

VIEWPOINT

The Proportion of Catagen and Telogen Hair Follicles in Occipital Scalp of Male Androgenetic Alopecia Patients: Challenging the Established Dogma

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Received: 16 May 2024 | **Revised:** 26 September 2024 | **Accepted:** 29 September 2024

Funding: The authors received no specific funding for this work.

Keywords: alopecia | hair | hair cycle | hair follicle | telogen

ABSTRACT

The hair follicle can cycle throughout a lifetime, undergoing periods of growth (anagen), regression (catagen) and relative quiescence (telogen). The time that a hair follicle spends in each of these stages is crucial to determine the length of hair fibre that it produces. Perturbations in this regard can manifest in various hair diseases such as anagen effluvium, or acute and chronic telogen effluvium. The established 'dogma' when considering how many hair follicles there are in each stage has long been that the majority are in anagen (85%–90%), followed by telogen (10%–15%) and catagen (1%–2%). These values are based on various studies using different methodologies such as hair plucking, phototrichograms and histology. However, these methods have flaws when it comes to differentiating between catagen and telogen follicles. We sought to determine the catagen:telogen ratio through the ex vivo stereomicroscopic examination of hundreds of hair follicles removed from the occipital scalp of 14 Caucasian males during routine hair transplantation procedures. Using this methodology, and in agreement with a similar observation by another research group, we found that the percentage of catagen hair follicles was higher (7.5%) than telogen (3.5%) in all patients assessed. Consequently, we believe that the percentage of catagen follicles is clearly underestimated and therefore challenge the current established dogma.

1 | Introduction

The hair follicle (HF) has the unique capacity to undergo periods of growth (anagen), regression (catagen) and quiescence (telogen), before self-regeneration and restarting of the cycle [1–4]. These three phases of the hair follicle cycle correlate with distinctive follicular morphologies [5]. At the end of the telogen phase, there is a fourth 'shedding' phase, called exogen [3], which can occur before or after a new hair shaft emerges. Unlike in many animals in which the pelage synchronously passes from one phase of the cycle to the next, in humans the

hair cycle is asynchronous, and the HFs are fully independent. Since scalp HFs are grouped in histologically well-defined structures known as follicular units (FUs) [6] the asynchronous character of the human hair cycle implies that each FU may contain follicles in different stages at any given time [7].

It is well known that the ratio of HFs at the different stages varies significantly at different body sites [8]. However, the area most extensively studied has been the human scalp due to the importance of scalp hair for quality of life and the psychological well-being of an individual. It has been widely accepted that at

any one time, 90% of the human scalp follicles are in the anagen phase, 10%–15% in telogen and 1%–2% in catagen. These percentages, with only very slight differences, are reported in all classic dermatology and trichology textbooks [9–12] and seem to have become an accepted ‘dogma’ of the scientific community.

To our knowledge, only one article, published by Oh et al. [13], has contradicted these percentages. These authors established a set of morphologic criteria to identify human HFs at different stages of the cycle [13] using a combination of stereomicroscopic morphology *ex vivo*, vertical histological sections and immunohistochemical staining for proliferation and apoptosis. Although their primary aim was not to study the hair cycle ratio, they wrote the following in the Discussion section: ‘our current histological analysis of HFs *in situ* suggests that the number of catagen HFs can exceed that of telogen HFs (catagen: 5%–10%, telogen: 1%–2%)’. Inspired by this intriguing and contradictory observation and by the unique opportunity of having access to the microscopic evaluation of hundreds of ‘*ex vivo*’ FUs from different patients, we decided to further investigate the hair follicle cycle ratio.

2 | Background: Previous Studies Evaluating the Percentage of Scalp Follicles in the Different Phases of the Hair Cycle

To put things in perspective, it is important first to review the methods used to evaluate hair cycle staging, which can be classified as invasive, for example biopsies [6, 12], semi-invasive, as in trichograms [14, 15], or noninvasive, that is, phototrichogram (PTG) techniques [16–18]. The most practical and informative of these methods are described below:

2.1 | Trichograms

The trichogram is a semi-invasive (plucking) microscopic method for hair root and hair cycle evaluation based on the root morphology [19]. The first study describing the morphology of hair roots was published by Van Scott in 1957 [4]. More than one hundred scalp hair roots were plucked and examined in 16 healthy donors from 18 to 38 years old. The proportion of growing anagen hair ranged from 63% to 96%, and 15% were found to be in telogen phase. In this study, the catagen phase was not calculated as it was uncommonly seen according to the author, likely due to the structural similarity to telogen [4].

2.2 | Phototrichograms

The basic principle of the phototrichogram (PTG) consists of shaving hairs from a scalp area of around 1 cm², taking a photograph of this area and, 2 days later, taking another photograph of this same area. Comparison of these two pictures enables the differentiation between the anagen hairs, which have grown during these 2 days, and hairs that have not grown. The PTG method has been significantly improved by Van Neste by dyeing the hair before taking the photograph (contrast-enhancement PTG) [18, 20]. The automated PTG method essentially works on the same principle, but using image analysis software that

allows *in vivo* measurement of the hair growth cycle (anagen %), the total number of hairs in a selected area, the hair density (*n/cm*²), the linear hair growth rate (LHGR; mm/day) and hair thickness. This method was also used to determine the periodicity of the hair cycle in males with and without androgenetic alopecia (AGA) [21–23].

We have to consider that a major pitfall of the PTG method is the impossibility of distinguishing between follicles in catagen and in telogen, because in both of these phases cell proliferation in the hair matrix ceases, with the hair follicle initially regressing (catagen) until it enters relative quiescence (telogen), and hairs do not grow [3, 13]. Therefore, when hair cycle studies based on PGT mention a specific percentage of telogen follicles, in reality they are grouping the telogen and catagen follicles together. For example, the largest PTG study by Loussouarn et al. with 2249 volunteers from different racial groups reported an average telogen rates of 10%–12% (ranging from 8% hairs in Danish to 14% in Thai individuals) [24, 25].

In reality, this 10%–12% telogen count indicates the percentage of non-growing hairs, which can belong to follicles either in catagen or in the telogen phase.

2.3 | Histology With Vertical and/or Horizontal Sectioning

Histology-based hair cycle staging is an accurate method to distinguish the microscopic anatomy between the different phases but is not an appropriate method for observation of the succession and duration of the hair cycles. The first histologic studies by Kligman in 1959 [2], Fleck and Fleck [26] and Witzel and Braun-Falco [27] calculated the ratio of each phase to the entire growth cycle scalp hair in adults and infants. Kligman reported 13% of HFs in telogen, while Witzel and Braun-Falco in 1963 found 83% in anagen and 15% in telogen. All these studies were performed using vertical tissue sections, which is known to have limited value for counting follicles. In contrast, the horizontal sectioning method described by Headington in 1984 [6] and currently considered the best method for scalp histopathologic diagnosis [28, 29] ensures that all follicles in the specimen are counted and examined at multiple levels, thus providing more accurate information about the percentages of follicles encountered in each cycle phase [29–31]. However, when determining the telogen count, it is common that pathologists group together the catagen and telogen phases as one ‘catagen/telogen phase’ (Table 1) because it is not considered to be important for diagnostic purposes [40]. Likewise, most research studies reporting the different hair cycle phases based on histologic sections count the percentage of anagen follicles and group together the percentage of catagen/telogen follicles (Table 1).

2.4 | Stereomicroscopic Morphology of Ex Vivo Hair Follicles

This method is based on the *ex vivo* stereomicroscopic evaluation of the morphology of the inferior segment (non-permanent portion) of the HF. It is highly reliable since in most follicles it is very straightforward to distinguish the anagen follicle from

TABLE 1 | Scope of literature and the methodologies used to assess hair follicle growth and anagen:Telogen:Catagen ratio from 1957 to the present day in chronological order.

Study reference	Donor type	Methodology	Area	Average ratio Anagen:Telogen:Catagen
Van Scott (1957) [4]	16 Caucasian donors (11 male and 5 female)	Trichogram	Parieto-occipital scalp	A: 63%–96% T: 15% C: not mentioned
Kligman (1961) [32]	28, Caucasian males	Histology Vertical Sections	Occipital scalp	A: 87% T/C: 13%
Pecoraro (1964) [19]	26 newborns (3–76 h after birth)	Trichogram	Occipital	A: 94% C: 1% T: 4%
Saito (1970) [17]	3 Asian donors, 21–61 years of age	Capillary tube and photography at very close range	Vertex	A: 79% T: 21% C: not mentioned
Whiting (1993) [33]	Caucasian	Histology Horizontal sections	Vertex posterior	A: 93.5% T/C: 6.5%
Frishberg (1996) [31]	Caucasia	Histology Horizontal sections	Clinically healthy scalp	A: 94.5% T/C: 5.5%
Sperling (1999) [34]	African American	Histology Horizontal sections	Clinically healthy scalp	A: 94% T/C: 6%
Lee (2002) [35]	Asian AGA patients	Histology Horizontal sections	Occipital scalp	A: 93.6% T/C: 6.4%
Mulinari-Brenner (2006) [36]	20 cadavers (4 punches per cadaver)	Histology Horizontal sections	Frontal, vertex, occipital and temporal scalp	A: 92.2% T: 6.2% C: 1.6%
Aslani (2009) [37]	Middle Eastern patients	Histology Horizontal and vertical sections	Central mid-scalp in females and frontal or vertex in male	A: 93.7% T/C: 6.3%
Loussouarn (2016) [24]	2249 adults from 24 countries	Phototrichogram	Occipital, vertex and temporal scalp	A: 86%–92% T/C: 8%–14%
Oh (2016) [13]	Asian males	Ex vivo stereomicroscopic morphology followed by histologic vertical sections and immunohistochemistry	Occipital scalp	A: 88%–94% C: 5%–10% T: 1%–2%
Hu (2022) [38]	Asian males	Histology Horizontal sections	Occipital scalp	A: 91.1% T/C: 8.9%
Rutnin (2022) [39]	60 Thailand cadavers	Histology Horizontal sections	Occipital, frontal, vertex, temporoparietal	A: 92% T/C: 8%
Current study	14 Caucasian males (100 FUs per donor)	Ex vivo stereomicroscopic morphology followed by methylene blue staining/histology in difficult cases	Occipital scalp	A: 89% C: 7.5% T: 3.5%

Abbreviation: T/C, telogen and catagen are grouped together in eight out of nine histological studies.

the non-pigmented apoptotic epithelial strand and the dermal sheath thickening of the catagen follicle and from the typical ‘club’ hair image of the telogen follicle [5, 13] (Figure 1). If there

is difficulty differentiating between late catagen and telogen follicles, a useful method is to stain the follicle with the intravital dye methylene blue (MB) [5, 41]. This allows visualisation

of the epithelial strand of the late catagen follicle which is absent in telogen follicles and otherwise invisible to the naked eye (Figure 2).

3 | Hypothesis: The Percentage of Scalp Follicles in Catagen Is Greater Than in Telogen, Which Contradicts the Established Dogma

The hair cycle evaluation and data presented here were performed in the setting of a hair transplant clinic with access to thousands of ex vivo HFs, providing us with the opportunity to create a large database on the number of HFs in different cycling stages.

As part of our standard follicular unit excision (FUE) hair transplant procedure, all FUs harvested from the donor area (1500 to 2500 FUs on average) are observed under the stereomicroscope

to group them by the number of HFs that they contain (1-hair FU; 2-hair FUs; 3-hair FUs; 4 or more hair FUs). This phase is important for planning the graft implantation in the recipient area, since 1-hair FUs should be placed in the frontal hairline and the 2–3 and 4 or more hair FUs placed behind, thus creating a transition zone that results in a natural look following transplantation [42].

Taking advantage of this routine stereomicroscopic evaluation, for this study we randomly separated 100 FUs from 14 different patients after written informed consent and recorded the number of anagen, catagen and telogen follicles based on the standard morphologic criteria reviewed by Oh et al. [13] The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Fernando Pessoa, Canary Islands (Approval number 03/2020).

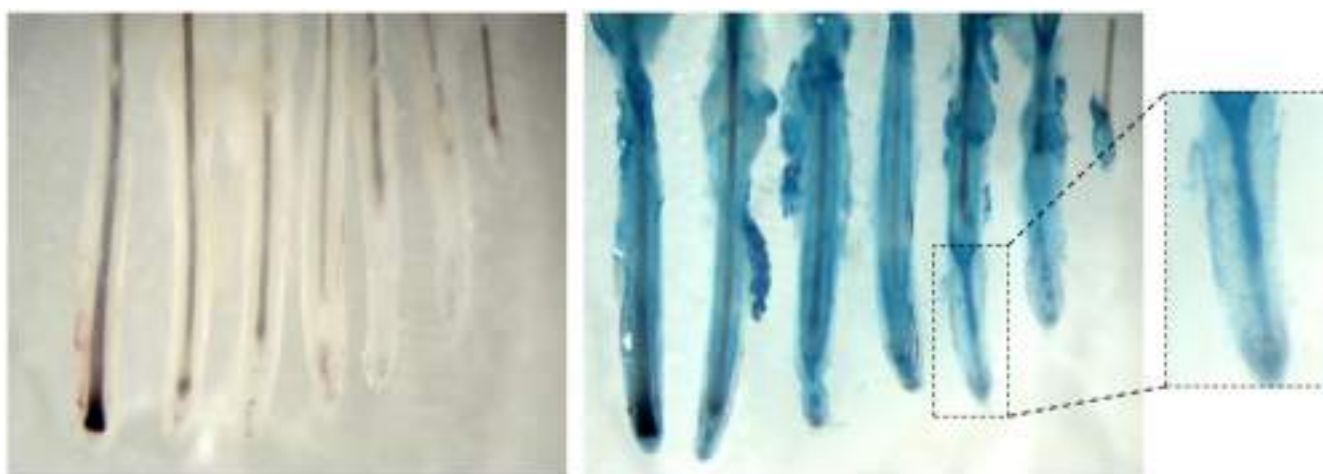


FIGURE 1 | Distinct morphological differences between the anagen, catagen and telogen stages in human scalp hair follicles. (Left) A representative example of the different hair cycle stages in terminal scalp hair follicles under the stereomicroscope. The transit from anagen (far left follicle) to telogen (far right follicle) is a continuous process. During catagen, the follicle can be morphologically classified as early, mid or late catagen (Right) (Oh et al. [13]) The same hair follicles after being stained with the vital dye methylene blue which helps to visualise distinct anatomical features of the hair cycle such as the regressing epithelial strand of a catagen follicles (Inset) can be clearly seen following staining. (Alam et al. [5], reproduced with permission from British Journal of Dermatology).

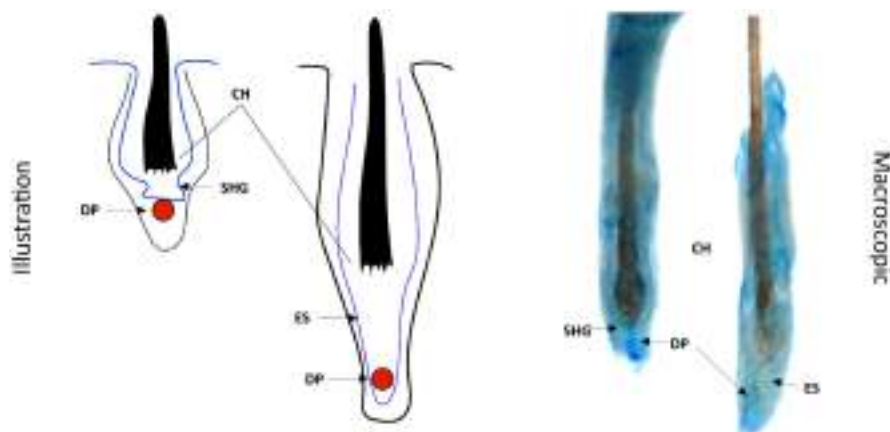


FIGURE 2 | Illustrative and macroscopic images highlighting the subtle difference between telogen and late catagen hair follicles. Illustration (left) depicting telogen and late catagen hair follicles (HFs). It is difficult to distinguish the 'nipple like' morphology of the telogen secondary hair germ from the epithelial strand of a late catagen follicle. This subtle difference can be highlighted by staining the HF with methylene blue (right). A club hair can be seen in both telogen and late catagen HFs. CH, club hair; DP, dermal papilla; ES, epithelial strand; SHG, secondary hair germ.

All HFs evaluated corresponded to the same scalp area, the occipital donor hair transplant zone, which is considered unaffected by AGA [43]. In total, 1400 FUs (100 FUs from each of 14 white male patients) were evaluated. As most FUs contain between 1 and 4 terminal hair follicles, we assessed in this study a total of 3607 terminal HFs (average of ~256 HFs per patient).

In the vast majority of follicles, the anagen, catagen and telogen stages were easily identifiable and only those follicles in which it was difficult to distinguish between late catagen and telogen

were immersed in 0.02% MB saline solution for 15 min, as described previously [41]. In addition, histological sectioning was performed in a very few limited cases to further solidify the classification following MB staining.

Our results showed a greater percentage of catagen (average 7.5%) than telogen follicles (average 3.5%) in all patients evaluated. Anagen follicles, as expected, comprised most of the HFs (89%) (Table 2). These results confirm the observation reported by Oh et al. [13] and contradict previously accepted percentages (Table 1).

TABLE 2 | Average percentage of anagen, catagen and telogen HFs identified by ex vivo stereomicroscopic analysis.

Patient ethnicity/gender/ age/AGA severity scale	Anagen	Catagen	Telogen	Total number of hair follicles
W/M/38/V	185 (88.5%)	15 (7.2%)	9 (4.3%)	209
W/M/41/III	245 (91.8%)	14 (5.2%)	8 (3.0%)	267
W/M/30/IV	245 (92.1%)	13 (4.9%)	8 (3.0%)	266
W/M/51/V	227 (78.5%)	39 (13.5%)	23 (8%)	289
W/M/32/II	225 (91.1%)	14 (5.7%)	8 (3.2%)	247
W/M/63/IV	246 (91.4%)	12 (4.5%)	9 (3.35%)	267
W/M/49/III	247 (92.5%)	15 (5.6%)	4 (1.4%)	266
W/M/42/III	223 (90.2%)	17 (6.94%)	5 (2.04%)	245
W/M/44/III	250 (88.2%)	25 (8.95%)	8 (2.87%)	283
W/M/54/III	204 (88.2%)	24 (9.4%)	3 (1.18%)	231
W/M/59/V	277 (90.92%)	27 (9.04%)	11 (1%)	315
W/M/39/IV	194 (81.11%)	23 (9.28%)	12 (2.14%)	229
W/M/42/IV	232 (83.07%)	28 (9.91%)	16 (3.12%)	276
W/M/37/III	210 (89.35%)	5 (2.26%)	2 (0.93%)	217
Total	3210	271	126	3607
Average	228	17.42	7.54	256
SD	24.9	8.71	5.46	29.59
SE	6.66	2.33	1.46	7.91
Percentage	88.99%	7.51%	3.49%	100%

Note: Methylene blue staining was used when it was difficult to differentiate between catagen and telogen follicles. Only in a few cases follicles required histological confirmation.

Abbreviations: I–VI, AGA Norwood severity scale; M, male; W, White Caucasian [43].

4 | Discussion: Challenging the Current Dogma

Our results, in agreement with the observation of Oh et al. [13], show a higher percentage of scalp follicles in catagen (7.5%) than in telogen (3.5%) at a given time. This finding implies that the current dogma cited by textbooks and generally accepted by the scientific community of 10%–15% telogen and 1%–2% catagen needs to be reevaluated.

We believe that these conflicting results are due to the inaccuracy of the methodologies that have been used in the literature to differentiate between the catagen and telogen stages of the hair follicle cycle.

For example, the trichogram is regarded as an inaccurate method since most of the epithelial and mesenchymal follicular sheaths are left behind when plucking. In fact, the literature emphasises the discrepancies in classifying a HF as telogen, with the same hair classed by others as catagen based on the presence of adhering follicular tissue [44].

PTG, as noted above, detects hair shaft growth and thus cannot differentiate between the catagen and telogen phases of the follicles because the hair shafts do not grow in either stage. However, at least PTG can give as an indirect but accurate estimation of the catagen/telogen follicles, grouped together as non-growing hairs. In this regard, the average percentage of 10%–12% of non-growing hairs reported by Loussouarn et al. [24] correlates nicely with our finding 7.5% catagen and 3.5% telogen follicles if we would group them together (11%). As our study only consisted of White Caucasian males, it would be interesting to see if there are any differences between different ethnic groups and between males and females using the methodology we utilised for our study. The study by Loussouarn et al. compared hair growth rates, diameter and density across various ethnic groups and between male and female. Although they found variances in hair density and growth in vertex and temporal regions between ethnic groups and between males and females, no notable differences in occipital scalp hair were mentioned between the groups.

Only histologic evaluation and the ex vivo stereomicroscopic evaluation of HF sections are methods that can morphologically distinguish between catagen and telogen follicles. However, histologic evaluation, even by experienced pathologists, relies on correct sample sectioning. The fact that most histological studies performed with horizontal section group together the catagen and telogen follicles as one group indicates that their differentiation is not always straightforward. Moreover, when vertical sections are not completely cut parallel to the HF epithelial strand (angling) seen in catagen follicles or when follicular sectioning is incomplete, histology can give rise to interpretation errors and late catagen follicles can be misdiagnosed as telogen follicles. This, in our opinion, may explain the underestimated rate of catagen follicle percentages [41].

5 | Conclusion

There is enough convincing evidence to support that the percentage of human scalp follicles in the anagen phase at any given

time must be around 88%–90%. However, there is still an evident lack of consensus regarding to which non-proliferative cycle phase (catagen or telogen) corresponds the rest of the 10%–12% non-growing hairs. While the current dogma of 10% telogen and 1%–2% catagen is still conveyed through reviews and textbooks to newer generation physicians, the findings from our study and by Oh et al. questions this dogma and justifies a need to definitively resolve this issue in the most rigorous scientific way as possible.

Although all subjective imaging-based methods have errors and pitfalls in their interpretation, and none of them is perfect, only the ex vivo hair stereomicroscopic morphology and the histologic evaluation enable to identify and classify the follicles either in catagen or telogen phases. The most pragmatic way that we imagine our hypothesis could be tested is that those catagen and telogen follicles classified as such by the ex vivo stereomicroscopic analysis should be strictly scrutinised by a thorough histologic analysis of vertical and horizontal serial sections which includes the complete length of the follicles. This painstaking analysis would require many HFs from many subjects. As taking multiple biopsies from healthy controls is unapproachable from an ethical perspective, such a study could only be performed in samples donated from cadavers or from redundant scalp skin after, for example, plastic surgery, allowing in situ analysis of the whole tissue and hair.

The accuracy of the anagen:catagen:telogen ratio is important because minor variations in the cycling phase may have major clinical effects [9]. Another implication of our hypothesis is that the common belief that it is normal to shed up to 100 scalp hairs per day, which is based on the assumption that there are an average number of scalp hairs of 100000 [45] and that 10% of scalp hairs are in telogen is also likely to be incorrect and likewise needs to be revisited. Although the FU samples evaluated in this study corresponded to AGA patients and thus the ratio of A/C/T may differ in comparison with non-AGA individuals, we believe that our data are unlikely to reflect sampling bias as HFs were harvested from donor occipital scalp, considered to be ‘androgen-resistant’ and generally unaffected by AGA [46].

Author Contributions

F.J. and M.A. conceived, designed carried out the study, analysed the data and wrote the manuscript. We would like to thank Mercedes de Mirecki-Garrido for technical assistance for analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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