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# A link between Androgenetic Alopecia and Aging

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**Abstract**:
**Background** :Among the several forms of hair thinning, androgenetic alopecia predominates.There are several factors that contribute to the development of androgenetic alopecia. Some of these variables include inflammation, oxidative stress, hormones, the environment, and heredity. As oxidative stress and levels of reactive oxygen and nitrogen species (RONS) rise, organ and tissue function deteriorates with age. Two components of the aging process indicators are elastin and nicotinamide adenine nucleotide (NAD). The goal is to use nicotinamide adenine dinucleotide and elastin as indicators of ageing in order to establish a connection between androgenetic alopecia and aging.Final Thoughts: The piece implies that aging is associated with androgenetic alopecia. There seems to be a strong interplay between the chronic information, metabolic dysregulation, and elevated oxidation.

**Keywords**: As we age, androgenetic alopecia occurs. An adenine dinucleotide nicotinamide, also known as Elastin.

## 1.Introduction:

Androgenetic Alopecia areata, a kind of hair loss that affects both sexes equally, is caused by an increased sensitivity to androgens and a hereditary tendency. The receding hairline or thinning of the crown is the end consequence of male pattern hair loss (MPHL), which usually starts around the temples (1).The hairline is unaffected by female pattern hair loss (FPHL), which instead affects the area between the crown and the nape of the neck. In AGA, the hair growth cycle is disrupted, which shortens the growth phase and causes catagen and telogen to end prematurely. As new hair comes in, the diameter of the hair follicle and the hair shaft gradually decrease, leading to the shrinkage of the follicle (2).

Many elements, including heredity, epigenetics, the environment, and social interactions, contribute to the complexities of the aging process. As a result, the body's ability to do daily tasks decreases with age, and the likelihood of developing neurodegenerative diseases, cardiovascular disease, cancer, and other age-related chronic illnesses increases (3). One of the leading causes of mortality as we get older is cardiovascular disease, which is responsible for 30% of all fatalities globally (4).

A large panel of biomarkers would likely be required to foretell the physiological processes of aging that cause the myriad of unfavorable outcomes often experienced by the elderly, given the complexity of the aging process. At first, it was thought that telomere shortening—which happens during cell replication—could forecast aging and its consequences. Nevertheless, newer research shows that the effects of aging on an individual's telomeres are minimal. There is no reliable correlation between telomere shortening and health, longevity, functional results, or clinical outcomes. Predicting outcomes associated with aging requires additional biomarkers (5).

In several important physiological processes, nicotinamide adenine dinucleotide (NAD) plays an indirect or direct role as an enzyme or metabolite. A few examples of these processes include glycolysis and DNA repair, gene expression, stem cell regeneration, and oxidative stress management. Decreases in NAD levels are a hallmark of age-related illnesses, progeroid syndromes, and frailty (6).

The suppleness and rigidity of human tissues are mediated by elastin, a protein found in the extracellular matrix. It develops into elastic fibers outside of cells and is an insoluble polymer of several isoforms of tropoelastin, its soluble precursor. Embryogenesis and the first several months of a baby's life are peak times for elastin production. Elastases modify elastin fibers to a lesser extent and the turnover of insoluble elastin is very minimal under physiological circumstances in adulthood. Proinflammatory environments may activate postnatal elastase activity, which in turn can play a role in the development of immune-mediated illnesses and age-related pathologies, such as atherosclerosis (7).

Fibroblasts in the epidermis, cells that line the walls of blood vessels, and endothelial cells are all linked to diminished elastogenesis as we age (8).

The age-related macular degeneration (AMD) is an age-related eye disease that causes significant vision loss and blindness,

particularly in industrialized nations. It typically begins around the age of 60 and is intimately associated with aging, as the name indicates (9).

Inflammation and oxidative stress interact with one another, which has been the focus of many investigations. Evidence suggests that inflammation induced by oxidative stress has a role in the pathophysiology of AMD. Pathological oxidative damage creates "oxidation-specific epitopes," induces pro-inflammatory responses, and promotes macrophage infiltration and polarization (10). It also damages proteins, lipids, and DNA and causes mitochondrial malfunction.

When it comes to the elderly, cardiovascular diseases—of which atherosclerosis is a major factor—are the top cause of death and disability (11).

Multiple studies have shown that antioxidant enzyme concentrations (such as GSH-Px and SOD) decline with age, causing a decline in the heart's tolerance to oxidative stress and, ultimately, the onset of cardiovascular changes (12).

An ultrasound-measured surrogate for subclinical atherosclerosis, common carotid intima-media thickness (CCA-IMT) has been shown to be an indicator of cardiovascular risk in both CAD and non-CAD patients (13).

Furthermore, androgenetic alopecia

A hereditary disease known as androgenetic alopecia (AGA) occurs when the body produces an excess of androgens, affecting as many as half of all men and women. The gradual thinning down of the scalp's hair at the ends, which may happen at any point after puberty and affects both sexes equally, is the hallmark of this condition. When it comes to hair loss, men tend to experience it more in the vertex and frontotemporal areas, while women usually just experience widespread apical hair loss, which manifests as a broader frontal hairline (14).

According to epidemiology, the greatest number of patients impacted are Whites, then Asians, African Americans, Native Americans, and Eskimos. For white men, the incidence of affection peaks at 70 years of age (affecting up to 80% of the population) and drops to 50% at 50. The condition is frequent in women and becomes more common after menopause (15).

Androgenetic alopecia, as the name implies, is most likely caused by an overreaction to androgen (16). It is also known to have a strong hereditary component.

Genetic factor:

The large variety of expressed phenotypes in AGA, together with its great frequency, establishes a polygenic mechanism of inheritance. Heredity is shaped by genetic variations in DNA sequence, which can manifest as SNPs, microsatellite repeats, insertion mutations, deletion mutations, and variations in copy number. Alterations to DNA can also occur epigenetically, such as X chromosome inactivation, hypermethylation (turning off gene expression) or hypomethylation (turning on gene expression) of DNA in gene promoter regions (17).

There are two main genetic risk loci: one on chromosome X called the AR/EDA2R locus, and one on chromosome 20 called PAX1/FOX A2. Additional susceptibility loci have been found to be located on chromosome 7, namely at the HAD C9 gene (18).

A gene for the androgen receptor: A cell's sensitivity to androgen is controlled by the androgen receptor. The amount of androgen that the hair follicle can use is controlled by the AR gene. The Stu 1 polymorphism is the most strongly associated with AGA of the other known AR gene variants (19).

Several additional genes, including as 5α reductase, aromatase, estrogen receptor α, and IGF-2 genes, also lacked solid evidence of correlations. Additional thorough genome-wide analysis is required to determine the Y chromosome's function (20).

Biological component:

Numerous skin tissues participate in the metabolism of testosterone and other less potent androgens such dehydroepiandrosterone and androstenedione. Dihydrotestosterone (DHT) is produced in the cytoplasm by 5 α reductase, mostly Type II, and testosterone is able to pass easily across the cell membrane. With the assistance of the AR co-activators, the complex consisting of DHT and the androgen receptor (AR) is translocated to the nucleus. Transcription of the target gene and subsequent translation into genes that carry out biological functions are the end outcomes of this process (21).

The production of several substances by the dermal papillae is the cause of the androgen-induced cross-talk between the cells of the hair follicles. The dermal papillae are autocrinely affected and the epithelial cells of the hair follicles are paracrinely affected by these (22).

The components under consideration include both growth factors such as Insulin Like Growth Factor (IGF-1), basic fibroblast factor (bFGF), and vascular endothelial growth factor (VEGF), and cytokines such as transforming growth factor beta 1 (TGFβ 1), interleukin 1 alpha (IL-1α), and tumor necrosis factor alpha (TNF α) (23).

The natural hair growth cycle has a shorter anagen, or growth phase, when the androgen

receptor is activated. The hair follicles in androgenetic alopecia are so small because the anagen phase becomes shorter and shorter due to over-activation; eventually, these follicles may not be able to pass the epidermis at all. The typical ratio of anagen to telogen hair is 12:1, while pathological specimens will reveal a lowered ratio of 5:0 (24).

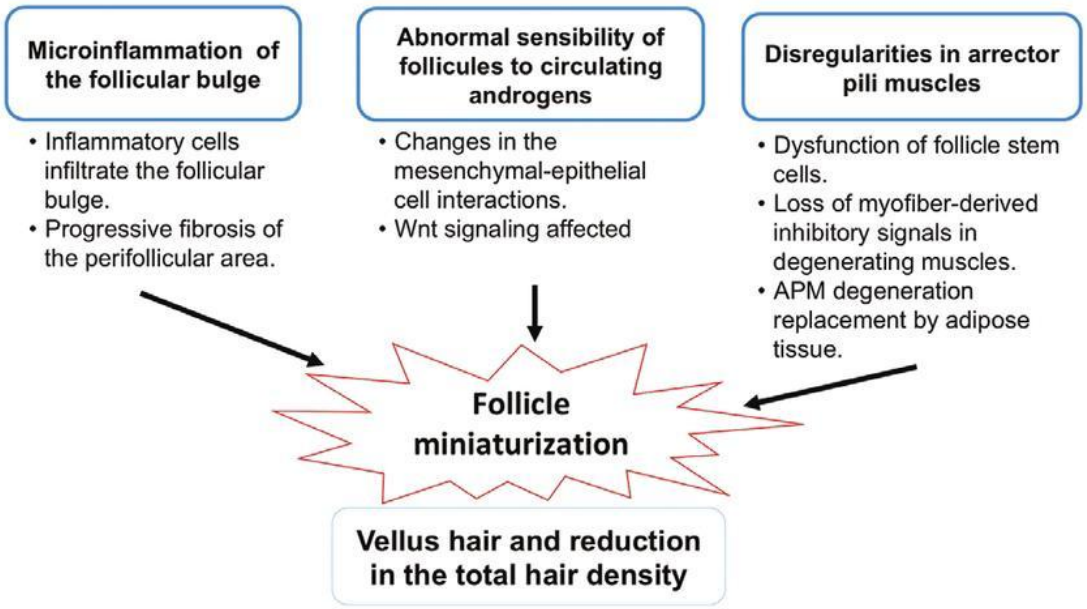
Inflammation of the hair follicles and environmental factors:

Multiple investigations have shown that follicular inflammation is a factor. In contrast to traditional scarring alopecia, which is characterized by an inflammatory and destructive process, this one is sluggish, subtle, and indolent. One possible mechanism by which microbial toxins belonging to the genus Demodex, Propionibacterium, Staphylococcus, or Malassezia contribute to the development of an inflammatory response is as follows (25).

Despite AGA's reputation as a noninflammatory illness, histological investigations have shown inflammation in the top third of hair follicles, indicating that inflammation may play a pathogenic role in the condition (26).

Because of the strong relationship between oxidative stress and inflammation in living systems, it has been shown that dermal papilla cells from androgenetic alopecia patients exhibit signs of oxidative stress (27).

On the other hand, keratinocytes may release nitric oxide and reactive oxygen species in reaction to actinic damage, pollutants, and irritants found in cosmetics and grooming products (28).




**Androgenetic alopecia etiology involves several components, as seen in Figure 1. Vellus hair, a clinical term for tiny hair follicles caused by microinflammation, aberrant androgen sensitivity, and arrector pilli muscle abnormalities (17).**

**3.Comorbities of Androgenetic Alopecia**

➢ **Endocrine Disease**:

The Circulating hormones primarily control hair growth and density. Therefore, hair loss is a common symptom of illnesses affecting the endocrine system (29). Excessive testosterone secretion by the ovaries and adrenal cortex is known as hyperandrogenemia (HA). Androgenic alopecia is one of the most prevalent androgenic skin alterations (30).

Despite its prevalence, AGA is not a reliable clinical indicator, according to a review of cutaneous symptoms in women with elevated androgen levels (31).

It is common for people with polycystic ovarian syndrome (PCOS) to have hyperandrogenemia. The incidence of AGA was 30% in a prospective study of PCOS individuals (32).

Early clinical signs of insulin resistance include polycystic ovary syndrome (PCOS), androgenetic alopecia (Androgenetic alopecia)—all of which increase the likelihood of acquiring type 2 diabetes (33).

Concerning cancer, there have been research that link AGA to the disease, although the conclusions drawn from these investigations are contentious.Prostate cancer and AGA could have a strong connection. Androgens, however, may explain the correlation between these two illnesses (34).

When the metabolism of proteins, lipids, carbs, and other substances in the body becomes abnormal, a condition known as metabolic syndrome (MetS) develops. As a risk factor for cardiovascular and cerebrovascular illnesses in

diabetics, it is a complicated metabolic syndrome. Twenty years of research have shown a link between AGA and MetS (35).

Cardiovascular Diseases: Multiple studies have shown a link between AGA and an increased risk of cardiovascular disease (36). There was a stronger correlation(37) observed in younger men (<55 years or ≤60 years) with AGA and an increased risk of heart disease compared to men without baldness, according to a meta-analysis of nine studies (eight on AGA and one on alopecia areata, totaling 44,806 participants) screened in the Medline and Embase databases.

Distress Disorders:

Suffering from hair loss and the associated cosmetic issues may have a negative impact on mental health. Isolation, which may cause feelings of despair, anxiety, and lack of self-assurance, is becoming more and more linked to AGA (38).

Illnesses of the Urinary System:

The androgen-dependent illnesses include androgenetic alopecia, benign prostatic hyperplasia (BPH), and prostate cancer. It has been shown that finasteride has excellent therapeutic effects in AGA and BPH (39).

COVID-19: Androgen receptors signaling is related with severe COVID-19 symptoms in males and plays a key role in the genesis of AGA. A biological connection exists between these characteristics (40).

Fourthly, aging and disorders related to aging

As we become older, our tissues and organs gradually lose their ability to operate (41). The oxidative stress theory of aging, which was formerly known as the free radical theory of aging, postulates that the functional losses that come with getting older are caused by the buildup of oxidative damage to macromolecules (such as lipids, DNA, and proteins) by reactive oxygen and nitrogen species (RONS) (42).

Although the precise process by which oxidative stress causes aging remains unknown, it is likely that elevated amounts of reactive oxygen species (ROS) cause cellular senescence, a physiological response that halts cell growth in reaction to replication-induced damage. The secretion of soluble substances (such as interleukins, chemokines, and growth factors), enzyme-like matrix metalloproteases (MMPs), and insoluble proteins/extracellular matrix (ECM) components is an irreversible senescence-associated secretory phenotype (SASP) that senescent cells acquire (43). Aging is characterized by chronic low-grade inflammation, which is an important factor in the onset of age-related diseases (44).

Diseases related to aging

Atherosclerosis, cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension, and Alzheimer's disease are all examples of age-related disorders. All of these disorders have an age-related exponential rise in incidence (45).

Aging skin: Various factors contribute to the aging process of the skin. Intrinsic (inherited traits) and extrinsic (environmental) variables both have a role. Fine lines, dry skin, changed pigmentation, and loss of suppleness are clinical manifestations of intrinsic aging, which is particularly noticeable in sun-protected skin. In a biological sense, chronological skin thinning is caused by a decrease in the reservoirs of epidermal stem cells and a slowdown in epidermal regeneration owing to keratinocyte stem cells' diminished proliferative potential. Lower estrogen levels, which have a major impact on how a woman's skin looks, can hasten the aging process for certain women going through menopause (46)

Heart disease:

Vascular remodeling, plaque buildup, and diminished arterial flexibility all contribute to atherosclerosis, an age-related illness. These mechanisms have the potential to harden the vasculature over time. This is why being elderly is considered a significant risk factor for atherosclerosis (47).

Between fifteen and twenty percent of all ischemic strokes are caused by carotid atherosclerosis, which is both a big cause and one that may be avoided (48). Even before atherosclerotic plaque forms, atherosclerosis starts developing in the early years of life and stays dormant for quite some time (49).

In order to begin active vascular disease preventive efforts early, it is necessary to identify patients with subclinical atherosclerosis (50).Consequently, there is a growing need to identify additional indicators of carotid atherosclerosis. Changes in arterial stiffness and carotid intima-media thickness (CIMT) are key indicators of potential severe atherosclerosis because they may be detected early (51).

The development of carotid atherosclerotic plaques follows CIMT and arterial stiffness as indicators of advanced illness. One common noninvasive method for detecting CIMT and arterial stiffness, two early structural changes in the carotid artery, is carotid ultrasonography (52).

Cancer: Immunosenescence is thought to be responsible for some of the correlation between becoming older and developing cancer (54).The endocrine system undergoes certain changes with age, which may explain

why cancer is more common in older people (55). DNA damage and inflammation promote cancer as we age, but vascular aging and endocrine changes block it (56). This makes understanding the impact of aging on cancer complex.

Noncancerous prostate growth:

Prostate illnesses, such as benign prostatic hyperplasia (BPH) and prostate cancer (PCa), are most often seen in older men. An enlarged prostate, often known as benign prostatic hyperplasia (BPH), is caused by an overpopulation of cells in the transition zone, which is the area of the prostate closest to the urethra. BPH is a condition that develops with age and may block the urethra of the prostate. In males aged 40–50, the prevalence ranges from 5% to 10%, whereas in men aged 70–80, it exceeds 80%(57).

A "protein misfolding" disorder is the medical term used to describe Alzheimer's disease. Protein folding mutations brought on by aging lead to the buildup of aberrant mutated proteins in some brain regions (58). As a result of the damaging metabolic route they initiate, these deposits are neurotoxic and lead to cognitive impairment (59).

Long-term, progressive neurodegenerative illness affecting primarily the motor system is known as Parkinson's disease (PD). Dementia, depression, and anxiety are just a few of the numerous consequences that may arise from this condition (60). Dementia caused by Parkinson's disease is more common as people become older, and the longer they have the condition, the more common it is (61).

Brain attack

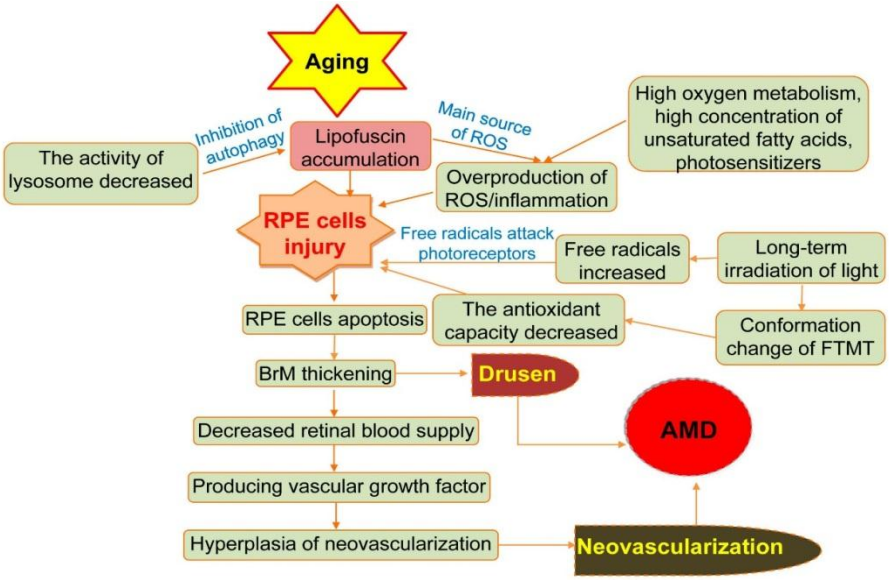
Strokes are more common in the elderly due to the increased prevalence of cardiovascular disease with age, and one of the most important risk factors for stroke is advanced age (62).

Untreated age-related macular degeneration is a major contributor to permanent vision loss or blindness in adults aged 60 and above (63).

Age, race, hypertension, and way of life are among the many risk factors for age-related macular degeneration. An increased likelihood of developing AMD is associated with becoming older.Systemic variables, including cardiovascular illness, high blood pressure, and atherosclerosis, may further raise the incidence of age-related macular degeneration (64). Patients with diabetes are more likely to develop AMD if they have diabetic retinopathy (DR), high-density lipoprotein (HDL) (66), are overweight, or have high systolic blood pressure (67).

Several pro-inflammatory markers are found in age-related macular degeneration (AMD) drusen, suggesting that local inflammation is an indicator of early AMD. The innate immune system, of which the complement system is a part, is crucial for keeping the intraocular microenvironment stable and healthy. Patients with AMD had a higher level of C-reactive protein (68).

Series of changes produced by aging of Retinal pigment epithelium( RPE) cells may lead to AMD. As they deteriorate, RPE cells in the macular region disrupt the Bruch membrane's enzyme balance in the extracellular matrix.A buildup of metabolites on the BrM causes vitreous warts, harms neighboring retinal tissues, and decreases blood flow to the retina. Vascular endothelial growth factor is produced by immune cells in response to senescent RPE cells. Blood vessels are produced by calcification, rupture, and phagocytosis of the Bruch membrane, which ultimately leads to AMD (69).



**As we age, AMD develops (Figure 2). Here we can see the nongenetic causes of AMD, such as oxidative stress, hemodynamics, RPE cell senescence, and so on, as we age (70).**

**5.Nicotinamide adenine dinucleotide (NAD)**

Nicotinamide NAD+, a multifunctional metabolite, is primarily characterized as a key role in diseases associated with aging (71).

Mediating cellular signaling transmission, nicotinamide adenine dinucleotide is involved in oxidative reductive reactions of cellular respiration and regulates the activity of NAD+-consuming enzymes (72).

Three distinct pathways—the Preiss-Handler, de novo synthesis, and NAD+ salvage pathways—are responsible for maintaining nicotinamide adenine dinucleotide levels (73).

Why NAD+ Is Important for Aging:

Nicotinamide adenine dinucleotide levels decrease as people become older. There is a decline in NAD+ production with aging. Secondly, NAD+ levels drop when the body experiences damage from oxidative stress, DNA dysfunction, inflammation, or both. Lots of NAD+-dependent cellular processes become messed up because of it (74).

Many age-related issues revolve on low nicotinamide adenine dinucleotide levels. When NAD+ levels drop, healthy cellular metabolism also drops. Loss of muscle tone, diminished exercise ability, obesity, fragility, and other well-known indications of aging are subsequent outcomes of this process. Loss of NAD+ is associated with a plethora of age-related illnesses (75).

Genomic instability, telomere attrition, epigenetic changes, proteostasis (protein stability) loss, mitochondrial failure, cellular senescence, stem cell exhaustion, altered intercellular communication, and unregulated nutrient-sensing are the biological hallmarks of aging (6).

Uncertainty in the Genome:

When the mechanisms that regulate cell division are flawed, a condition known as genomic instability results. Because of these changes, the genome isn't able to replicate the original pattern precisely throughout cell division. Mistakes in DNA replication or repair lead to changes in the genetic code (76).

When levels of NAD+ drop, cells are less able to proliferate and repair damaged DNA. Restoring NAD+ levels in old mice improved their cells' ability to repair DNA damage, according to the study (77).

Telomere shortening:

Many age-related chronic diseases are connected with telomere shortening (78).

Sirtuins are a class of proteins that protect the length and function of telomeres. One of the several things that sirtuins do is control and postpone the aging of cells; for this, they rely on NAD+ (79).

Cellular senescence is an additional expression of aging in biology. The term "senescence" refers to the natural aging process. Normal functioning of the immune system involves the elimination of damaged and old cells from the body (76).

In contrast, senescent cells are defective cells that have ceased dividing but have not yet died off and continue to exist in the body. As a result of their accumulation with age, they exacerbate age-related diseases (80).

Elastin 6.

The extensibility and elastic recoil of several vertebrate tissues—including some ligaments and cartilages, epidermis, pulmonary tissues, and major arteries—are attributed to elastin, an extracellular matrix (ECM) protein (81).

Organs including blood arteries, lungs, and skin undergo elastogenesis, the process of elastin production, mostly during fetal and early neonatal development (82). The slow turnover rate of elastin makes it vulnerable to a wide range of environmental stresses throughout time. During early development, tropoelastin, the principal component of elastin, is expressed at its maximum level; nevertheless, as an adult, its expression diminishes (83). Looser, droopier, and more easily damaged skin are visible signs of age-related decline in elastin synthesis and elastin degradation (84).

Aged, sun-protected skin loses some of its structural integrity and suppleness due to a progressive decline in elastin, collagen, and hyaluronic acid levels (85).

Elastin and skin aging:

Skin becomes less elastic and wrinkled as a consequence of both natural and accelerated aging. Aging disrupts the skin's elastic fiber network, which in turn causes structural damage, disturbed homeostasis, decreased tissue compliance and rebound, and other issues (86).One distinctive feature of elastin and elastic fibers is their very modest and gradual turnover rate. The total half-life of elastin in skin is really rather close to that of a human being (87).The proteins and fibers that make up these long-lasting materials are not expected to be significantly replaced, even after years of repetitive mechanical and environmental injury (86).

Degradation of elastin fibers may occur due to elastases, which are elastolytic enzymes that can be produced by a variety of sources, including inflammation, free radical damage, sun exposure, and illness (87). Sunlight doesn't have to be present for intrinsically aged skin to

show signs of a broken elastic fiber network. First, the elastic fibers shrink and break; second, the protein sustains damage via lipid and calcium buildup, glucose-mediated crosslinking, and changes to aspartic acid residues (86). When the dermal components hyaluronan, versican, and elafin are disturbed, it might be a sign that the elastic fiber network is deteriorating (88).

In the context of heart and lung illnesses, elastin:

Vascular aneurysms (89) and COPD with emphysema (90) are two examples of the many inflammatory and degenerative disorders characterized by a loss of elasticity.

Matrix metalloproteinases (MMPs) are one of many proteases that damage components of the extracellular matrix (ECM). Elastin degradation and, by extension, cardiovascular (91) and respiratory (92) illnesses have been linked to human neutrophil elastase (HNE), matrix metalloproteinase-9, and matrix metalloproteinase-12.

Patients with acute coronary syndrome have been shown to have higher Matrix Metalloproteases 9 (MMP-9), and there is pharmacogenetically evidence linking MMP-9 and −12 to hypertension (94).

Elastin and eye disorders:

Several eye illnesses have been linked to abnormalities in elastin turnover, breakdown of elastic fibers, and elastase activity. Critical to the eye's structural stability are elastic fibers dispersed throughout the cornea and sclera. Predicted to have a role in controlling intraocular pressure, scleral elastin is densest in the peripapillary area or close to the optic nerve head (95).

With age comes a thickening of Bruch's membrane, a relative loss of elastin, and an increase in calcification of elastin, in addition to lipid accumulation (96).

Here are some suggestions:

Studying the aging process and finding biomarkers to diagnose and predict age-dependent risks can greatly benefit the prevention of age-related diseases and the improvement of the health status of the elderly. By monitoring aging, medical interventions can be done before early symptoms or the onset of chronic diseases show up, which is a huge step forward in the field of aging research.

## 8.**Conclusions and Future Prospectives:**

This This article seeks to examine the possible connection between Androgenetic Alopecia and aging by looking at nicotinamide adenine dinucleotide and elastin, two markers of aging. The two conditions share certain associations, such as cardiovascular disease and age-related macular degeneration. According to the report, those who have androgenetic alopecia are at a higher risk of developing age-related conditions including cardiovascular disease and age-related macular degeneration.This analysis lends credence to the idea that androgenetic alopecia sufferers age more rapidly than the general population due to increased RONs, oxidative stress, and systemic damage.

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