Evaluation of oxidative stress markers in Androgenetic Alopecia Patients: A Comprehensive Review

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Abstract

Background: Men and women can both experience the common type of hair loss known as androgenetic alopecia (AGA). Hair follicle miniaturisation is affected by a complicated interplay of inflammatory agents, hormones, and genetic predisposition. Advanced Glycation End Products (AGEs) and their receptors (RAGE) have been identified as putative participants in the pathophysiology of AGA, connecting inflammation and oxidative stress to changes in hair follicles. **Objective:** The purpose of this review is to investigate the relationship between AGA pathogenesis, RAGE production, and serum levels of AGEs. It explores the potential applications of AGEs and RAGE as diagnostic indicators or therapeutic targets, clarifying the molecular pathways by which they may affect follicular miniaturisation and hair loss. **Conclusions:** The pathogenesis of AGA is intricately linked to AGEs and RAGE, which may exacerbate oxidative stress and inflammation in the microenvironment of the hair follicle.

Keywords: Androgenetic Alopecia, Advanced Glycation End Products, Inflammation, Oxidative Stress; Hair Loss.

1. Introduction

Androgenetic Alopecia (AGA) is defined by non-scarring progressive hair follicle miniaturisation in susceptible men and women in a pattern distribution. It is among the most typical reasons for a hair consultation. According to epidemiologic data, AGA prevalence rises with age, affecting 80 percent of Caucasian males and 40 to 50 percent of Caucasian women at some point in their lives [1].

It's known that AGA is caused by a combination of hormonal (androgens) and hereditary factors. In affected areas, the genetic targeting of the hair follicles for androgen activation results in the shrinkage of the hair follicles and pigmented, large hairs (terminal hairs) replacement with thinner, depigmented, shorter hairs (vellus hairs) [2].

The pathophysiology of AGA is also influenced by environmental variables, such as smoking, UV radiation, metabolic syndrome, and dietary effects [3].

Even though AGA is classified as a non-inflammatory illness clinically, histological examinations revealed perifollicular inflammation in hair follicles' upper third, demonstrating that inflammation has a pathogenic function in the condition [4].

Because inflammation and oxidative stress are strongly associated in biological systems, oxidative stress has also been shown to be seen in androgenetic alopecia patients' dermal papilla cells [5].

One of the main indicators of aging is persistent low-grade inflammation, which is also essential for the emergence of age-related diseases [6].

AGEs are chemicals that are extremely reactive and oxidant. The majority of AGEs are created by non-enzymatic glycation as well as oxidation. There are several lipids, amino acids, and saccharides that can be converted into these glycoxidation products [7].

Receptors that are triggered by Advanced Glycation End Products (RAGE) are seen on keratinocytes, immunological cells, and endothelial cells. The reaction between RAGE and its ligands stimulates reactive oxygen species formation, boosts metalloproteinase activity, stimulates immune cells, and encourages gene transcription that codes for proinflammatory cytokines. In this degenerative cycle, the inflammatory reaction subsequently causes an elevation in AGE formation, which causes even more inflammation [8].

Oxidative damage is thought to be the main cause of age-associated degenerative illnesses, and aging contributes to its accumulation [9].

This review intends to investigate the relationship between RAGE expression, AGE levels in the serum, and AGA etiology. By exploring their potential as diagnostic markers or therapeutic targets, it clarifies the molecular pathways via which AGEs and RAGE may affect follicular miniaturisation and hair loss.

2. Androgenic Alopecia (AGA)

By the age of 70, at least 80% of men and 50% of women will have AGA, also referred to as pattern hair loss. The frequency of AGA increases with age [10].

The syndrome is autosomal dominant and is characterized by terminal hair progressive transformation into vellus and intermediate hairs. Shorter hairs and eventual baldness are the results of changes in the hair cycle, which include a shorter anagen phase and a longer telogen phase [11].

❖ **Etiology**

As the name implies, AGA has a distinct hereditary propensity and is most likely caused by an increased androgen sensitivity [12].

❖ **Epidemiology**

The majority of affected patients are White, then Asians, African Americans, Native Americans, and Eskimos. In Caucasian males, the incidence roughly corresponds to age, with 50% afflicted by age 50 and up to 80% impacted by age 70. The illness is rather frequent in females, and its occurrence rises after menopause [13].

❖ **Pathophysiology**

Stimulation of the androgen receptor shortens the anagen in the normal hair growth cycle. Through a gradually shorter anagen phase, excessive activation in AGA leads to follicular miniaturisation, leading to thinner and shorter hair follicles that may not even ultimately reach the epidermis [14].

AGA is caused by a variety of multifactorial and even polygenic etiologies, of which the significance of microinflammation, which is frequently present in the hair follicles of AGA patients, has gradually come to light [15].

❖ **Clinical features**

Male AGA starts as bitemporal frontal scalp thinning that extends to the vertex (figure 1). When AGA affects women, the frontal hairline is usually spared, and there is widespread hair thinning between the frontal scalp and vertex. The histological hallmark of AGA is follicular miniaturisation, yet the diagnosis is typically symptomatic [16].

Clinical diagnosis is typically made based on a history of delayed onset starting after puberty and, sometimes, a family history of pattern hair loss. Generally speaking, unless the diagnosis is ambiguous, a biopsy is not required [17].
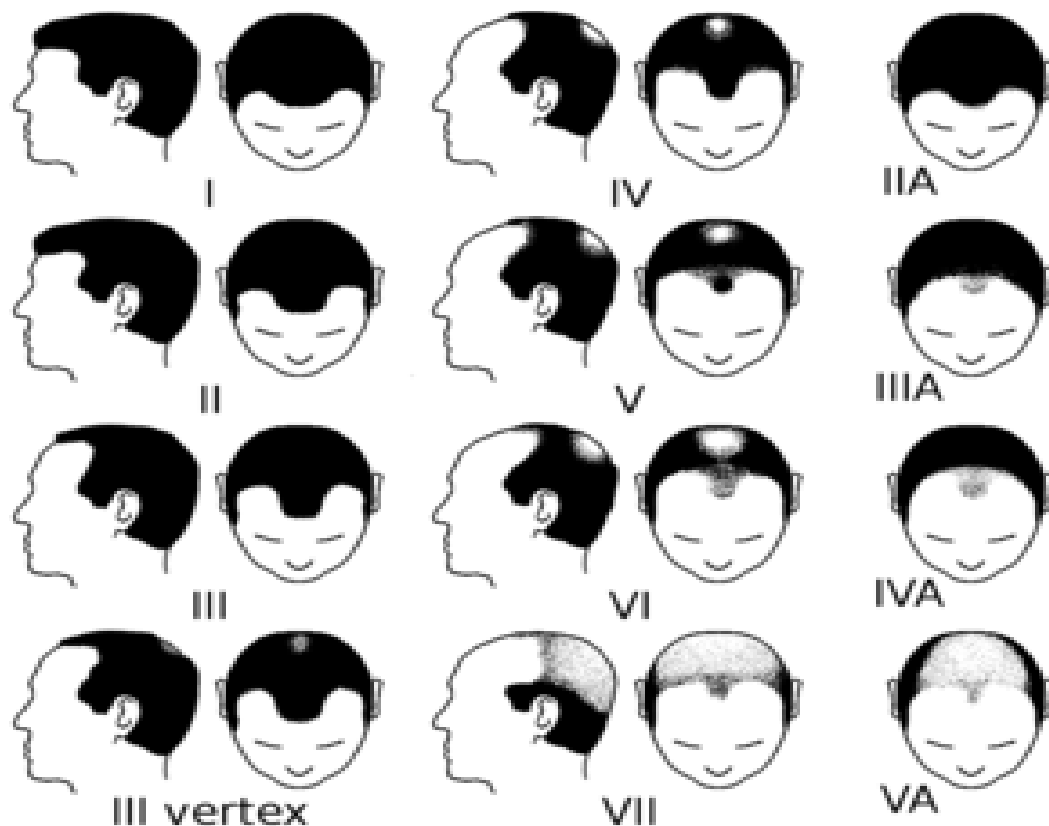

Fig. (1) Hamilton–Norwood scale for male pattern baldness [18].

❖ **Treatment**

Topical minoxidil and finasteride are the two FDA-approved therapies for pattern baldness. Both take at least a 4- to 6-month trial period before showing results, and constant use is necessary to sustain a reaction [19].

The patient is satisfied with the cosmetic outcome and efficacy of the hair transplant. To fill the bald area, patients must, however, have a sufficient quantity of donor plugs (more than 40 follicular units/cm2) [20].

For pattern baldness, red light or laser at 660 nm has also shown promise in treating hair loss and is sold over the counter [21].

3. Advanced Glycation End Products

The non-enzymatic byproducts of interactions between glucose or other saccharide derivatives and proteins or lipids are heterogeneous compounds known as advanced glycation end products or AGEs. In human blood and tissues, as well as in food, more than 20 distinct AGEs have been found. There are two types of AGEs: nonfluorescent and fluorescent. The most significant ones are pentosidine, pyrraline (nonfluorescent AGEs), carboxyethyl-lysine (CEL), methylglyoxal-lysine dimer (MOLD), and carboxymethyl-lysine (CML) (fluorescent AGEs) [22].

Aggregate degradation products (AGEs) produce oxidative stress, which triggers the stimulation of many stress-induced transcription factors. This process results in the synthesis of proinflammatory and inflammatory mediators, including acute-phase proteins and cytokines (figure 2)[23].
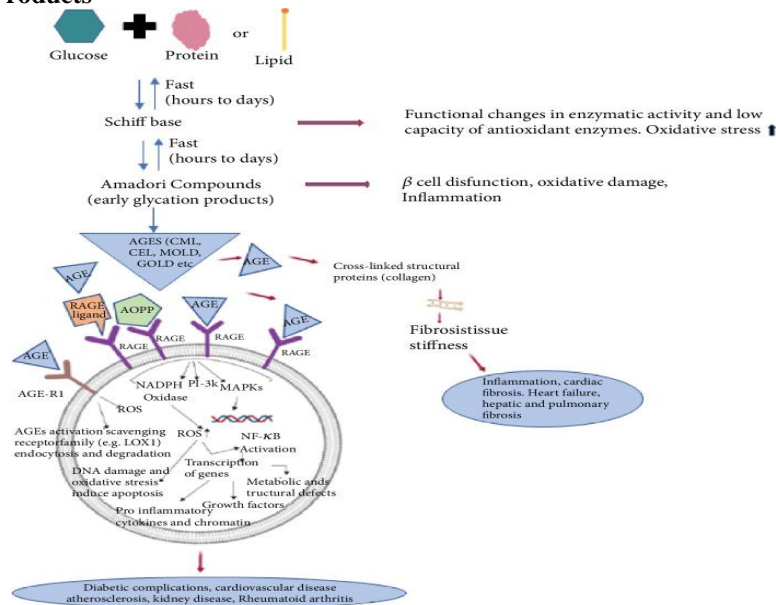
4. Receptor for Advanced Glycation End Products

A gene on chromosome 6 close to the major histocompatibility complex III encodes the transmembrane protein known as the receptor for advanced glycation end products (RAGE), which is a member of the immunoglobulin superfamily of cell surface receptors. It is composed of an extracellular portion with the transmembrane-spanning domain, short cytoplasmic tail, and types V1, C1, and C2 immunoglobulin domains [24].

RAGE molecule extracellular domain consists of two constant (C-type) domains that are the key sites of binding for different types of ligands, after a variable (V-type) domain. However, a RAGE molecule's cytoplasmic tail is essential for signaling. AGEs (endogenous or food-derived), advanced oxidation protein products (AOPPs), implicated in oxidative stress, -amyloid linked to Alzheimer's disease, calcium-binding S100 proteins linked to multiple human cancers, and high-mobility group box-1 (HMGB), expressed in cancer and inflammation, are just a few of the molecules bound by the RAGE type V1 and type C1 domains [25].

Once ligands bind to RAGE, multiple signaling pathways are triggered, which in turn activates nuclear factor-kappa B (NF-κB), the transcription factor that elevates many proinflammatory genes transcription, MAPK, transducers, and Janus kinase signal from transcription (JAK-STAT) activators, as well as phosphoinositol 3 kinase. These events ultimately result in angiogenic, proliferative, thrombogenic, apoptotic, and fibrotic responses [26].

Fig. (2) Biochemical formation of AGEs, their signaling, and molecular signal transduction that led to pathological effects [27].

5. Sources of Advanced Glycation End Products in the Skin

The two primary categories of AGE sources in the skin are exogenous ingestion and endogenous formation. Endogenous AGEs are created and collected in the skin as a result of aging and regular physiological metabolism, as well as conditions linked to inflammatory reactions and long-term metabolic disorders. Exogenous AGEs come from air pollution, cigarettes, sunlight, and the food we eat [28].

During the process of aging, the body naturally produces endogenous AGEs on its own when metabolic conditions are suitable. Nevertheless, when enzymes are not present, this reaction is slow. Because skin has a long collagen turnover period, the main factor contributing to the accumulation of AGEs (CML, CEL, and pentosides) in skin collagen is age. Inflammatory reactions and long-term metabolic illnesses, including diabetic mellitus (DM) and chronic renal failure, are significant sources of endogenous AGEs. One of the main

6. Association between AGEs and AGA

In the cutaneous field, it has been shown that AGEs promote apoptosis and cellular senescence in the skin. AGEs are known to grow with age in most organs and tissues and to be involved in the beginning of aging-related disorders by disrupting cellular functioning [31]

Through their interactions with other cells, including hair matrix cells, dermal papilla cells (DPCs) play vital roles in maintaining hair follicular homeostasis. Hair abnormalities may result from disturbances in the mesenchymal epidermal interface. DPCs upregulate TGF- and IL-6, among other cytokines in AGA. These cytokines prevent hair matrix cells from proliferating [32].

According to theory, AGEs cause AGA to occur sooner by increasing inflammatory cytokines, mostly through the ROS-mediated NF-kB pathway in DPCs, which prevents mesenchymal-epidermal interaction [33].

7. Recommendations and future prospectives:

In order to manage androgenetic alopecia, investigating therapies that target Advanced Glycation End Products (AGEs) and their receptors (RAGE) seems like a potential path (AGA). Techniques to reduce inflammation-induced damage to hair follicles by modifying the AGE/RAGE pathways have the potential to be novel treatment approaches. Furthermore, researching compounds that can prevent AGE

causes of diabetes problems is a chronically high blood sugar state, and AGEs develop and accumulate as a result of diabetes, with diabetes mellitus playing a significant role in their production [29].

AGEs are produced in the human body and then accumulate, according to multiple studies. This accumulation causes skin tissue destruction by controlling gene expression, breaking down protein structures, binding to RAGEs, mediating multiple signaling pathways, and influencing skin-related cell apoptosis and differentiation. AGEs have an impact on the skin at every level, resulting in inflammation, aging, yellowing, and other problems [30].

RAGE production was seen in the dermis as well as the epidermis, and it was higher in places exposed to the sun than in areas shielded from UV radiation. RAGE is expressed by keratinocytes, fibroblasts, dendritic cells, and to a lesser degree by endothelium and lymphocyte cells [34].

development or stop RAGE activation may provide new ways to stop or lessen hair loss in individuals with AGA. In order to cure AGA symptoms and restore the health of hair follicles, more study into certain inhibitors or drugs that target these pathways may open the door to effective molecularly-based interventions. Furthermore, more research into diagnostic markers linked to AGEs and RAGE expression may result in better early detection techniques, allowing for proactive AGA treatment in clinical settings.

8. Conclusions:

To sum up, the thorough investigation into the connection between AGEs, their receptors, and androgenetic alopecia (AGA) highlights the critical roles that these molecules play in the etiology of this common hair disorder. The review clarified how AGEs exacerbate the miniaturisation of hair follicles in AGA by causing oxidative stress and inflammation. Furthermore, AGE-induced RAGE activation sets up signaling cascades that intensify inflammatory reactions, potentially upsetting the delicate equilibrium in the follicular milieu. This enhanced comprehension of the molecular interactions among AGEs, RAGE, and AGA presents opportunities for innovative diagnostic methods and focused treatment plans intended to reduce hair loss in those who are impacted.

Moreover, the identification of AGEs and RAGE participation in AGA not only reveals their impact on follicular modifications but also emphasizes their potential as therapeutic targets or diagnostic indicators.

This review highlights the importance of investigating therapies that could control AGE/RAGE pathways by clarifying the processes behind hair follicle miniaturisation caused by AGE-induced inflammation.

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