Comorbidities in Androgenetic Alopecia: A Comprehensive Review

Shuang Chen · Xiaohang Xie · Guoqiong Zhang · Yong Zhang

ABSTRACT

Androgenetic alopecia is the most common form of hair loss, affecting 85% of men and 40% of women. Androgenetic alopecia is a disease caused by multiple factors, such as genetics, hormones, and systemic diseases; however, the exact cause remains undetermined. Recent studies have found that it is associated with a high incidence of endocrine diseases and other comorbidities. It may not only be a skin disease but also an early signal of underlying systemic diseases. Effective management requires timely diagnosis and treatment initiation. However, in current clinical practice, androgenetic alopecia is still not fully understood or treated. Recognizing the true physical, social, and emotional burden of androgenic alopecia, as well as its associated comorbidities, is the first step in improving the prognosis of affected patients. This review aimed to gather the known pathological factors and provide a reference for clinical physicians to understand androgenetic alopecia and its comorbidities in depth, thereby enabling early recognition of the underlying systemic diseases and providing timely treatment.

Keywords: Androgenetic alopecia; Comorbidities; Systemic diseases

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Key Summary Points

Androgenetic alopecia is a multifactorial disease that seriously affects people’s work, love, and interpersonal relationships. At present, its specific pathogenesis is still elusive, and the existing treatment cannot give satisfactory results to patients.

We reviewed recent studies on the systemic diseases associated with androgenetic alopecia.

It is hoped that our research will lead to a better understanding that this disease is not a simple skin disease, as well as early diagnosis and treatment of other diseases to improve patient outcomes.
INTRODUCTION

In modern society, hair is an important part of one’s self-image. Therefore, hair loss brings many troubles to people, such as impaired image, impacted self-confidence, failure of a marriage, and love, and may impact people’s health. Studies have shown that hair loss can cause various psychological difficulties, such as anxiety, depression, and trauma, and further impair quality of life (QoL) [1–3]. Androgenetic alopecia (AGA), commonly known as male or female pattern baldness, is the most common progressive hair loss disorder [4]. Although studies have reported that androgens and their receptors, gene expression patterns, inflammation mediators, signaling pathways, and disorders might be related to the occurrence of AGA, the etiology and pathogenesis of AGA still require further investigation [5–7], which might provide novel targets for prevention and therapy. Dihydrotestosterone (DHT), a metabolite of testosterone, is regularly considered one of the key mediators of AGA. It acts on androgen receptors in hair follicles, thereby shortening the anagen (growth) phase and prolonging the telogen (resting) phase of hair growth, resulting in an increase in immature hair and a decrease in new hair [4, 8–10]. The current treatment plan for AGA mainly includes oral finasteride, topical external use of minoxidil, low-intensity laser, hair transplantation, etc. Finasteride is a 5α-reductase inhibitor that has a significant effect on the treatment of AGA; however, it can also exhibit unacceptable side effects in a small subset of patients. Occasionally, side effects persist even after treatment cessation in the form of the post-finasteride syndrome [11]. Minoxidil effectively inhibits the hair loss process; however, once the drug is discontinued, hair from minoxidil-mediated hair growth begins to fall out. Therefore, patients must use it indefinitely and persistently to maintain efficacy [12]. Additionally, minoxidil can cause undesirable adverse effects. Currently, low-intensity laser therapy has shown promising results in the treatment of AGA; however, the effectiveness of its treatment remains controversial [5].

ENDOCRINE DISEASE

The growth, circulation, and density of hair are mainly regulated by circulating hormones. Thus, endocrine system diseases are often accompanied by hair loss [21]. Hyperandrogenemia (HA) refers to a condition in which the ovaries and adrenal cortex secrete excessive testosterone. One of the common androgenic skin changes is androgenic alopecia [22]. The earliest suspected relationship between HA and AGA can be traced back to the Renaissance period and the 18th century [23]. A study reviewed other skin manifestations in women with high androgen levels and found that AGA is a common clinical manifestation but cannot be used as a useful clinical marker [24]. In a report of a 63-year-old woman with hirsutism...
and alopecia, her experimental data emphasized an increase in androgen levels [25]. For post-menopausal women with hirsutism and AGA, to achieve a better therapeutic effect, we must find the cause of elevated androgen levels, such as the source of a tumor [26, 27]. Nevertheless, most studies have shown that AGA is not yet a sign of HA [24, 27–29]. Many studies have discussed female androgen excess, but recently, a cross-sectional study of male HA has been conducted. A study of 100 men with elevated androgen levels found that patients with

| Symptom no. | Comorbidities | Symptoms | References |
|-------------|--------------|----------|------------|
| 1           | Hyperandrogenemia | An increase in androgen levels, hirsutism, alopecia | [21–25] |
| 2           | Polycystic ovary syndrome, obesity, and so on | Alopecia, acne, infertility | [27–31, 34, 35] |
| 3           | Insulin resistance | Acanthosis nigricans, polycystic ovary syndrome, type 2 diabetes | [36–38] |
| 4           | Hypothyroidism | High thyroid-stimulating hormone, alopecia | [42–44] |
| 5           | Prostate cancer | Hyperandrogenemia, alopecia | [45, 46] |
| 6           | Testicular germ cell tumors | Androgenic alopecia, especially frontal baldness | [45] |
| 7           | Androgen-secreting tumors | Hirsutism, alopecia, hirsutism | [48, 50] |
| 8           | Thyroid cancer | Androgenic alopecia | [49] |
| 9           | Metabolic syndrome | Abdominal obesity, hypertension, high-density lipoprotein, and androgenic alopecia | [52–57] |
| 10          | Atherosclerosis | Androgenic alopecia | [61–63] |
| 11          | Hypertension | Hyperaldosteronism, alopecia | [65–67] |
| 12          | Psychological disorders | Depression, anxiety, obsessive–compulsive disorder, and loss of confidence | [69–72] |
| 13          | Urinary calculi | Total alopecia, pattern alopecia | [76] |
| 14          | Benign prostatic hyperplasia | A larger prostate | [74, 75, 77] |
| 15          | Nutritional deficiencies | The levels of hair and serum zinc and copper in patients with AA and AGA were significantly lower. the lack of amino acids | [76, 81–84] |
| 16          | Seborrheic dermatitis | Androgenic alopecia | [85] |
| 17          | Acne vulgaris | Androgenic alopecia | [104, 105] |
| 18          | Myotonic dystrophy type 1 | Alopecia, myotonia, myasthenia | [106, 107] |
| 19          | Autoimmune diseases | Early onset androgenic alopecia | [108, 109] |
elevated DHT levels had a higher frequency of hair loss [30]. These studies continue to prove that patients with HA are more prone to AGA. However, the existing evidence generally shows that the androgen level in the blood circulation of patients with AGA is maintained at a normal level. The association between HA and AGA may not be attributable to increased levels of androgens in the blood. Apart from androgens, what else exists between them?

HA does not appear alone and is often one of the manifestations of other diseases. It mainly originates from ovarian and adrenal diseases and other rare causes, such as local androgen abnormalities in target organs, drugs using exogenous androgens, and hyperprolactinemia. We speculated that AGA and HA may be common manifestations of ovarian and adrenal diseases. HA occurs most often in patients with polycystic ovary syndrome (PCOS). In a prospective study of patients with PCOS, the prevalence of AGA was 30% [31]. However, this study involved 20 patients with PCOS. In an Anahita Jalilian meta-analysis of Iranian women with PCOS and its comorbidities, the prevalence of AGA was estimated to be 9% [32]. In the Molly Quinn study, 56 PCOS patients had AGA (22.0%) [29]. The difference in prevalence might be attributed to different population groups, as well as different screening methods used to diagnose PCOS. Feng et al. also agreed that AGA was a common dermatological manifestation in women with PCOS and those without. There were no significant differences in the age of patients with PCOS between the AGA and non-AGA groups (P = 0.453) [28]. Based on the autosomal genetic transmission of PCOS and symptoms of PCOS in men of families where women are often affected by PCOS, researchers have proposed the existence of a male equivalent of PCOS [33, 34]. A cross-sectional study in Taiwan, China, showed that overweight women with PCOS are at a significantly higher risk of female pattern hair loss (FPHL). This study also showed that there may be ethnic differences in the susceptibility of patients with PCOS to the development of FPHL [35]. However, Molly Quinn’s study concluded that there was no significant difference in the incidence of AGA between White participants and non-White participants (21.8 vs. 21.1%; P = 0.91) [29]. In contrast, Timothy and Schmidt had different results. Their cross-sectional study aimed to determine the skin and body characteristics of patients with PCOS to help diagnose PCOS. They found that women who met the PCOS criteria had an increased prevalence of AGA than those who did not, but this difference was not statistically significant (22.4% [53 of 237] vs. 11.4% [5 of 44], P = 0.10) [36]. In general, patients with PCOS are more likely to develop AGA. However, there is still insufficient evidence to explain this. We believe that, to some extent, this is related to heredity, weight, and gender. To the best of our knowledge, no study has found an association between adrenal gland disease and AGA.

AGA, acanthosis nigricans, and PCOS are recognized as early clinical manifestations of insulin resistance, and these manifestations represent the risk of further developing type 2 diabetes [37]. A study directly elucidated that diabetes was significantly associated with FPHL frontal alopecia (P = 0.023) [38]. Insulin resistance might induce a hormonal imbalance in circulating androgens, which may explain the relationship between diabetes and AGA [39]. A prospective study in Taiwan concluded that moderate-to-severe AGA was an independent predictor of diabetes [40]. However, another study did not show any significant association between type 2 diabetes and AGA [41]. It is well known that the main bridge between AGA and diabetes is insulin resistance. Insulin resistance plays an important role in diabetes onset.

Baseline and stimulated thyroid-stimulating hormone levels were significantly increased in patients with AGA following thyrotropin-releasing hormone (TRH) stimulation [42]. According to the results of a study of 65 men with AGA (average age, 24 years) and 46 women with AGA, AGA in women was associated with hypothyroidism [43]. A retrospective study by Tee Wei Siah found that 12% (aged 24–73 years) of 210 patients with FPHL had a long-term history of hypothyroidism [44]. Babaei et al. suggested that if hair loss occurs early, there may be concomitant diseases such as hypothyroidism [45]. Patients with AGA may be accompanied by hypothyroidism.
Unfortunately, there is insufficient evidence and low quality; however, this possibility must be considered.

**CANCER**

Recently, some scholars have proposed that AGA is also related to cancer, but the results of these studies are controversial [46–51]. A meta-analysis assessed the relationship between cancer incidence or cancer-specific mortality and AGA categories using retention odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI). A significant increase in risk was observed in relation to high-grade prostate cancer (PC) (OR 1.42; 95% CI 1.02–1.99), and vertex with/without frontal baldness was associated with PC risk. Nevertheless, using AGA as a phenotypic marker for PC risk was poorly supported [46]. Rokni et al. also showed that there is a significant relationship between PC and AGA. However, the association between these two diseases may be due to androgens [47]. Prostate-specific antigen (PSA) is a biomarker for PC. It has been approved by the US Food and Drug Administration as an aid for the early detection of PC [52]. In a case and control study involving 100 AGA cases (20–50 years), MetS were observed in 53% of cases and 17% of controls (P = 0.001) [54]. Gopinath and Upadya conducted a hospital-based, analytical, cross-sectional study of 85 men with early onset AGA. The results showed that the MetS was observed in 19 (22.4%) patients with AGA and eight (9.4%) control groups (P = 0.021). Compared to the patients in the control group, those with AGA had significantly higher reductions in abdominal obesity, hypertension, and high-density lipoprotein. However, the subgroup of the study only had a small sample size and lacked evidence of a temporal relationship between MetS and AGA [55]. Another study showed that there were 37 (64.9%) and 29 (53.7%) patients with AGA in the case and control groups, respectively, and the difference was statistically significant (P < 0.0001) [56]. Only approximately 10% of the patients had MetS, although the difference was not statistically significant (P = 0.092). Compared with control group patients, those with AGA had significantly higher reductions in abdominal obesity, hypertension, and high-density lipoprotein levels [57]. A study by Ola Ahmed Bakry stated that MetS is more common in patients with AGA with severity of 12/40 (30%) than in 2/60 (3.3%) patients with mild-to-moderate severity. However, compared to patients with extremely severe AGA, those with mild to moderately severe AGA had a lesser tendency to develop metabolic conditions [58].

**METABOLIC DISEASE**

Metabolic syndrome (MetS) refers to the pathological state in which the body’s proteins, fats, carbohydrates, and other substances are metabolically disordered. It is a complex metabolic syndrome and a risk factor for diabetic cardiovascular and cerebrovascular diseases. Over the past two decades, the relationship between AGA and MetS has been proven [53].
Most studies have unanimously concluded that there is some evidence linking AGA to MetS. However, there are insufficient studies on the correlation between AGA severity and MetS.

CARDIOVASCULAR DISEASES

Cardiovascular diseases are a major cause of morbidity and mortality worldwide [59]. Several studies have reported an association between AGA and cardiovascular risk [60]. Amamoto Misato et al. screened a total of nine studies (eight on AGA, one alopecia areata: 44,806 participants) in the Medline and Embase databases for a meta-analysis and found that compared to men without baldness, those with AGA had an increased risk of heart disease, and younger men (< 55 years or ≤ 60 years) showed a stronger correlation [61]. Salvador Arias-Santiago confirmed the association between early onset AGA and a higher cardiovascular risk in men and women groups. They found that the prevalence of carotid atherosclerosis (atherosclerotic plaque) in patients with AGA was higher than that in the control group. Moreover, the prevalence of family history of cardiovascular disease in the men and women AGA groups was significantly higher than that in the control group [62]. Wang Ya-Xin’s research further found that AGA status (OR 2.247; 95% CI 1.396–3.617, \( P = 0.001 \)), severe AGA (OR 2.360; 95% CI 1.506–3.699, \( P < 0.001 \)), and early onset AGA (OR 3.54%; 95% CI 2.069–5.832, \( P < 0.001 \)) were independently correlated with the severity of coronary atherosclerosis [63]. A meta-analysis revealed that the serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels in the AGA group were significantly higher than those in the control group, and the standardized mean differences were 0.377 (95% CI 0.182–0.572, \( P < 0.001 \)), 0.426 (95% CI 0.164–0.688, \( P = 0.001 \)), and 0.450 (95% CI 0.171–0.728, \( P = 0.002 \)), respectively [64], which further confirmed the results of previous studies. In a prospective case–control study in India, there were 468 confirmed cases of coronary artery disease (CAD) and 912 age-matched healthy men. The results showed that the prevalence of AGA (49.1 vs. 27.4%) was higher in the CAD group than in the control group. Multiple logistic regression analysis indicated that AGA [5.619, 95% CI 4.025–7.845, \( P < 0.0001 \)] was the strongest predictor of CAD in young Asian men. This may indicate that AGA can be effectively used for the early prediction of CAD [65]. Several studies have investigated the association between AGA and hypertension. In addition, Serge Ahouansou claimed that hypertension and AGA are strongly related and that this association was independent of age [66]. In a case–control study, the aldosterone level and blood pressure of patients with AGA were significantly higher than those of the control group (\( P < 0.05 \)) [67]. Women with early onset AGA have high systolic blood pressure, diastolic blood pressure, and aldosterone levels [68]. Unfortunately, Danesh-Shakiba et al. did not find a significant association between certain cardiovascular risk factors (e.g., hypertension and smoking) and AGA. Although patients with severe AGA have significantly higher systolic and diastolic blood pressures, their average age is also significantly higher [69]. Elevated aldosterone levels are considered the cause of AGA and high blood pressure. Existing evidence indicates that AGA is independently related to cardiovascular disease and may be an indicator for early prediction of cardiovascular disease in the future.

MENTAL ILLNESSES

Hair loss and subsequent beauty problems can adversely affect mental health. AGA is increasingly associated with social isolation, which leads to depression, anxiety, and loss of confidence [70–73]. Therefore, mental health problems are more common in patients with AGA than in healthy individuals. However, no systematic evaluation has been performed of the association between AGA and mental illness. Wang Xia et al. evaluated the psychological use of the SCL-90-R scale for AGA in 355 Chinese college students. There were significant differences in obsessive–compulsive disorder, depression, and phobic anxiety between college students with AGA and the control group [70].
A meta-analysis of the association between AGA and health-related quality of life (HRQOL) and mental illness (41 studies involving 7995 patients) found that AGA was significantly related to HRQOL and moderate emotional impairment, but not depressive symptoms. This meta-analysis also found that physician-rated hair loss severity is unrelated to HRQOL in AGA [71]. Tas Betul et al. evaluated self-awareness, self-esteem, sexual experience, and anxiety in 353 patients with AGA aged 15–63 years (men: 283 cases, women: 70 cases). They found that women had more serious psychological disorders than men [72]. Tabolli Stefano et al. also confirmed the high prevalence of depression/anxiety in patients with AGA, and the prevalence in women with AGA was significantly higher than that in men [73]. Except for depression and anxiety, the prevalence of AGA in patients with schizophrenia was significantly higher than in those without schizophrenia [74]. Because the hair loss assessment instrument and classification of severity in each evaluation tool varied among the included studies, which may have caused inconsistencies in the results of the above studies, the potential mechanism is worth investigating.

**URINARY SYSTEM DISEASES**

AGA, benign prostatic hyperplasia (BPH), and PC are androgen-dependent diseases. AGA and BPH have good therapeutic responses to finasteride [75, 76]. Therefore, we aimed to investigate the relationship between AGA and urinary system disease more closely. Interestingly, in a retrospective survey, the age, body mass index, hypertension, diabetes, baldness patterns, and serum T levels of 200 patients were collected from urinary calculi. They found that compared with patients without hair loss, the risk of urolithiasis increased by 1.3-fold in patients with vertex pattern alopecia, whereas the risk of total alopecia increased by 2.1-fold [77]. WenChieh Chen et al. showed that a larger prostate was associated with a higher prevalence of AGA, but not with its severity [75]. Naglaa F Agamia also conducted related studies (including 300 patients diagnosed with AGA and 100 controls). They found that there was a significant increase in patients with AGA meeting the diagnostic criteria for BPH (36 vs. 6.8%) than those of the control group. BPH is an important pathogenic factor associated with AGA [78]. In contrast to the above studies, the other two studies did not find any correlation between AGA and prostate volume [79, 80]. Therefore, the correlation between BPH and AGA still requires high-quality research.

**NUTRITIONAL STATES**

Evidently, nutritional deficiencies are a common cause of AGA. Ching-Huang Lai et al. investigated the concentration of heavy metals in patients with AGA, and the results showed that the concentrations of blood lead, copper, cadmium, and zinc were lower in individuals with moderate-to-severe AGA, while urine levels of lead, cadmium, and zinc in patients with AGA were higher than those in the controls. This study found for the first time that there was a significant correlation between blood vanadium concentration and the prevention of moderate-to-severe AGA [81]. Amirmia Mehdi et al. assessed the zinc and copper content in the hair of patients with AGA and alopecia areata (AA) (27 patients with AGA and 27 patients with AA; the control group comprised 27 age- and sex-matched healthy control participants). The results showed that the average hair zinc levels of patients with AA, AGA, and the control group were 98.33, 105.35, and 129.52 μg/dl, respectively, which correlated with the previous study. The average levels of copper in the hair of participants in the study and control groups were 7.91, 7.25, and 10.34, respectively. The levels of hair and serum zinc and copper in patients with AA and AGA were significantly lower than those in the control group (P < 0.05) [82]. Dinesh Gowda proposed that hair loss is not only related to the lack of trace elements but also the lack of amino acids. His results showed that histidine deficiency was observed in > 90% of AGA, leucine deficiency in 100% of participants with FPHL, alanine deficiency in 91.67% of FPHL and 91.18% of male pattern hair loss (MPHL), cysteine...
deficiency in 55.58% of participants with MPHL, zinc deficiency in 11.76% of participants with MPHL, copper deficiency in 29.41% of MPHL participants, and low transferrin saturation and ferritin levels in patients with FPHL [83]. Kondrakhina and Irina used direct colorimetry or atomic absorption spectroscopy to estimate the plasma element content (magnesium, calcium, zinc, copper, selenium, iron) and vitamin status (B12, D, E, and folic acid) in patients with AGA. The data revealed that compared with healthy controls, patients with AGA had a 21.4% reduction in zinc content (\(P = 0.003\)), 42.1% reduction in copper (\(P < 0.001\)), 10% reduction in magnesium (\(P = 0.005\)), and 30% reduction in selenium (\(P = 0.002\)), vitamin B12 decreased by 15.5% (\(P = 0.012\)), while vitamin D increased by 53.3% (\(P < 0.001\)). However, none of these micronutrients are related to the severity of hair loss. In contrast to previous studies, another study did not find any iron or ferritin deficiency in patients with AGA [84]. The analysis of single-nucleotide polymorphism profiles found that compared with healthy controls, patients with AGA had elevated levels of dihydrotestosterone, 17-OH-progesterone, insulin, magnesium, copper, zinc, selenium, vitamins D and E, and folic acid [85]. Another study also found that testosterone deficiency was more frequent in patients with urinary stone disease and severe AGA (\(P = 0.041\), OR 2.38) [77]. These studies showed that nutritional deficiency or sufficiency are associated with AGA, which may provide a novel avenue for the treatment of AGA with drugs. In addition to medication, monitoring micronutrient levels before treatment may also be a necessary step.

**GENETIC POLYMORPHISM**

Genetic polymorphism, cigarette smoking, drinking, eating habits, sleep, infection with SARS-CoV-2 (COVID-19), infection, Cancer and metabolic diseases are high risk factors for AGA (Table 2). Genetic polymorphism has become a research hotspot in AGA. Currently, researchers have identified androgen receptor (AR), 7p21, 20P11, and 2Q35 susceptibility genes on the X chromosome and other susceptibility genes that contribute to the development of male androgenetic alopecia (MAGA). The concomitant familial cases of FPHL and MAGA suggest that FPHL and MAGA share a common genetic background [86], but these study samples were mostly European populations. Myung Hwa Kim et al. further justified genetic susceptibility genes of AGA high-risk individuals in Asian populations [87].

**HUMAN BEHAVIORS**

The role of cigarette smoking in hair loss has become a topic of great interest to scientists. Studies have found that smoking affects female pattern baldness by causing women to have relatively low estrogen levels through aromatase inhibition and hydroxylation of estradiol. Most studies have found a positive association between cigarette smoking and hair loss, especially in AGA. However, a case–control study found that smokers were less likely to develop AGA than non-smokers. This provides an alternative explanation for the link between previous smoking and hair loss: an increased risk of smoking due to AGA [57, 88–90]. A cross-

| Risk factors                        | Population       | References |
|------------------------------------|------------------|------------|
| Genetic polymorphism               | Familial cases   | [86, 87]   |
| Cigarette smoking                  | Female cases     | [91]       |
| Quality of life                     | Female cases     | [3, 92]    |
| Sleep disturbances                 | Male and female  | [93, 94]   |
| Alcohol intake                      | Male and female  | [95]       |
| Meat consumption and insufficient  | Male cases       | [96]       |
| fruits and vegetables              |                  |

| Risk factors                        | Population       | References |
|------------------------------------|------------------|------------|
| Genetic polymorphism               | Familial cases   | [86, 87]   |
| Cigarette smoking                  | Female cases     | [91]       |
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| Alcohol intake                      | Male and female  | [95]       |
| Meat consumption and insufficient  | Male cases       | [96]       |
| fruits and vegetables              |                  |

Table 2 Genetic polymorphism and human behaviors of androgenic alopecia

△ Adis
sectional study evaluating the effect of cigarette smoking on early onset AGA found that the prevalence of AGA was statistically higher in smokers than in non-smokers, but there was no significant association between hair loss severity and smoking intensity [91].

Quality of life also has an important impact on hair loss. A cross-sectional study identified that stressful environments related to urban living standards and anxiety about hair loss are key triggers for AGA progression [3]. A study by Atallah et al. reported that the prevalence of female pattern baldness in urban areas was significantly lower than in rural areas, and there was no significant correlation with parental education and family income [92]. Liamsombut Somprasong et al. found an increased risk of sleep disturbances in AGA patients [93]. Another study also found a significant association between sleep disturbances (going to bed late or having poor sleep quality) and increased AGA severity [94].

People’s dietary habits also affect AGA. Yanhua Yi et al. found that alcohol intake increased the severity of female pattern baldness [95]. Agaoglu et al. believe that red meat consumption and insufficient intake of fruits and vegetables are risk factors for early onset AGA in young men [96].

COVID-19

Androgen signaling plays a central role in AGA etiology and has been shown to be associated with severe COVID-19 symptoms in men. There is a biological link between these traits [98]. In Dunja Veskovic’s observational study, AGA severity was associated with poor prognosis of COVID-19 [99]. Wambier et al. noted that COVID-19-positive patients have a higher prevalence of AGA compared with the general population of the same age [100]. Meta-analysis by Betty Nguyen suggested that AGA may be a risk factor for severe COVID-19 [101]. Among hospitalized patients with COVID-19, males have a significantly higher incidence and severity of AGA than females, and have a worse prognosis. The study also found a significant association between the severity of AGA and adverse outcomes in men compared with women [102]. In contrast, Moein Baghani et al. found that the severity of COVID-19 in hospitalized patients was not associated with the severity of AGA [97].

OTHER ILLNESSES

In addition to the role of androgens in AGA development, scalp inflammation can exacerbate AGA development. Bhoyrul Bevin confirmed that AGA was accompanied by seborrheic dermatitis (SD) using microscopic examination of hair [103]. Sevil Alan examined the clinical and laboratory signs of 141 women with acne vulgaris and 73 healthy women and found that the incidence of AGA and HA in the acne group was significantly higher than that in the control group [104]. Another case–control study also found that the prevalence of AGA was significantly higher in the acne group than in the control group. This study did not find an association between serum androgen levels and acne [105]. These studies suggest that acne and AGA may be independently related, and it was not previously thought that hyperandrogenism plays a role in it. However, current research on this topic is still limited. Myotonic dystrophy type 1 (DM1) is an autosomal dominant genetic disease that causes multiple system involvement [106]. Early AGA (P = 0.01) was more common in patients with DM1 than in controls and was higher in men (P < 0.0001) [107]. Colombia surveyed 330 students and found that 84% of them with autoimmune diseases had alopecia [108]. Another study of 67 young men with autoimmune thyroiditis found that 37% of them had early onset AGA [109]. These studies have indicated that AGA is a complication of most diseases.

CONCLUSIONS

This review summarizes the pathological factors of AGA, including endocrine disease, cancer, mental disease, metabolic disease, cardiovascular diseases, urinary system diseases, nutritional states, genetic polymorphism, social and daily
behaviors and infection with COVID-19, indicating that AGA may be a complication and manifestation of underlying systemic diseases. Clear causes of AGA may be important for obtaining the correct treatment. For secondary AGA, it is critical to treat the primary disease, which is important to improve AGA. However, the relationship between AGA and other diseases remains unclear. Therefore, uncovering the potential mechanisms would provide a new therapeutic target for AGA. In summary, dermatologists and patients need to increase the potential risk of AGA-related comorbidities. This may play an important role in the occurrence and development of AGA. Similarly, AGA may also be one of the manifestations of underlying systemic diseases.

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**Compliance with ethics guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Data availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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