

Conflicting Reports Regarding the Histopathological Features of Androgenic Alopecia: Are Biopsy Location, Hair Diameter Diversity, and Relative Hair Follicle Miniaturization Partly to Blame?

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Abstract: Despite decades of study, debate persists over the role of inflammation, fibrosis, and prostaglandins in the histopathology of androgenic alopecia (AGA). This brief review proposes that inconsistent findings across histological studies are a consequence of three inadequately controlled variables: 1) biopsy location, 2) hair diameter diversity (HDD), and 3) relative hair follicle miniaturization (HFM) within and across subjects. We suggest new methodological considerations to improve AGA histopathological research, as well as a novel classification system to quantify HFM by its stages. Finally, we hypothesize a dynamic relationship between inflammation, fibrosis, and prostaglandin activity dependent on relative HFM.

Keywords: androgenic alopecia, hair diameter diversity, inflammation, fibrosis, prostaglandins

Introduction

AGA is a progressive hair loss disorder that predominantly affects skin tissues above the galea aponeurotica. It is well-established that AGA is mediated by androgens and genetics.¹ However, there is less consensus surrounding its histopathology – particularly in regard to the presence of inflammation, fibrosis, and prostaglandin activity in balding tissues.

In his landmark study, Whiting discovered inflammation and/or fibrosis in 70% of AGA-affected biopsied vertices compared to 40.9% of non-balding controls.² These findings were corroborated in a follow-up investigation demonstrating inflammation and/or fibrosis in 71.4% versus 37% of balding and non-balding controls, respectively.³ Since then, histological studies have built on and conflicted with Whiting's work (Table 1).⁴⁻¹⁵ For instance, Goyal et al found no evidence of inflammation or fibrosis in men with moderate AGA.¹⁴ El-Domyati et al found that the magnitude of fibrosis increased alongside Norwood gradients – with follicular destruction observed in AGA's advanced stages.¹¹ Recently, Valdebran et al noted fibrosis in 68% of AGA biopsies and 82% of non-balding controls – calling into question the role of inflammation and fibrosis in AGA.¹⁵

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Table 1 A Summary of Investigations Reporting Inflammation and/or Fibrosis in AGA Biopsies

| Author (Year) | Subjects | | | Biopsy Methodologies | Balding Subjects | | Control Subjects | | |
|---|--------------------|-------------------------|--------------------|---|---|--|--|---|--|
| | Number | Age (Years) | Sex | | Hamilton-Norwood /Ludwig Gradient | Inflammation (%) | Fibrosis (%) | Inflammation (%) | Fibrosis (%) |
| Lattanand & Johnson (1975) ⁴ | 23 (347 specimens) | 21–48 | Male | Not specified | Biopsies from hair transplants | 50% | NE | NE; no control group | NE |
| Kligman (1988) ⁵ | 13 | 21–48 | Male | 7 with early AGA; 6 with late AGA | Transverse and vertical | NE; early AGA: inflammation in the infundibulum, sebaceous gland, and follicular streamers; late AGA: inflammation still present | NE; early AGA: collagen bundles and fibroblasts noted in follicular streamers; late AGA: fibrosis more evident in follicular streamers with some becoming fibrous tracts | NE; inflammation absent in specimens derived from senescent balding scalps; sparse, mild inflammation noted in normal scalps. | NE |
| Abell (1988) ⁶ | 603 | Not specified | 600 male, 3 female | Not specified | 3–6mm punch biopsy; transverse | 77% | 25% | NE; no control group | NE |
| Sperling & Winton (1990) ⁷ | 5 | Not specified | Male | Not specified | 3.5mm punch biopsy; transverse and vertical | 100% | NE; increased dermal collagen surrounding follicular groups | NE; no control group | NE |
| Jaworsky et al (1992) ⁸ | 4 | 25–67 years | 3 males, 1 female | Segmented samples by location: samples were obtained from the most affected region, transitional region (perimeter of affected pattern regions), and non-alopecic regions | Not specified | NE; significant inflammation in the infundibulum of specimens derived from transitional scalp | NE; balding samples: mature collagen noted in adventitial sheath; transitional samples: collagen noted in adventitial sheath, but less pronounced | NE; inflammation and fibrous tract remnants scarce among non-alopecic regions | NE |
| Whiting (1993) ² | 106 | 16–70, average 37 years | Male | Not specified | 4mm punch biopsy; horizontal and vertical | 70% (inflammation and fibrosis grouped together) | 70% (inflammation and fibrosis grouped together) | 40.9% (inflammation and fibrosis grouped together) | 40.9% (inflammation and fibrosis grouped together) |

| | | | | | | | |
|---------------------------------------|-----|--|----------------------|--|---|---|--|
| Whiting (1996) ³ | 412 | 15–80, average 40 years | 193 male, 219 female | Not specified | 4mm punch biopsy; horizontal and vertical | 71.4% (inflammation and fibrosis grouped together); moderate inflammation and/or fibrosis found in 11% | 40% (inflammation and fibrosis grouped together); moderate inflammation and/or fibrosis found in 11% |
| Deloche et al (2004) ⁹ | 40 | 19–51 in male group, 21–65 in female group | 21 male, 19 female | Norwood I: 2 Norwood II: 10 Norwood III: 3 Norwood IV: 5 Norwood VI: 1 Ludwig I: 4 Ludwig II: 12 Ludwig III: 3 | One 4mm punch biopsy, one 2mm punch biopsy; horizontal and vertical | 100% in males, 100% in females | NE; no control group |
| Won et al (2008) ¹⁰ | 10 | 20–35 | Male | Norwood III to Norwood IV; specimens were taken from both balding vertex and non-balding occipital region | 4mm punch biopsy; horizontal | NE; significantly increased collagen bundles and elastic fibers in vertex samples correlated with higher mast cells | NE; collagen and/or elastic fiber deposition absent in non-balding occipital samples |
| El-Domyati et al (2009) ¹¹ | 40 | 20–80 | Male | Norwood I: 3 Norwood II: 4 Norwood IIa: 3 Norwood III: 1 Norwood IIIa: 1 Norwood IIIv: 5 Norwood IV: 3 Norwood IVa: 3 Norwood V: 5 Norwood Va: 2 Norwood VI: 8 Norwood VII: 2 | 4mm punch biopsy; biopsies taken from balding area, non-balding occipital area, and frontal area from control subjects; horizontal and transverse | 90% | 17.5% |

(Continued)

Table 1 (Continued).

| Author (Year) | Subjects | | | | Biopsy Methodologies | Balding Subjects | | Control Subjects | |
|--------------------------------------|----------|--|--------------------|--|--|----------------------------------|-----------------------------|----------------------|--------------|
| | Number | Age (Years) | Sex | Hamilton-Norwood /Ludwig Gradient | | Inflammation (%) | Fibrosis (%) | Inflammation (%) | Fibrosis (%) |
| Aslani et al (2018) ¹² | 61 | 11–50 years in the female group, 18–37 in the male group | 46 female, 15 male | Not specified | 4mm punch biopsy; horizontal, vertical, and transverse | 66.7% of males, 35.7% of females | NE | NE; no control group | |
| Tandon et al (2019) ¹³ | 30 | 28–45 years | Female | Not specified | 4mm punch biopsy | 56% | 30% | NE; no control group | |
| Goyal et al (2019) ¹⁴ | 9 | 26–30 in men, 25–48 in women | 5 male, 4 female | Norwood II: 1 Norwood IV: 2 Norwood VI: 2 Ludwig I: 2 Ludwig II: 2 | 4mm punch biopsies; transverse | 0% in males, 0% in females | 0% in males, 25% in females | NE; no control group | |
| Valdebran et al (2020) ¹⁵ | 37 | Not specified | Not specified | Not specified | Examined specimens with at least one vertical section | 73% | 68% | 84% | 82% |

Abbreviation: NE, not estimated.

Conflicting histological reports have also emerged regarding prostaglandin activity in balding scalps. In 2012, Garza et al found that prostaglandin D₂ (PGD₂) and prostaglandin J₂ (PGJ₂) levels were elevated in balding scalps, and that prostaglandin E₂ (PGE₂) levels were higher in non-balding scalps.¹⁶ However, follow-up investigations by Villarreal-Villarreal et al found no significant differences in PGD₂ levels across balding and non-balding subjects, and concluded that PGE₂ synthase was only elevated in biopsies of early-stage AGA subjects.¹⁷ Most recently, Chovarda et al found higher PGD₂ and PGI₂ and lower PGE₂ and PGF_{2a} in balding scalps – further elucidating a complex relationship between prostaglandins and AGA.¹⁸

Some authors suggest that inconsistent histological findings are due to differences across study subject demographics (ie, age, sex, and/or race) and methodologies (ie, transverse versus horizontal biopsies and/or the use of demographic-matched, non-balding controls).^{19,20} These are plausible considerations. Nonetheless, three additional variables may greatly influence study outcomes, none of which are adequately controlled for in histological investigations: biopsy location, HDD, and relative HFM.

We propose the hypothesis that biopsy location, HDD, and relative HFM are responsible for the majority of conflicting findings across AGA histological studies. We introduce a classification system to quantify relative HFM and control for these variables. Finally, we hypothesize a dynamic relationship between inflammation, fibrosis, and prostaglandin activity in AGA that attempts to make sense of conflicting histopathological reports: a model dependent on relative HFM.

Discussion

Histopathological Challenges

AGA progresses through reductions in hair diameter, also known as HFM.²¹ HFM is considered a single step-process; it is believed to occur during reentry into anagen and worsen with each subsequent hair cycle.²¹ In AGA, hair cycling rates are not uniform. As such, AGA-affected locations often present with hair diameters ranging from full-thickness to miniaturized to vellus – even within 1mm zones. This phenomenon is termed anisotrichosis, also known as HDD.²² When terminal HDD varies by more than 20%, it is used as a diagnostic tool for AGA.²³ In all likelihood, HDD of less than 20% may also indicate early-stage AGA, albeit at cosmetically imperceptible levels.²⁴

HDD is ubiquitous but variable across AGA locations, gradients, and subjects.²³ As such, its presence poses a unique challenge in histopathological research. Current understandings of AGA histology come from analyses of 2–4mm punch biopsies. Biopsies are conducted on subjects with cosmetic AGA – often at gradients of Norwood 2–4. Due to concerns of scarring, investigators often biopsy regions where incisions are less conspicuous, like the vertex (Table 1).

Under these circumstances, a 4mm vertex biopsy may contain anywhere from 10 to 50 hairs – 80% of which are terminal.² However, within each biopsy, terminal HDD varies: some terminal hairs appear unaffected by HFM, while others appear toward the final stages of HFM. Resultantly, 1mm adjustments to biopsy location can skew HDD and HFM toward earlier or later miniaturization cycles (Figure 1). As such, HDD and relative HFM are phenomena that reduce the usefulness of standardizing biopsies based only on subject demographics, general location (ie, vertex), and Norwood gradient – particularly if research objectives involve elucidating histological changes throughout AGA's multi-stage progression.

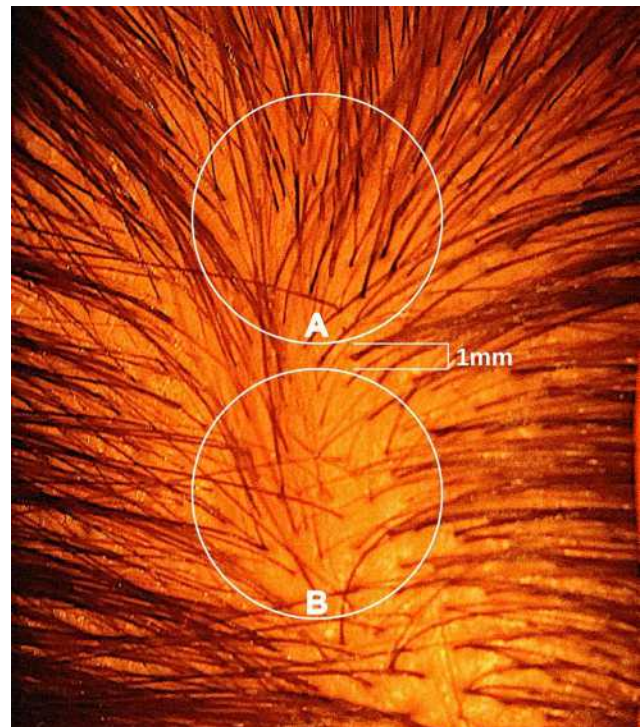


Figure 1 A photograph of a male vertex in the early stages of AGA. Zones represent potential biopsy locations separated by approximately 1 mm. Zone A features relatively high hair counts, low HDD, and terminal hair follicles skewed toward earlier cycles of HFM. Zone B features relatively low hair counts, high HDD, and terminal hair follicles skewed toward later cycles of HFM.

Abbreviations: AGA, androgenic alopecia; HDD, hair diameter diversity; HFM, hair follicle miniaturization.

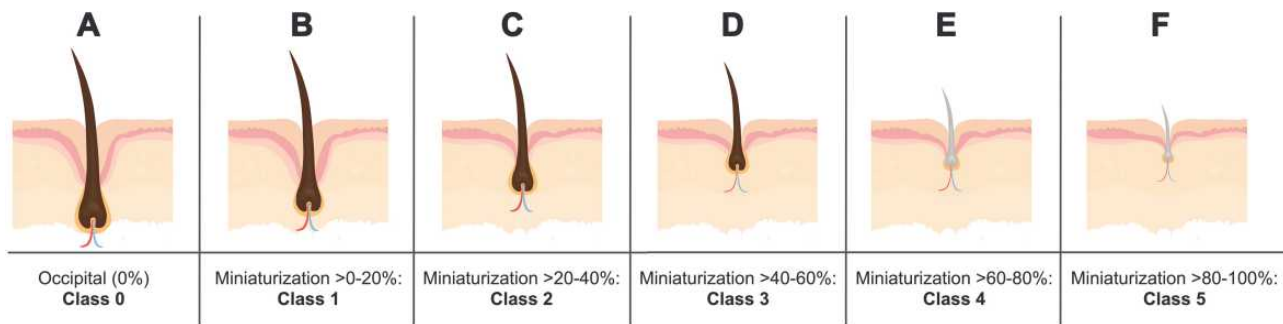


Figure 2 A proposed classification system to quantify relative HFM within the same subject. (A) Class 0 represents full-thickness hairs unaffected by AGA. (B–F) Classes 1–5 represent AGA-affected hairs benchmarked to Class 0, with miniaturization segmented by 20% increments per class.

Abbreviations: HFM, hair follicle miniaturization; AGA, androgenic alopecia.

Dermatopathologists stress the importance of performing biopsies at the edge of disease onset to capture both affected and unaffected tissue.²⁵ However, AGA's slow and widespread progression often obfuscates an early diagnosis due to change blindness. Therefore, by the time AGA becomes a cosmetic concern, HDD is already greater than 20%, HFM has already occurred over several hair cycles, and its initial edge of onset is difficult to discern. Therefore, as investigators continue to preferentially select for AGA subjects with visual hair loss, histological research continues to under-represent AGA in its earliest of stages (Table 1).

Lastly, in private conversations with dermatologists, trichoscopic examinations tend to show some degree of HDD in nearly all post-pubertal patients. If true, this suggests that the incidence of AGA is higher than previously reported, that AGA initiates much earlier than it cosmetically presents, and that inflammation in non-balding controls may actually indicate early-stage AGA – albeit with HDD of less than 20%. This draws into question the utility of comparing biopsies of balding scalps to location- and demographic-matched non-balding controls – at least without intrasubject evaluations to measure hair diameter in balding-prone versus donor-safe scalp regions.

Methodological Considerations

It is imperative that future histopathological AGA investigations not only control for Norwood gradient and biopsy location, but also HDD and relative HFM within and across subjects. Without accounting for HDD and relative HFM, conflicting reports regarding the presence of inflammation, fibrosis, and prostaglandins in AGA are likely to persist.

Historically, HDD is used as a binary measurement: it is present if an arbitrary examination zone shows hair diameter variations greater than 20%. Measuring HDD is simple; however, its usefulness in histological research is limited

without also capturing relative HFM. For example, HDD is often undetectable in biopsies of early- and late-stage AGA where hair diameters present uniformly as near-full thickness or near-completely miniaturized, respectively. Therefore, in addition to HDD, we propose that research teams also control for relative HFM within balding and non-balding controls.

Relative HFM can be established for each subject by averaging terminal hair diameters in a biopsied region, D_{biopsy} , to compare against average terminal diameters in a donor-safe region, D_{donor} . Preferably, donor-safe hairs would be measured in occipital zones A1, B1, and C1, where Yun et al found the widest hair diameters.²⁴

$$\left(1 - \frac{D_{biopsy}}{D_{donor}}\right) \cdot 100\% = \text{Relative HFM}$$

Finally, relative HFM can be segmented by 20% increments and denoted by five classes to distinguish magnitudes of miniaturization (Figure 2). In adult male scalps, the average diameter of terminal hair versus AGA-affected vellus hair ranges from 70 to 90 μm and 25 to 35 μm , respectively.^{24,26,27} Thus, a five-stage classification system would allow for histological observations across three stages of terminal HFM (Figure 2B and C) and two stages of vellus HFM (Figure 2E and F) in relation to a hair follicle unaffected by AGA (Figure 2A).

Altogether, controlling for HDD and relative HFM would serve to (1) identify balding subjects inadvertently featured as non-balding controls, and (2) clarify the histological role of inflammation, fibrosis, and prostaglandin activity across all classes of HFM, and thereby multiple stages of AGA.

Hypothetical Model

Conflicting histological reports regarding inflammation and fibrosis have stirred debate over whether AGA should be considered a scarring or non-scarring alopecia – with many

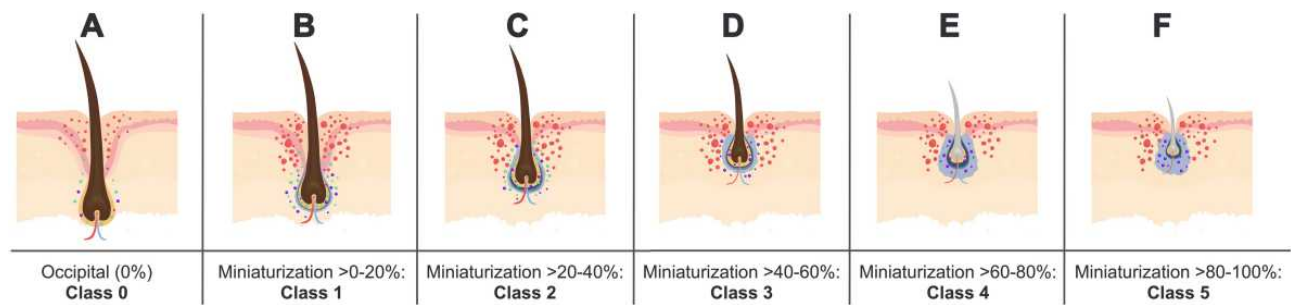


Figure 3 A hypothetical model showing a dynamic relationship between AGA and the presence of inflammation, fibrosis, and prostaglandin activity based on relative HFM. Inflammation is denoted by red markings; PGE₂ synthase is denoted by green markings; PGD₂ and PGJ₂ are denoted by purple markings; fibrosis is denoted by blue perifollicular shading. **(A)** Class 0 hair follicles unaffected by AGA show no fibrosis and relatively low levels of inflammation, PGE₂ synthase, PGD₂, and PGJ₂. **(B and C)**: Class 1–2 hair follicles in the early stages of HFM show relatively low levels of fibrosis but increased inflammation, PGE₂ synthase, PGD₂, and PGJ₂. **(D–F)** Class 3–5 hair follicles in the mid- to late-stages of HFM show increasing levels of fibrosis, decreased activity of PGE₂ synthase, and sustained levels of PGD₂ and PGJ₂.
Abbreviations: AGA, androgenic alopecia; HFM, hair follicle miniaturization; PGE₂, Prostaglandin E₂; PGD₂, Prostaglandin D₂; PGJ₂, Prostaglandin J₂.

investigators settling on a biphasic definition.²⁸ Inconsistent findings regarding prostaglandin activity have led Villarreal-Villarreal et al to suggest that PGE₂ synthase is upregulated in the early stages of AGA in order to protect hair follicles from miniaturization.¹⁷ Taking these stances into consideration, we hypothesize a dynamic relationship between AGA and the presence of inflammation, fibrosis, and prostaglandins dependent on relative HFM (Figure 3).

In the absence of HFM, our model suggests that hair follicles show no fibrosis and relatively low levels of inflammation, PGE₂ synthase, PGD₂, and PGJ₂ (Figure 3A). During early stages of HFM (ie, hair diameter reductions greater than 0% and up to 40%), hair follicles show relatively low levels of fibrosis but increased inflammation, PGE₂ synthase, PGD₂, and PGJ₂ (Figure 3B and C). During mid- to late-stages of HFM (ie, hair diameter reductions greater than 40%), hair follicles show increasing levels of fibrosis, decreased activity of PGE₂ synthase, and sustained levels of PGD₂ and PGJ₂ (Figure 3D–F). This hypothetical model would help make sense of decades worth of conflicting histological reports without undermining or dismissing any past findings.

Testing the Hypothesis

Testing our hypothesis would require, for each participant, the collection of five datapoints from both affected and unaffected AGA scalp regions: hair counts, hair diameters, and histological assessments of inflammation, fibrosis, and prostaglandin activity. Hair counts and hair diameters could be established non-invasively through dermoscopy and image analysis software. However, to the best of our knowledge, determining the presence and magnitude of inflammation, fibrosis, and prostaglandin activity in scalp skin would require a biopsy. This

poses a methodological challenge: most AGA patients are not diagnosed through biopsies, nor are they eager to undergo invasive procedures that potentiate scarring. Thus, to improve the testability of our hypothesis, there is a need to develop non-invasive methods to measure inflammation, fibrosis, and prostaglandins in cutaneous tissues.

There are non-invasive devices to assess inflammatory, proliferative, and remodeling phases of wound-healing in vivo for cutaneous tissues.²⁹ Some of these technologies may soon evolve to support hair loss research. Recently, Mogensen et al demonstrated that optical coherence tomography – in combination with topical gold nanoshells – enhanced the contrast of hair follicles and allowed for in vivo histological analysis at a resolution of 2 to 6 μm, but only to a depth of 1.2 mm.³⁰ Çildağ and Çildağ found that sonoelastography could assess the magnitude of skin fibrosis in subjects with diffuse cutaneous systemic sclerosis, albeit with lower accuracy in early stages of disease development.³¹ Laistler et al found that magnetic resonance imaging alongside highly-sensitive superconducting surface coils could achieve in vivo skin images that distinguished cutaneous layers and blood vessel walls, but only up to a resolution of 80 μm.³² Interestingly, magnetic resonance imaging has demonstrated utility in diagnosing AGA, determining hair follicle depth, and measuring epidermal, dermal, and hypodermal layer thickness.³³ Finally, Mize et al found that non-invasive reverse iontophoresis could measure, in vivo, changes to cutaneous PGE₂ from drug-induced irritation, but not from agents that induced vasodilation or vasoconstriction.³⁴ With continued advancements, optical coherence tomography, sonoelastography, magnetic resonance imaging, and reverse iontophoresis may allow for real-time in vivo monitoring of inflammation, fibrosis, and

prostaglandins in AGA – thereby accelerating histopathological research across a variety of hair loss disorders.

Conclusion

In AGA, the ubiquitous but variable presence of HDD and relative HFM undermine the utility of controlling histological investigations only for subject demographics and biopsy locations. We hypothesize that biopsy location, HDD, and relative HFM are responsible for the majority of conflicting findings across AGA histopathological investigations – and that a dynamic relationship exists between inflammation, fibrosis, and prostaglandins dependent upon relative HFM. We propose methodological considerations to account for HDD and relative HFM, as well as a novel classification system to establish relative HFM within each subject. Controlling for HDD and relative HFM can be accomplished by (1) measuring hair diameters within a biopsy to establish HDD, and (2) comparing biopsied hair diameters to those found in regions protected from AGA (ie, the occipital) to establish relative HFM. Such methodologies would not significantly complicate any investigation. They might, however, clarify decades worth of conflicting reports regarding AGA's histopathology.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

Robert English and Sophia Ruiz have no conflicts to declare.

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