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Original Article

TESTOSTERONE-INDUCED ANDROGENETIC ALOPECIA MICE MODEL: A PRELIMINARY STUDY

ARIE KUSUMAWARDANI*, NURRACHMAT MULIANTO, ADNIANA NARESWARI, PRISTIA WIDYA MONICA, TRYA OKTAVIANI

Department of Dermatology and Venerology of Dr. Moewardi General Hospital/Sebelas Maret University, Jalan Kolonel Sutarto, Surakarta-57126, Centra Java, Indonesia

***Corresponding author: Arie Kusumawardani; *Email: arie_k@staff.uns.ac.id**

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ABSTRACT

Objective: Androgenetic alopecia (AGA) is the world's most common type of hair loss caused by an exaggerated response to androgens. The pathophysiology of AGA has been extensively studied to date, but the process of developing small animal trials remains a challenge.

Objective: This study aims to develop a testosterone-induced AGA mice model to facilitate future research related to AGA, either to understand the pathophysiology or to develop new therapeutic modalities. This AGA mice model may also be clinically useful, especially to facilitating drug testing for AGA therapies.

Methods: This is a preliminary *in vivo* study to develop AGA mice model. This study used BALB/c white mice. The AGA model was induced by subcutaneous injection of testosterone. The subjects were divided into three different groups, group a (0.05 ml testosterone subcutaneous injection), group B (0.075 ml testosterone subcutaneous injection) and group C (0.1 ml testosterone subcutaneous injection). Dermal thickness (DT) and hair follicle density (HFD) were the assessment parameters used to determine the optimal testosterone dose to induce the AGA model.

Results: BALB/c mice in group B obtained DT of 385.59 µm ($p = 0.006$) and HFD of 13.38/mm^2 ($p = 0.001$), which were significantly lower than the other groups. This value is lower than group A with DT of 643.82 µm and HFD of 36.13/mm^2 and group C with DT of 477.00 µm and HFD of 15.75/mm^2.

Conclusion: Testosterone at dose 0.075 ml with subcutaneous injection can produce the most ideal AGA mice model and most similar to the condition of dermis and hair follicles in AGA patients.

Keywords: AGA, BALB/c Mice, Dermal thickness, Hair follicle density, Mice model

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INTRODUCTION

Androgenetic alopecia (AGA), also known as male pattern baldness, is the most common form of hair loss worldwide [1]. This condition arises from an excessive response to androgens, particularly dihydrotestosterone (DHT), in genetically predisposed individuals [2, 3]. DHT is converted from testosterone catalyzed by 5α-reductase [4]. The worldwide prevalence of AGA is approximately more than 50% in men, with prevalence increasing with age [5]. This prevalence increases to 80% by the age of 80 [6]. This condition is characterized by progressive and diffuse hair loss with a certain pattern that starts in the frontal hair [7, 8]. AGA is not a life-threatening condition, but it can cause psychological burdens such as depression and anxiety that further impact on quality of life [9, 10].

To date, DHT is thought to be most responsible agent for causing AGA. Excessive response to DHT can lead to shrinkage of hair follicles, which results in terminal hairs turning into vellus [11]. DHT binds to androgen receptors on dermal papilla cells and triggers activation of signaling pathways in the cells, resulting in protein shape changes and hair follicle miniaturization [12]. Apart from the excessive response to DHT, genetic factors are also thought to play a major role in the development of this disease. Genetic factors include changes in the structure of androgen receptors due to genetic mutations on X chromosome. These mutations will cause androgen receptors to have an excess response to DHT compared to normal androgen receptors [5].

While the pathophysiology of androgenetic alopecia has been extensively studied in humans, the development of appropriate animal models has been challenging, especially the small animal model. These challenges are also related to the cost, availability and difficulty of manipulating animal models [13]. BALB/c mice are one of the most popular and widely used animal in biomedical research. This mice breed could generally represent a disease condition in human, therefore make it a reliable animal model [14]. These mice have high genetic homogeneity and have been used extensively in hair loss research, including new therapeutic modalities and pathophysiology [15-17]. BALB/c mice had well-characterized hair follicle cycles. It's hair follicles undergo synchronized cycles, which are structurally analogous to human hair cycles. This synchronization allows for precise timing in experimental interventions and assessments [18].

This preliminary study aims to establish a BALB/c mice model of testosterone-induced AGA to facilitate further research into the underlying mechanisms and potential therapeutic interventions. This AGA mice model may also be clinically useful, especially to facilitating drug testing for AGA therapies.

MATERIALS AND METHODS

Design

This preliminary study was an *in vivo* study with aim to developed the mice model of AGA. This study used BALB/c mice to developed the AGA model. This research was conducted in the Center Laboratory for Food and Nutrition Study, Gajah Mada University, Yogyakarta, Indonesia and Laboratory of Anatomical Pathology, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia. The research protocol was approved by the Head and Research Ethics Committee of Dr. Moewardi General Hospital with Ethical Clearance approval number 1.853. B/X/HREC/2023 (Surakarta, Indonesia).

Animal preparation

There were 15 white BALB/c mice with 5 mice for each group. BALB/c white mice were obtained from the House of Experimental Rats Gajah Mada University Yogyakarta, Indonesia. The minimum size of sample calculated based on the minimum sample for a one-way ANOVA design ($n = 10/k+1$, n was the minimum size of sample for each group and k was the number of group) [19]. The inclusion criteria for subjects were mice aged 7 w, male, body weight 20-30 g

and in good health. Meanwhile, the exclusion criteria were mice with disabilities suffered from illness during the adaptation period, and mice that died before the study was completed. We choose only male mice, because even tough AGA manifests in both males and females, the underlying pathophysiology differs between the sexes. Prior to treatment, mice underwent 7 d of adaptation to a 17.5 x 23.75 x 10 cm cage, lighting with a dark-light cycle every 12 h with a light intensity 130-325 lux and room temperature of 18-26 °C. A 7 d adaptation period was chosen based on standard protocols in rodent studies, which generally consider one week sufficient for animals to acclimate to new environmental conditions and for physiological parameters, including stress-induced hormonal fluctuations, to stabilize [20]. Mice were given access to food and drink with standard composition (water 12%, crude protein 20-22%, crude fat 5%, crude fibers 5%, crude ash 7.5%, calcium 0.09-0.1%, phosphor 0.6%, coccidiostat and antibiotic). The food was obatained from the House of Experimental Rats Gajah Mada University Yogyakarta, Indonesia. The cages in which the mice were kept were made of polycarbonate plastic. Cage mats, feeders and manure are cleaned every 2 d to prevent the spread and development of disease.

AGA model induction

Induction of the AGA model was carried out after the adaptation period. Induction of the AGA model is done by giving Sustanon® (Organon Pharma, Indonesia), which contains testosterone propionate, testosterone phenylpropionate, testosterone isocaproate and testosterone decanoate, administered subcutaneously on the back. Before injection, the hair on the mice back was shaved to trigger the telogen phase of the hair. Mice were then divided into three groups, group A injected with 0.05 ml Sustanon®, group B injected with 0.075 ml Sustanon® and group C injected with 0.1 ml Sustanon®. Sustanon was injected once daily for 10 d. The dosage and duration of injection were determined based on a pilot study that we conducted previously. The experiment was only conducted once. There was a reason why we have used subcutaneous testosterone injections instead of DHT, a major mediator in the pathophysiology of AGA. While DHT is recognized as the primary androgen implicated in the pathophysiology of AGA, administering testosterone subcutaneously offers several advantages in modeling the disease in mice. Testosterone serves as a precursor to DHT and is converted *in vivo* by the enzyme 5α-reductase, which is present in the skin and hair follicles. This conversion allows for a more physiological simulation of androgen activity, as it mirrors the endogenous hormonal processes occurring in humans [21].

Animal termination

Termination of mice was performed on day 11 after induction of the AGA model and skin biopsy. The termination process in mice is done physically by neck dislocation after the mice are anesthetized with chloroform. The dislocation process begins by holding the tail of the mice and placing it on a surface that can be reached to stretch the bodies. The body of the mice is then held at the nape of the neck using the left hand, while the tail is pulled firmly using the right hand to conduct neck dislocation and end the life of the mice. Afterwards, the mice are put into a plastic bag and then decomposed.

Dermal thickness and hair follicle density measurement

Two parameters were assessed to develop the AGA model in this study, dermal thickness (DT) and hair follicle density (HFD) from the terminated mice. DT was assessed using histopathological examination of skin biopsy samples from the back of mice obtained on day 11 after induction. Skin samples were then stained with hematoxylin-eosin (H and E). Dermis thickness was measured µm. Meanwhile, HFD was assessed by histopathological examination of skin samples with H and E and Masson's trichrome staining. Skin samples were then observed with an inverted microscope. HFD was assessed by counting the number of hair follicles per mm^2 (fig. 1).

Statistical analysis

Statistical analysis in this study used IBM SPSS version 20. Data are presented as mean. To analyze DT and HFD difference between group, we used one-way ANOVA test and Turkey's post-hoc test. We also conducted an eta square test to determine the effect size. P-value of less than 0.05 was considered statistically significant.

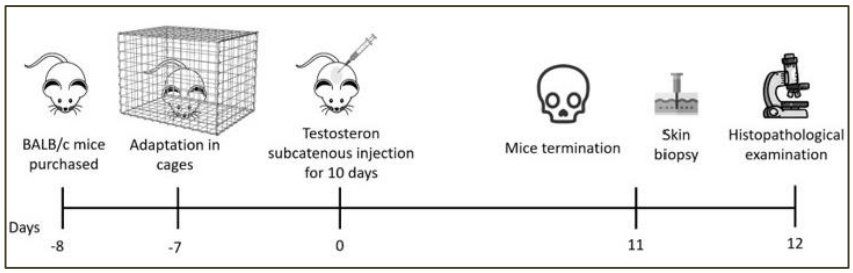

Fig. 1: Illustration of the testosterone-induced AGA mice model

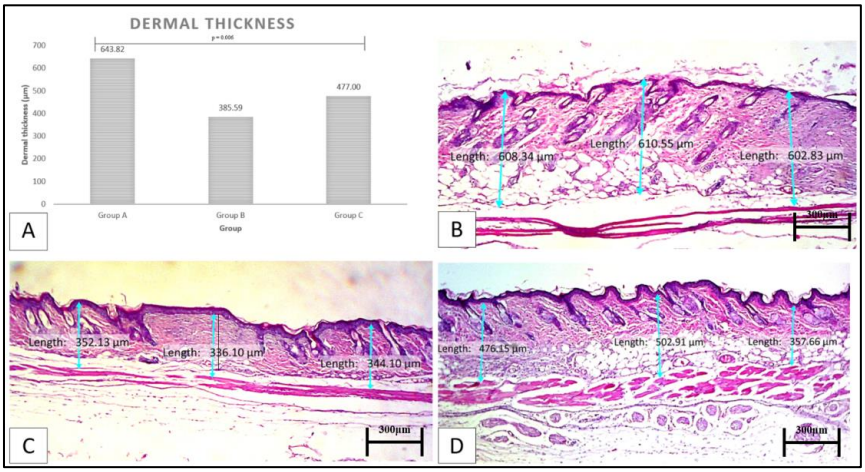

Fig. 2: Dermal thickness measurement. (A) Dermal thickness statistical analysis of all group. (B) Dermal thickness histopathological picture of group A (C) group B and (D) group C

RESULTS AND DISCUSSION

This study focuses on the development of AGA mice model, especially the optimal dose of testosterone to induce AGA model. To assess the optimal dose, two parameters, DT and HFD, were compared. DT from the group B showed the smallest result, followed by the group C and A. The data analysis showed that there were significant differences of DT between all the group with large effect size ($p = 0.006$; $\eta^2 = 0.676$). Turkey's post-hoc tests showed that DT in group B was significantly smaller than group A ($p = 0.012$) and group C ($p = 0.043$). Group A was also found to have a significantly smaller DT than group C ($p = 0.022$). This result indicated that the testosterone subcutaneous injection produced significant and smallest DT at doses 0.075 ml compared at dose 0.05 ml and 0.1 ml. The analysis of DT showed in fig. 2.

The next parameter in this study in HFD by measured the number of hair follicle per mm^2. The HFD between group showed the lowest result from group B, followed by the group C and A. The data analysis showed significant differences and large effect size in HFD between all groups ($p = 0.001$; $\eta^2 = 0.986$; CI 95%). Turkey's post-hoc tests showed that HFD in group B was significantly lower than group A ($p = 0.001$) and group C ($p = 0.035$). Group A was also found to have a significantly lower HFD than group C ($p = 0.001$). This result indicated that the testosterone subcutaneous injection produced significant and lowest HFD at doses 0.075 ml compared at dose 0.05 ml and 0.1 ml. The analysis of HFD showed in fig. 3.

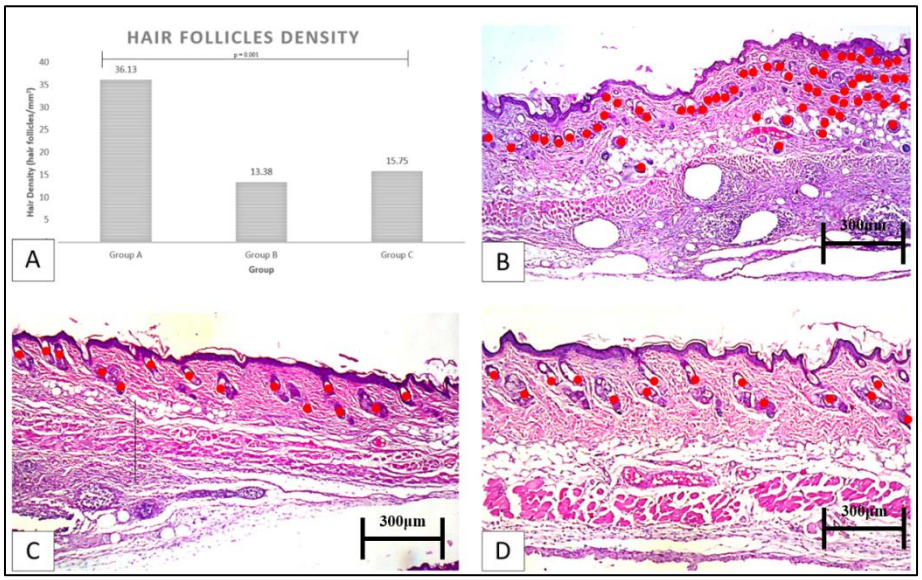

Fig. 3: Hair follicle density. (A) Hair follicle density statistical analysis of all group. (B) Hair follicle density histopathological picture of group A (C) group B and (D) group C. Red dots = Hair follicles

DISCUSSION

This study attempts to develop AGA mice model through testosterone induction to facilitate future research related to AGA in animals. The results showed that testosterone at a dose of 0.075 ml for 10 d given by subcutaneous injection was the best dose to induce an AGA model characterized by thin DT and low DHT. This provides a condition similar to the human scalp, which may provide insight into the real condition of AGA patients. In this preliminary model, DT and HFD were used as primary histological endpoints to assess androgenic effects on the skin and follicular architecture. While more detailed parameters such as follicular miniaturization, anagen/telogen ratio, or immunohistochemical would strengthen mechanistic insight, our aim was to first establish a simplified yet reliable AGA model. The result of this study is in line with a study by Soga *et al.* in Japan who found that patients with AGA had a lower HFD than healthy person [22]. Another study by Li *et al.* in China reported that AGA patients had thinner dermis and subcutaneous layers of skin compared to healthy person [23]. DHT can inhibit the WNT/β-catenin signaling pathway, which results in disruption of skin homeostasis and proliferation. Disruption of the hair cycle also leads to miniaturization of hair follicles, which results in decreased HFD. Another study by Fu *et al.* in China reported on AGA model mice in C57BL6 mice induced by DHT. In these AGA model mice, DHT administration caused a decrease in HFD, miniaturization of hair follicles, and premature regression of hair [24].

AGA is a disease characterized by progressive hair loss and is one of the most common causes of hair loss worldwide [25]. The prevalence of AGA starts to increase significantly at age 30 and peaks at age 80 [3]. The underlying pathology of AGA is the disruption of the hair growth cycle, particularly in the anagen phase [26]. The human hair cycle is a complex and dynamic process consisting of three distinct phases: anagen, catagen, and telogen [27]. During the anagen phase, the hair follicle is actively growing, and the hair shaft is extending outward. This phase can last anywhere from 2 to 6 years [28]. The catagen phase is a period of controlled regression, where the hair follicle shrinks and prepares for the telogen phase [29]. The telogen phase is the resting state, where the hair follicle is dormant, and the hair shaft is eventually shed [30]. In AGA, the anagen phase is shortened and the telogen phase is prolonged, resulting in incomplete growth and involution of hair follicles [26, 31]. This disruption in the hair growth cycle is thought to be the result of an excessive response of the androgen receptor to testosterone, which is converted to DHT. In addition to the excessive androgen receptor response, AGA patients also have higher levels of DHT. DHT will bind strongly to the androgen receptor and cause transcription, resulting in disruption of the hair growth cycle. This higher levels of DHT and excessive androgen receptor response is strongly linked to genetic factors [5, 32]. Therefore, DHT is thought to play a vital role in the development of AGA.

There was a unique finding in the results of this study, where the 0.075 ml dose of Sustanon® was better than the 0.1 ml dose in inducing the AGA model. There are several factors that we suspect may contribute to this. First, regarding the negative feedback effect. When the level of testosterone contained in Sustanon® reaches a concentration that is too high, this will trigger negative feedback on the pituitary gland and hypothalamus to reduce the production of GnRH and LH, resulting in a decrease in testosterone levels [33]. Secondly, it is related to the oversaturation of androgen receptors on

dermal papilla cells. To cause hair loss, testosterone needs to bind to androgen receptors [12]. The number of androgen receptors is limited, so if testosterone levels are too high, there are no more receptors for androgen to bind to. Meanwhile, testosterone levels that are too high also reduce the expression of androgen receptors [34]. Third, high testosterone levels can lead to the conversion of testosterone to estradiol through the enzyme aromatase [35]. Estradiol has a protective effect on hair follicles [36]. As such, this can then lead to weaker hair loss effects despite higher concentration of testosterone.

CONCLUSION

The results of this study showed that administration of 0.075 ml testosterone by subcutaneous injection can produce mice with good AGA model. This is indicated by a thin dermis and low HFD. There were several limitations in this study. First, there were lack parameter for AGA such as anagen-telogen ratio, hair follicle length, hair shaft width, β-catenin levels and androgen receptor expressions. Therefore, we suggest for the further research to add more parameters such as stated before. Secondly, the assessment of DT and HFD parameters was only done once at the end of the study. In the future, we suggest to conducting multiple assessments and longitudinal studies so the exact time the process of changes in the skin and hair follicles occurs can be known.

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Nil

AUTHORS CONTRIBUTIONS

Arie Kusumawardani contributed to the study conceptualization and the study methodology. Nurrachmat Mulianto contributed to the original draft-making and conceptualization. Adniana Nareswari contributed to supervision and manuscript review. Pristia Widya Monica contributed to supervision and manuscript editing. Trya Oktaviani contributed to data analysis and original draft-making.

CONFLICT OF INTERESTS

We declare there are no conflict of interest in this study.

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