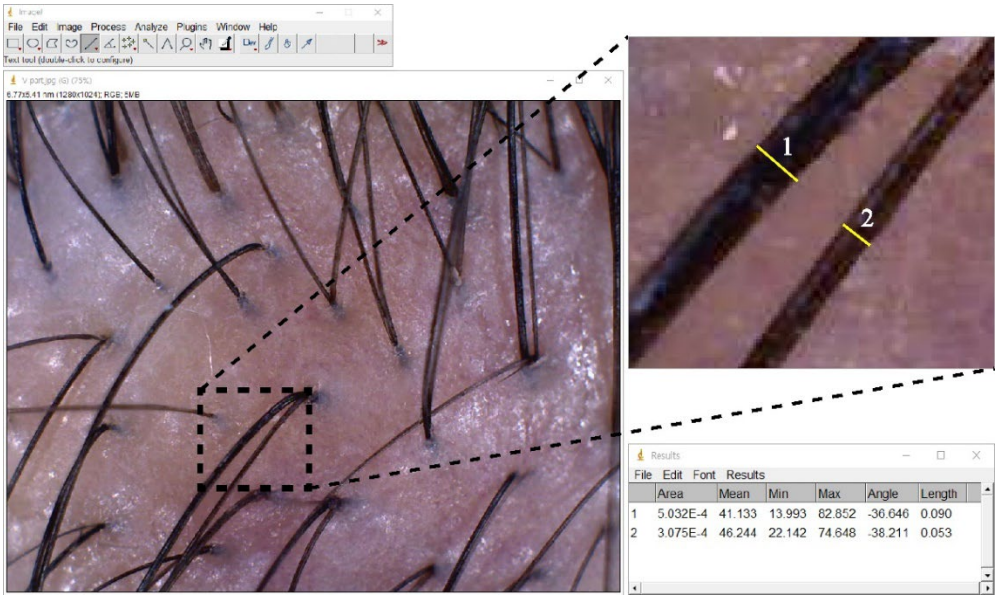


Figure 4. Hair diameter measurement using Image J software. This figure illustrates the use of Image J software for the precise measurement of hair diameter, using enhanced pixel-level magnification. All visible hairs are measured for diameter, except for hairs that are overlapped or at the periphery to ensure accuracy, as shown in the magnified inset.

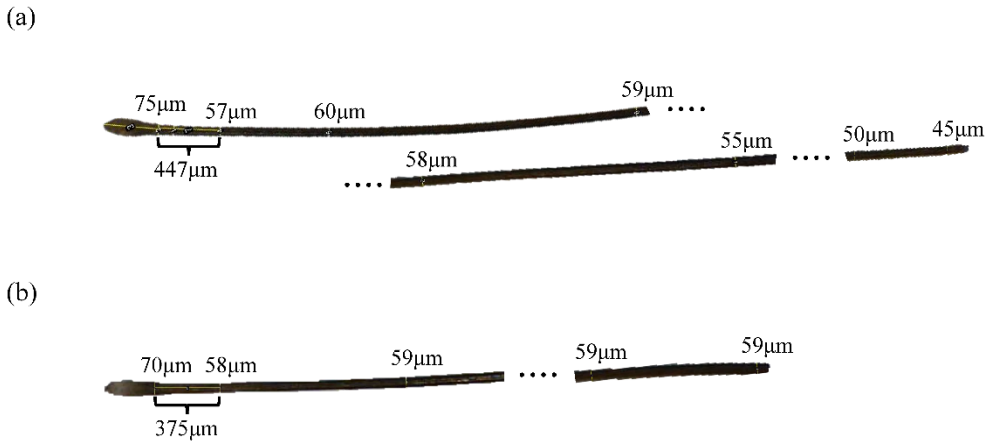


Figure 5. Standardized measurement of hair diameter at specified height from scalp. Measurement of hair diameter using telogen hair shafts from healthy donors, (a) a young female with long hair and (b) a young male with short hair, highlights that from 350-450 μm above the scalp up to the mid-shaft, the hair maintains its diameter before tapering towards the end due to wear.

2.6. Statistical analysis

Statistical evaluations were conducted using SPSS Statistics software (Version 29.0.0.0, IBM Corp, Armonk, NY; 2022) and R statistical software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) following the clinical evaluations and hair measurements. Continuous variables, like age and hair diameter, were reported as mean values and standard deviations (SD), and categorical variables were summarized as frequencies and percentages. The study is divided into two parts, where Part I is titled ‘Absolute criteria of hair diameter in vertex’. The study examined diverse hair diameter thresholds, including a specific 40 μm threshold for characterizing 'thin hair,' to evaluate the diagnostic effectiveness of the HDD≥20% criteria. It analyzed the positive predictive value (PPV) and negative predictive value (NPV) across different stages, distinguishing normal (V0) from AGA stages (V1-3). The threshold that yielded the optimal Youden index at the 20% level was further examined. This examination included receiver operating

characteristic (ROC) curve analysis for distinct HDD thresholds to identify the one with the greatest diagnostic accuracy, determined by the Youden index and the cutoff percentage. For Part II, titled ‘Change point analysis of hair diameter distribution in vertex and occiput’, the study analyzed the distribution of hair diameter in a graphical format, stratified by stages. This method defines the point where the graph's trend changes most dramatically in the hair diameter distribution as the 'change point'. The analysis of this change point, which will be referred to as "change point analysis" throughout the study, is conducted using segmented linear regression. The analysis was consistently conducted in both the vertex and occiput regions. The hairs measured in each patient were arranged from thinnest (0 percentile) to thickest (100 percentile), and the corresponding hair diameter was indicated for each percentile **(Figure 6)**. To assess the differences in hair diameter between the vertex and occiput, the average of the subtraction values of all measured hair diameters (occiput - vertex) was calculated and analyzed by stage. Furthermore, using the identified change point, along with stage and hair diameter data, in-depth analyses were conducted using box plots and scatter plots.

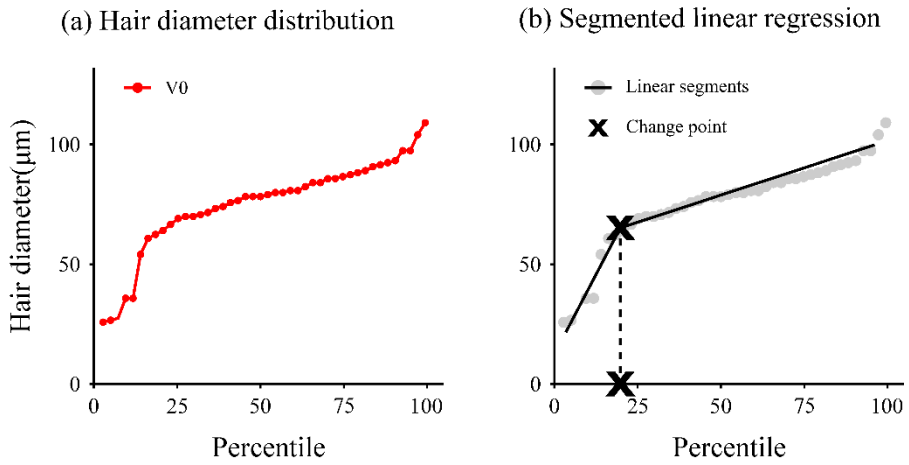


Figure 6. Change point analysis of hair diameter distribution. (a) represents an example of the hair diameter distribution for a single patient in the V0 control group, illustrating the percentile-based spread of hair diameters from thinnest (0 percentile) to thickest (100 percentile). (b) represents the result of segmented linear regression performed on (a), identifying the change point in the hair diameter distribution.

3. RESULTS

3.1. Baseline characteristics of male AGA patients by BASP V Stage

The study included 240 male participants with AGA, categorized into four groups according to the BASP classification's V stages: V0 with 53 participants, V1 with 104 participants, V2 with 55 participants, and V3 with 28 participants. The average age was 38.5 ± 12.4 years, with the youngest average ages observed in the V0 group at 31.2 ± 8.4 years, suggesting that patients without vertex involvement (control group) were younger. The average ages increased with AGA severity: 36.7 ± 12.2 years for V1, 43.9 ± 11.7 years for V2, and the oldest at 48.1 ± 9.4 years for V3, the group with the most severe AGA. This pattern aligns with AGA's progressive nature, where age and disease severity are interconnected **(Table 1)**.

Table 1. Baseline characteristics of male AGA patients by BASP V Stage.

Characteristics	BASP V stage				
	Total (N=240)	**V0 (N=53)**	**V1 (N=104)**	**V2 (N=55)**	**V3 (N=28)**
Age (years)					
Mean (±SD)	38.5±12.4	31.2±8.4	36.7±12.2	43.9±11.7	48.1±9.4
10-19, n (%)	6 (2.5)	1 (0.4)	5 (2.1)	0 (0)	0 (0)
20-29, n (%)	65 (27.1)	27(11.3)	31 (12.9)	7 (2.9)	0 (0)
30-39, n (%)	69 (28.7)	17 (7.1)	31 (12.9)	15 (6.3)	6 (2.5)
40-49, n (%)	40 (16.7)	5 (2.1)	14 (5.8)	12 (5.0)	9 (3.8)
50-59, n (%)	50 (20.8)	3 (1.3)	20 (8.3)	16 (6.7)	11 (4.6)
60-, n (%)	10 (4.2)	0 (0)	3 (1.3)	5 (2.1)	2 (0.8)
Duration of AGA (years)					
Mean (±SD)	7.4±6.0	5.2±3.9	6.1±4.9	8.7±6.0	12.9±7.8

Abbreviations: AGA, androgenetic alopecia; *BASP V stage*, vertex stage according to the Basic and Specific Classification

3.2. Quantitative evaluation of hair characteristics based on BASP V Stage

The average hair diameter was inversely related to AGA severity, with the V0 group having the thickest hair (51-98 μm, average 70 ± 10 μm) and the V3 group the thinnest (24-65 μm, average 38 ± 8 μm). Hair density slightly decreased from the V0 group, which had 77-231 hair/cm² (average 149 ± 30 hair/cm²), to the V3 group, with 46-208 hair/cm² (average 122 ± 37 hair/cm²). The proportion of thin hair (≤40 μm based on Olivier de L, et al.6) notably increased with the progression of BASP V stages, from 0-35% in V0 (average 13 ± 8%) to 18-94% in V3 (average 62 ± 19%), indicating a significant rise in thin hair percentage with advanced AGA stages **(Table 2)**.

Table 2. Quantitative evaluation of hair characteristics based on BASP V Stage.

BASP V stage	Average thickness (μm)		Hair density (hair/cm^2)		Thin hair* (%)		Intermediate hair* (%)		Thick hair*(%)	
	Range	Mean (±SD)	Range	Mean (±SD)	Range	Mean (±SD)	Range	Mean (±SD)	Range	Mean (±SD)
V0 (N=53)	51-98	70±10	77-231	149±30	0-35	13±8	0-89	53±20	4-94	34±21
V1 (N=104)	31-86	57±10	74-200	131±27	0-78	27±15	20-96	58±16	0-67	15±15
V2 (N=55)	33-75	49±9	71-216	126±32	6-79	38±18	21-84	54±15	0-41	8±9
V3 (N=28)	24-65	38±8	46-208	122±37	18-94	62±19	6-70	35±18	0-32	3±6

* Thin hair: ≤ 40 μm, Intermediate hair: 40-80 μm, Thick hair: > 80 μm. *Abbreviation*: *BASP V stage*, vertex stage according to the Basic and Specific Classification

3.3. Part I : Absolute criteria of hair diameter in vertex

3.3.1. Assessing predictive values of hair diameter thresholds for AGA diagnosis

Part I of the analysis measured HDD by the ratio of thin hair. In evaluating the diagnostic accuracy of the HDD≥20% criterion using Positive Predictive Value (PPV) and Negative Predictive Value (NPV), it was discovered that a 40 μm threshold—originally recommended for Caucasians—yielded a PPV of 73.8%. This rate is significantly lower compared to the PPVs at thresholds of 45 μm and 50 μm, which are 86.6% and 90.4%, respectively. This suggests that a 40 μm standard might result in a higher rate of false negatives in Korean males. Additionally, the NPV at 40 μm is 79.2%, compared to 73.6% at 45 μm and 54.7% at 50 μm **(Table 3)**. These results indicate that a 45 μm threshold may be more suitable for the Korean population, providing a more balanced diagnostic accuracy in distinguishing V0 (normal) from V1-3 (AGA).

Table 3. Assessing predictive values of hair diameter thresholds for AGA diagnosis

	Diagnostic accuracy (at least 20% of hairs with a diameter less than HDD μm)			
Predictive value	**HDD 30 μm**	**HDD 40 μm**	**HDD 45 μm**	**HDD 50 μm**
Positive predictive value* (%)	35.3	73.8	86.6	90.4
Negative predictive value* (%)	92.5	79.2	73.6	54.7

* The 'Positive Predictive Value' refers to the proportion of individuals diagnosed with AGA (V1 to V3) who have at least 20% of their hairs with a diameter below the specified HDD threshold. In contrast, the 'Negative Predictive Value' indicates the proportion of individuals without AGA (V0) whose hair diameters do not meet the 20% threshold for the specified HDD value. *Abbreviation*: *BASP V stage*, vertex stage according to the Basic and Specific Classification; *HDD*, hair diameter diversity

3.3.2. Establishing the optimal hair diameter threshold with a fixed 20% HDD cutoff using the Youden Index and ROC curve analysis

The evaluation of the Youden index to determine a diagnostic threshold for HDD was performed using a fixed HDD criterion of 20%. This analysis revealed that a 45 μm threshold for hair diameter produced the highest Youden index of 0.602 **(Figure 7)**. To evaluate the diagnostic precision of different hair diameter thresholds for AGA, ROC curve analysis was employed, showing the highest AUC at the 45 μm threshold **(Figure 8)**.

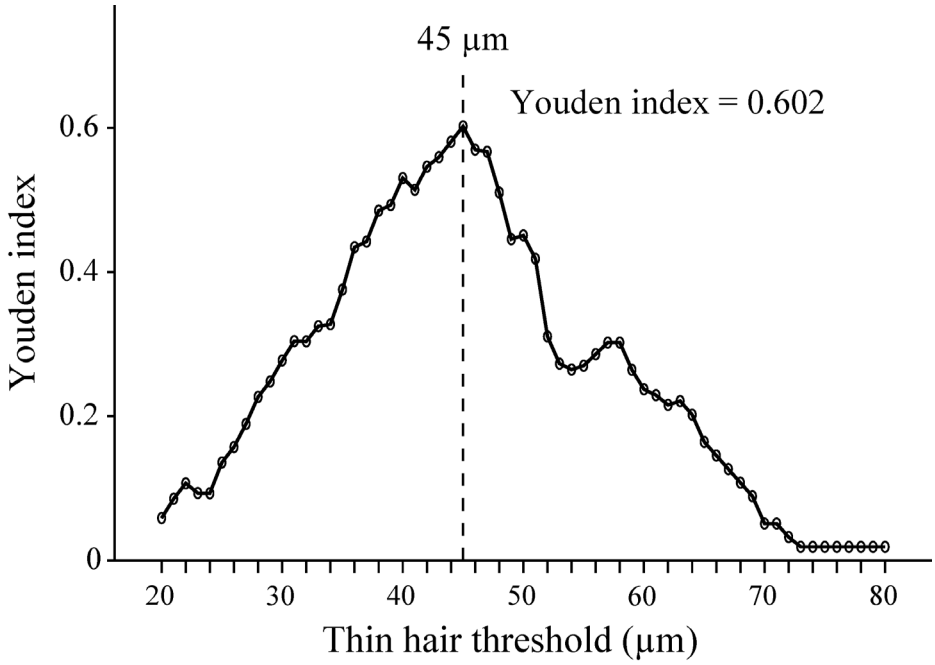


Figure 7. Youden Index-based hair diameter threshold with a 20% fixed cutoff. The graph displays the Youden Index across different hair diameters, with the peak at 45 μm indicating it as the optimal threshold for AGA diagnosis. *Abbreviation*: *AGA;* androgenetic alopecia

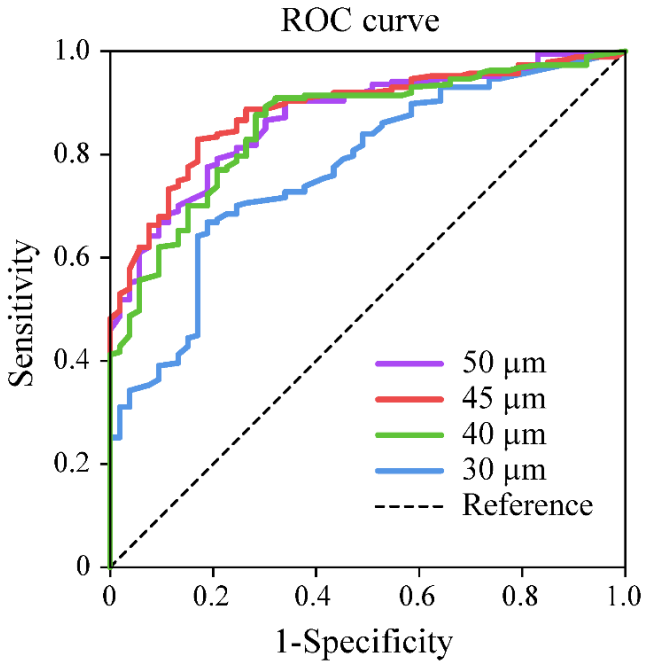


Figure 8. ROC curves for different hair diameter thresholds at 30 μm, 40 μm, 45 μm, and 50 μm. The ROC curves illustrate the diagnostic performance of different hair diameter thresholds for AGA, with the 45 μm line showing the highest AUC. *Abbreviation*: *AGA;* androgenetic alopecia, *ROC;* receiver operating characteristic

3.3.3. Identifying the most optimal hair diameter threshold irrespective of the fixed 20% HDD cutoff

Additional evaluations, aimed at identifying the most optimal hair diameter threshold for AGA diagnosis independent of the fixed 20% HDD cutoff, were depicted in **Table 4**. These assessments considered AUC, Youden index, and the optimal cutoff ratio for AGA diagnosis. The 30 μm threshold, traditionally associated with vellus hairs, had an AUC of 0.770 with a confidence interval of [0.703, 0.838] and a Youden index of 0.480, suggesting less diagnostic effectiveness. The threshold of 40 μm demonstrated an AUC of 0.858 and a Youden index of 0.594. The 45 μm threshold

exhibited the highest AUC at 0.884 and the greatest Youden index of 0.659, indicating greatest diagnostic accuracy. The 50 μm threshold had an AUC of 0.871 and a Youden index of 0.587. The optimal cutoff ratio for defining AGA increased with the threshold values, marked at 11.48% for 30 μm, 15.28% for 40 μm, 21.65% for 45 μm, and 30.28% for 50 μm **(Table 4)**. Separate analyses of retrospective and prospective cohorts consistently showed the 45 μm threshold as having the highest AUC and Youden index, with an optimal cutoff ratio at 21% **(Table 5)**. Consequently, when the 45 μm threshold is utilized as the optimal diagnostic criterion for HDD in the Korean population, the corresponding HDD threshold is defined at 21.65%. This threshold aligns well with the previously established 20% HDD standard, underscoring its significance and utility[6].

Table 4. Assessment of hair diameter thresholds for AGA diagnosis based on AUC, Youden index, and optimal cutoff point.

	AUC		**Youden index**	**Optimal cutoff point**
Thresholds	**Value**	**CI**	**Value**	**Value**
30 μm	0.770	[0.703,0.838]	0.480	11.48
40 μm	0.858	[0.806,0.919]	0.594	15.28
45 μm	**0.884**	[0.840,0.929]	**0.659**	**21.65**
50 μm	0.871	[0.824,0.918]	0.587	30.28

Abbreviation: *AGA;* androgenetic alopecia, *AUC;* area under cover, *CI;* confidence interval

Table 5. Assessment of hair diameter thresholds for retrospective and prospective patient data.

	AUC	Youden index	Optimal cutoff		AUC	Youden index	Optimal cutoff
Thresholds (Retrospective) N=116	**Value**	**Value**	**Value**	**Thresholds (Prospective) N=124**	**Value**	**Value**	**Value**
30 μm	0.801	0.651	11.48	30 μm	0.771	0.541	10.91
40 μm	0.860	0.697	18.01	40 μm	0.894	0.788	21.31
45 μm	**0.896**	**0.761**	**21.65**	45 μm	**0.924**	**0.849**	**21.83**
50 μm	0.893	0.734	27.10	50 μm	0.920	0.840	38.61

Abbreviation: *AUC;* area under cover

3.4. Part II : Change point analysis of hair diameter distribution in vertex and occiput

3.4.1. Hair diameter distribution analysis by stages at vertex and occiput

Part II of the analysis quantifies HDD in terms of hair diameter distribution. To evaluate the diversity of hair thickness, hair diameters were ordered from the thinnest (0th percentile) to the thickest (100th percentile) for all patients. The data was compiled in 5th percentile intervals and grouped by V stages. Analyses were systematically conducted at both the vertex and occiput to provide a comprehensive view of hair diameter distribution across these scalp areas **(Figure 9)**. Examining the trends at the vertex, the analysis reveals a distribution of hair diameters that shifts downward and to the right as the V stages progress. This trend indicates that as hair thickness decreases with each advanced stage, there is a concurrent rise in the proportion of thinner hairs **(Figure 9a)**. Conversely, occiput displays a different pattern; the shift in the graph towards the lower right is not as apparent. While V3 shows this trend, it is less pronounced compared to the vertex of V3. The stages V0, V1, and V2

maintain a consistent pattern without noticeable changes, suggesting a relative stability in hair diameter distribution in these earlier stages at the occiput area **(Figure 9b)**.

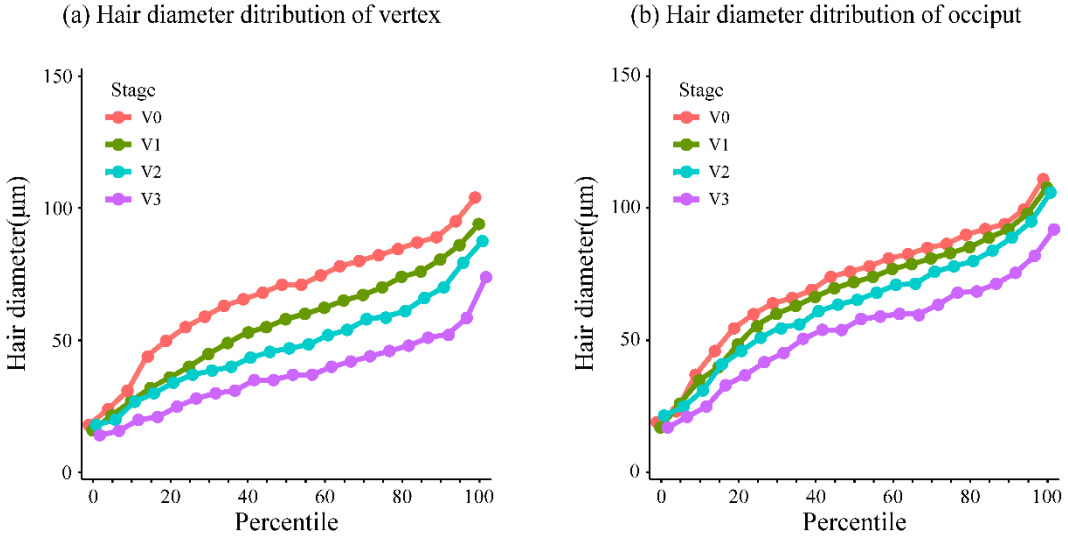


Figure 9. Hair diameter distribution analysis by percentile across stages in vertex and occiput**.** (a) represents a significant decrease in hair diameter at the vertex as stages progress, resulting in a noticeable shift of the graph toward the lower right. (b) illustrates a minor reduction in hair diameter at the occiput with stage advancement, causing an insignificant shift of its graph. The solid line connects the median hair diameter values at each 5th percentile.

3.4.2. Analyzing hair diameter differences between vertex and occiput

To analyze the differences in hair diameter between the vertex and occiput, we subtracted the hair diameter measurements at the vertex from those at the occiput for each V stage and calculated the average of these subtraction values. This method provided insights into the variation in hair thickness between the two areas, highlighting notable differences between the normal (V0) stage and the AGA stages (V1-3) **(Figure 10)**.

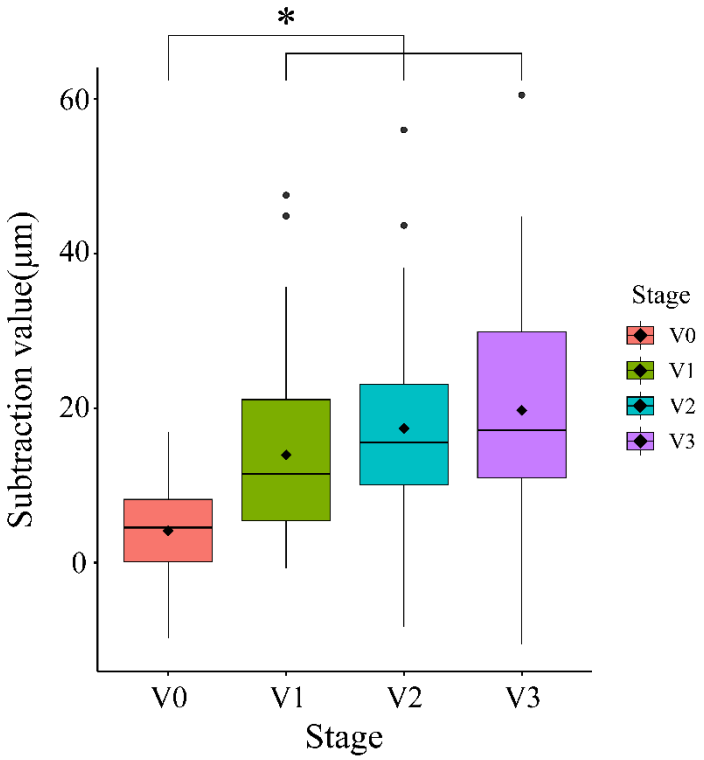


Figure 10. Comparative analysis of hair diameter differences between occiput and vertex. This figure presents a box plot depicting the differences in hair diameter between the occiput and vertex areas, with the mean marked by a black diamond. Each box plot corresponds to a V stage and illustrates the central tendency and dispersion of the difference in measurements, with higher stages typically showing greater differences. Significant differences are observed between V0 (normal) and V1-3 (AGA) (*$p < 0.0001$).

3.4.3. Identifying change points in hair diameter distribution at vertex and occiput

In the context of Figure 2, the graph demonstrates a trend towards the lower right as stages progress, indicating a shift at a change point in the pattern of hair diameter distribution. Segmented linear regression was utilized to investigate these change points for each patient's hair diameter distribution. This analytical method facilitates the exact determination of change points where significant alterations in hair diameter are observed, thereby delineating a quantifiable breakpoint that marks the transition points in the progression of hair thinning. The change point analysis by stage in the vertex showed that V0 had a change point at the 14.85th percentile (CI [12.87, 16.84]), V1 at the 33.38th percentile (CI [29.07, 37.70]), V2 at the 84.26th percentile (CI [81.10, 87.42]), and V3 at the 69.73rd percentile (CI [60.16, 79.31]). The AGA stages V1-3 had a change point at the 69.00th percentile (CI [65.09, 72.92]), distinctly different from the V0 (normal) stage, highlighting the progressive changes as stages advanced **(Table 6)**. Conversely, in the occiput, the change points were identified at the 21.33rd percentile for V0 (CI [19.54, 23.13]), the 28.33rd percentile for V1 (CI [24.70, 31.97]), the 28.28th percentile for V2 (CI [23.28, 33.27]), and the 74.12th percentile for V3 (CI [63.68, 84.55]). For stages V1-3 in the occiput, the change point occurred at the 35.19th percentile (CI [31.70, 38.68]). Unlike the vertex, the occiput displayed change points at similar percentiles for stages V0 through V2, with only V3 positioned at a higher percentile, indicating a distinct pattern in the occiput compared to the vertex **(Table 6)**. This difference in change points between the vertex and occiput is also evident when visualized through stage-wise box plots **(Figure 11)**.

Table 6. Change point analysis of hair diameter distribution by stage in vertex and occiput.

(a) Change point analysis of vertex by stage

	CP (95% CI)	Slope before CP	Slope after CP	Difference
V0	14.85 (12.87, 16.84)	2.54 (2.40, 2.68)	0.60 (0.55, 0.65)	-1.94 (-2.10, -1.80)
V1	33.38 (29.07, 37.70)	1.09 (0.99, 1.20)	0.81 (0.54, 1.07)	-0.29 (-0.52, -0.02)
V2	84.26 (81.10, 87.42)	0.51 (0.46, 0.55)	1.85 (1.44, 2.25)	1.34 (1.03, 1.84)
V3	69.73 (60.16, 79.30)	0.48 (0.37, 0. 60)	1.94 (1.11, 2.77)	1.46 (0.65, 2.29)
V1-3	69.00 (65.09, 72.92)	0.68 (0.63, 0.73)	1.70 (1.40, 2.00)	1.02 (0.65, 1.24)

(b) Change point analysis of occiput by stage

	CP (95% CI)	Slope before CP	Slope after CP	Difference
V0	21.33 (19.54, 23.13)	2.16 (2.06, 2.27)	0.56 (0.51, 0.61)	-1.60 (-1.72, -1.49)
V1	28.33 (24.70, 31.97)	1.70 (1.53, 1.88)	0.66 (0.39, 0.93)	-1.04 (-1.27, -0.83)
V2	28.28 (23.28, 33.27)	1.42 (1.24, 1.60)	0.69 (0.40, 0.98)	-0.73 (-0.97, -0.46)
V3	74.12 (63.68, 84.55)	0.73 (0.53, 0.93)	1.87 (1.03, 2.70)	1.14 (0.24, 1.87)
V1-3	35.19 (31.70, 38.68)	1.49 (1.37, 1.62)	0.80 (0.58, 1.03)	-0.69 (-0.86, -0.47)

Change points, determined by segmented linear regression, divide the hair diameter distribution graph into two linear segments, each with its own slope, before and after these points. This analysis reveals that in the vertex, the percentile of the change point increases as the stage progresses, whereas in the occiput, an increase in the change point's percentile is observed only at stage V3. *Abbreviations: CP*; change point

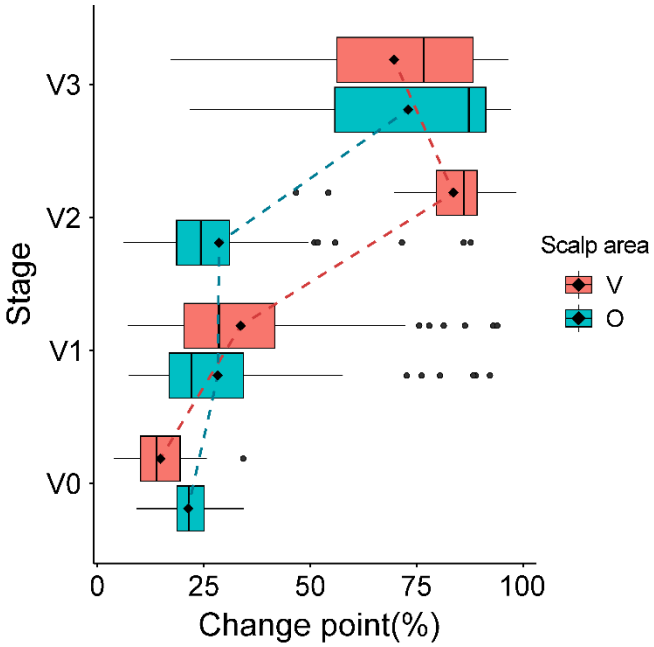


Figure 11. Box plot analysis of change point percentiles across stages and scalp areas. The colored dashed lines connect the mean values of the corresponding box plots of the same color. The vertex (V) displays a gradual increase in the percentile of the change point with each advancing stage, while the occiput (O) remains relatively stable until a marked increase is observed at V3.

3.4.4. Scatter plot analysis of hair diameter at change point percentiles in vertex and occiput

A scatter plot analysis of the hair diameter at identified change point percentiles revealed that, regardless of the change point pattern, both vertex and occiput demonstrated patient-specific variability in hair diameter. Notably, in V3, while the distribution of change points was similar between vertex and occiput, the occiput exhibited a higher prevalence of thicker hairs compared to the vertex. This observation

suggests that the occiput may display a greater resistance to hair thinning in the progression of AGA than the vertex (**Figure 12**).

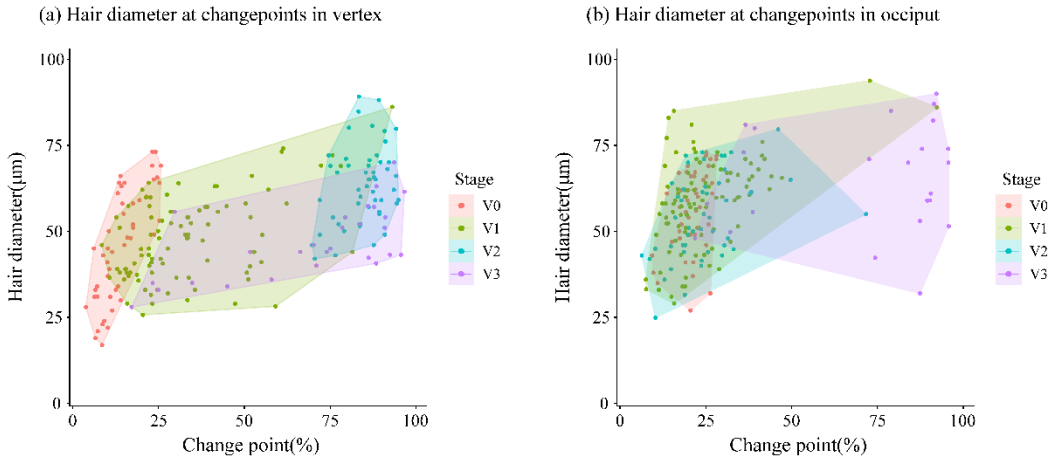


Figure 12. Scatter plot analysis of hair diameter at change points in vertex and occiput. The scatter plot analysis presents each patient's hair diameter in relation to the nearest percentile of the change point for each stage, with the shaded regions depicting the spread of these values. This data not only confirms the persistence of individual variations in hair thickness regardless of AGA progression, but also accentuates the sustained thickness of hair at the occiput (b) compared to the vertex (a) —most notably at stage V3—which signals the occiput's enduring resistance against AGA even at severe stages. *Abbreviations: AGA;* androgenetic alopecia

4. DISCUSSION

Our study presents two novel approaches for quantitatively validating the HDD standard in AGA, particularly focusing on disease progression. The objective measure of HDD≥20% for AGA evaluation originally employed a method similar to the phototrichogram, using macrophotographs for detailed hair analysis[6]. However, the definition of HDD≥20% lacks a precise quantitative characterization, leading some studies, in alignment with Part I of our study, to define HDD≥20% arbitrarily based on the proportion of thin hair exceeding 20%[2,4,17]. While the definition of thin hair can vary, it is commonly inferred to be 40 μm in Caucasian according to the paper that first introduced HDD[6]. Through our comprehensive evaluation of Part I with a fixed 20% HDD cutoff, we found that a 45 μm threshold offers better diagnostic accuracy for Koreans, as indicated by the highest Youden index. This is particularly important given that Koreans generally have thicker hair than Caucasians[18–23]. Additionally, further examination beyond the fixed HDD cutoff, using ROC curve analysis for different hair diameter thresholds, showed that the 45 μm threshold not only provides the highest AUC of 0.884, reflecting improved diagnostic precision for AGA, but also reaches a peak Youden index at a cutoff ratio of 21.65%. This finding supports the established HDD≥20% benchmark as valid across ethnicities, though the 45 μm threshold is specific to Koreans and does not consider individual variations in hair thickness.

In Part II of our study, concurrent change point analysis in the vertex and occiput regions was employed to explore another quantitative validation of HDD and address the limitations identified in Part I. Instead of relying solely on an absolute μm-based threshold, we explored HDD through the percentile distribution of hair diameter. Moreover, by including an analysis of the occiput, we were able to perform a comparative analysis with the vertex, offering a more nuanced understanding of HDD across different scalp areas. The hair distribution analysis revealed a pattern where, as the stages advanced, there was a notable shift towards the lower right, indicative of change points occurring at higher

percentiles. This pattern was clearly observed in the vertex but less so in the occiput, which is consistent with previous findings that the occiput is generally less affected by AGA than the vertex.[3,14]. However, at stage V3, the occiput exhibited change points at higher percentiles, contrasting with stages V0 to V2, indicating that the occiput may also be susceptible to AGA in more advanced stage. Interestingly, the change point of V3 in the vertex region is at a lower percentile than that of V2. This is speculated to be due to severe miniaturization, resulting in a general decrease in hair diameter and, consequently, inducing a more gradual slope in the graph. The change points in the vertex are below 20% for V0 (normal) and above 20% for V1-3 (AGA), while in the occiput, change points for V0 to V2 are distributed between 20% to 30%. These findings suggest that using the 20% threshold as a change point to assess AGA progression is feasible in both the vertex and occiput, except in severe stages. In scatter plot analysis, it was observed that individual differences in hair thickness persist regardless of AGA progression, and enduring resistance to AGA in the occiput region was noted even in severe stages. This underscores the need to consider individual variation in hair diameter assessment during HDD evaluation.

In conclusion, the traditional HDD≥20% has proven to be a valid metric in both Part I and Part II of our study, and applying this concept to the occiput, in addition to the vertex, can assist in distinguishing early-stage AGA.

This research has several limitations. Concentrating solely on Korean males constrains the applicability of our findings to other ethnic groups or females, who might display distinct hair characteristics. Moreover, the lack of baseline HDD data for a non-alopecia group, other than our V0 control group, hampers our understanding of HDD variations in a normal population, crucial for comparative analysis. The effects of aging on hair diameter and density were not considered. Although our sample size was adequate, a larger group would yield more conclusive data and facilitate detailed analyses of subgroups. The study's cross-sectional design may not fully reflect the progressive aspect of AGA or temporal changes in hair characteristics. AGA diagnostic evaluations often depend on conventional clinical scales like Norwood–Hamilton, Ludwig's, and BASP classifications[2,6,24], despite

being intuitive, suffer from subjective measurement limitations[23]. Future studies should investigate the relationship between clinician's perceptions of HDD and its objective assessments to address these subjective elements.

5. CONCLUSION

In this study, we sought to clarify the ambiguous quantitative definition of HDD≥20% using two distinct approaches: 'absolute threshold' and 'hair diameter distribution'. Our findings validate the 20% threshold, demonstrating its utility in assessing AGA progression through both quantitative definitions. When adopting an absolute μm-based standard, a 45 μm threshold was found to be appropriate for the Korean population. Additionally, when adopting the change point analysis, we found that the HDD≥20% threshold could be effectively applied to both the vertex and occiput, indicating its potential utility in identifying early-stage AGA.

REFERENCES

1. Ishino A, Takahashi T, Suzuki J, Nakazawa Y, Iwabuchi T, Tajima M. Contribution of hair density and hair diameter to the appearance and progression of androgenetic alopecia in Japanese men. Br J Dermatol. 2014;171:1052-59.

2. Kim BJ, Choi J, Choe SJ, Lee S, Lee WS. Modified basic and specific (BASP) classification for pattern hair loss. Int J Dermatol. 2020;59:60-5.

3. Khunkhet S, Chanprapaph K, Rutnin S, Suchonwanit P. Histopathological Evidence of Occipital Involvement in Male Androgenetic Alopecia. Front Med. 2021;8:790597.

4. Ishino A, Uzuka M, Tsuji Y, Nakanishi J, Hanzawa N, Imamura S. Progressive decrease in hair diameter in Japanese with male pattern baldness. J Dermatol. 1997;24:758-64.

5. Lolli F, Pallotti F, Rossi A, Fortuna M, Caro G, Lenzi, A, et al. Androgenetic alopecia: a review. Endocrine. 2017;57:9-17.

6. de Lacharrière O, Deloche C, Misciali C, Piraccini B, Vincenzi C, Bastien P, et al. Hair Diameter Diversity: A Clinical Sign Reflecting the Follicle Miniaturization. Arch Dermatol. 2001;137:641-46.

7. English R, Ruiz S. Conflicting Reports Regarding the Histopathological Features of Androgenic Alopecia: Are Biopsy Location, Hair Diameter Diversity, and Relative Hair Follicle Miniaturization Partly to Blame? Clin Cosmet Investig Dermatol. 2021;14:357-65.

8. Sewell LD, Elston DM, Dorion RP. “Anisotrichosis”: A novel term to describe pattern alopecia. J Am Acad Dermatol. 2007;56:856.

9. Kasumagic-Halilovic E. Trichoscopic Findings in Androgenetic Alopecia. Med Arch. 2021;75:109.

10. Inui S. Trichoscopy for common hair loss diseases: algorithmic method for diagnosis. J Dermatol. 2011;38:71-75.

11. Kibar M, Aktan Ş, Bilgin M. Scalp Dermatoscopic Findings in Androgenetic Alopecia and Their Relations with Disease Severity. Ann Dermatol. 2014;26:478.

12. Devjani S, Ezemma O, Kelley KJ, Stratton E, Senna M. Androgenetic Alopecia: Therapy Update. Drugs. 2023;83:701-15.

13. Inui S, Nakajima T, Itami S. Scalp dermoscopy of androgenetic alopecia in Asian people. J Dermatol. 2009;36:82-5.

14. Kim JY, Kim MH, Hong SP, Park BC. Characteristics of nonbalding scalp zones of androgenetic alopecia in East Asians. Clin Exp Dermatol. 2015;40:279-85. doi:10.1111/ced.12554

15. Lee SH, Kang JS, Jeon IK, Lee HS, Cho SB. Twopoint scoring method for the evaluation of pattern hair loss by phototrichogram using a headband and a tapeline. Skin Res Technol. 2013;19:183-88.

16. Lee EH, Kang JS, Kang DS, Han CS, Oh SH, Cho SB. Facilitated Scalp Measuring Using Phototrichogram with a Headband and Tapeline. Dermatol Surg. 2011;37:1150-152.

17. Rutnin S, Chanprapaph K, Pakornphadungsit K, Leerunyakul K, Visessiri Y, Srisont S, et al. Variation of Hair Follicle Counts among Different Scalp Areas: A Quantitative Histopathological Study. Skin Appendage Disord. 2022;8:24-30.

18. Loussouarn G, Lozano I, Panhard S, Collaudin C, El Rawadi C, Genain G. Diversity in human hair growth, diameter, colour and shape. An in vivo study on young adults from 24 different ethnic groups observed in the five continents. Eur J Dermatol. 2016;26:144-54.

19. Alsharif SH, AlGhamdi KM. Evaluation of Scalp Hair Density and Diameter in the Arab Population: Clinical Office-Based Phototrichogram Analysis. Clin Cosmet Investig Dermatol. 2022;15:2737-743.

20. Park J, Kim JI, Kim HU, Yun SK, Kim SJ. Trichoscopic Findings of Hair Loss in Koreans. Ann Dermatol. 2015;27:539-50.

21. Leerunyakul K, Suchonwanit P. Asian Hair: A Review of Structures, Properties, and Distinctive Disorders. Clin Cosmet Investig Dermatol. 2020;13:309-18.

22. Choi GS. Hair characteristics and androgenetic alopecia in Koreans. J Korean Med Assoc. 2013;56:45.

23. Kim JE, Lee JH, Choi KH, et al. Phototrichogram analysis of normal scalp hair characteristics with aging. Eur J Dermatol. 2013;23:849-56.

24. Lee WS, Ro BI, Hong SP, et al. A new classification of pattern hair loss that is universal for men and women: Basic and specific (BASP) classification. J Am Acad Dermatol. 2007;57:37-46.

Abstract in Korean

안드로겐탈모 진단 지표인 모발 직경 다양성의 정량적 계측과 임상적 활용

안드로겐탈모(Androgenetic alopecia, AGA)는 Norwood-Hamilton 및 Ludwig 분류법과 같은 주관적 방법으로 진단되는 흔한 탈모 형태다. 이 방법들은 널리 사용되지만, 임상의의 주관적 판단에 의존한다는 한계가 있어, 모발 직경의 변화를 나타내는 모발 직경 다양성(Hair diameter diversity, HDD) 같은 객관적 지표가 활용되고 있다. HDD는 직관적이고 이해하기 쉬운 지표이지만, 그 정량적 정의는 아직 명확하지 않다. 본 연구는 240명의 한국 남성 AGA 환자를 대상으로 HDD에 대한 두 가지 정량적 정의를 소개하고 평가하기 위해 정밀한 방법론을 적용했다.

연구의 첫 번째 부분에서는 정수리에서의 '얇은 모발 비율'을 통해 HDD를 탐구하며, 처음 얇은 모발의 비율로 제시된 40μm 이외에도 다양한 직경을 고려하여 얇은 모발을 정의했다. 이 접근법은 다양한 직경 값이 얇은 모발 비율과 AGA 진단 사이의 상관관계에 미치는 영향을 조사하여 한국 남성에게 가장 효과적인 직경 값을 분석하였다. 연구의 두 번째 부분에서는 정수리와 뒤통수에서 '모발 직경 분포의 변화점'을 분석하는 분포 기반의 HDD 정의를 탐구했다. 이 방법은 모발 직경 백분위수의 변화를 평가하여 이러한 분포 패턴의 변화가 AGA의 진행과 어떻게 상관되는지 분석하였다.

첫 번째 부분의 결과, 45μm 직경을 사용해 얇은 모발을 정의하고, 21.65%의 얇은 모발 비율을 적용하는 것이 한국 남성에게 최적의 진단 정확도를 제공했다. 두 번째 부분의 분석에서는 모발 직경 분포의 변화점이 AGA 진행에 따라 높은 백분위수에 위치하며, 특히 20-30% 범위 내의 변화점이 AGA 진단과 유의미하게 관련되어 있었다. 더불어, 정수리와 뒤통수 사이의 변화점 비교는 조기 AGA 진단에 대한 잠재적 이점을 제시했다. 또한, AGA 단계에 관계없이 개인별 모발 직경의 차이가 존재했으며 이를 통해 개인화된 평가의 중요성을 확인했다.

결론적으로, 본 연구는 전통적인 HDD 20% 지표의 유효성을 재확인했으며,

HDD가 AGA 진단에 있어 신뢰할 수 있는 지표임을 다시 한번 입증했다. 얇은 모발을 정의할 때는 45μm 직경 값을 사용하는 것이 한국인 남성에게 최적의 진단 정확도를 제공한다. 또한, 모발 직경 분포의 변화점은 정수리와 뒤통수에 적용될 수 있으며, 이 두 부위의 비교 분석은 AGA의 조기 진단에 잠재적인 이점이 있을 수 있다.

핵심되는 말 : 안드로겐탈모, 모발 직경 다양성, 한국 남성, 정량적 측정