



Review Article

A Precise Review on Premature Graying of Hairs

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ARTICLE INFO

Published: 27 Dec. 2024

Keywords:

Premature Graying of Hairs,
Canities, Management,
Pathogenesis, Premature.

DOI:

10.5281/zenodo.14561416

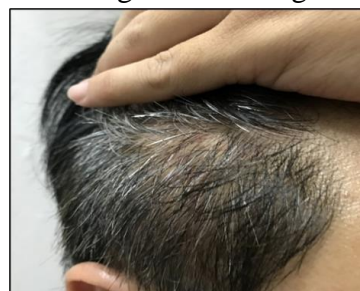
ABSTRACT

PHG is characterized by hair graying before age 20 (Caucasians) age 30 (African Americans) age 35 (Asians). Premature hair graying can erode an individual's self-assurance and body image. The underlying causes of premature hair graying remain unclear, but research suggests links to premature aging syndromes, allergic conditions, and autoimmune diseases. Individuals with premature hair graying (PGH) require to undergo evaluation for underlying syndromes and metabolic disorders. Managing PGH involves using calcium pantothenate, PABA, or a combination, while also addressing any underlying or co-occurring medical conditions. This paper provides a comprehensive overview of PGH, exploring its underlying mechanisms and management strategies, including natural, nutritional, and herbal approaches.

INTRODUCTION

PGH is defined as hair graying prior to 20 years in Caucasians, 25 years in Asians, and 30 years in individuals of African descent. Premature Hair Graying is caused by a combination of genetic, environmental, and lifestyle factors, and can also be associated with nutritional deficiencies and certain medical conditions^{[3][4]} Premature Hair Graying is caused by a combination of genetic, environmental, and lifestyle factors, and can also be associated with nutritional deficiencies and certain medical conditions^[2]. Premature Hair Graying has been observed in conjunction with

various medical conditions, including pernicious anemia, thyroid disorders, osteopenia, and rare syndromes like Progeria and Pangeria.



air, considered a vital aspect of one's appearance, significantly impacts self-perception and social confidence. Premature graying, particularly in

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



darker-haired individuals, can profoundly affect young people's self-esteem due to the stark visibility of gray strands. According to the classic 50/50/50 guideline, by age 50, half of the population will have lost half of their natural hair pigment, retaining 50% of their original black hair. Contrary to the traditional 50/50/50 rule, a recent study by Panhard et al. found that only 6-23% of individuals have 50% gray hair by the age of 50^[1]. 90% of the world's population has deep brown-black hair, which offers protection from sunstroke and supports salt balance due to melanin's role in efficient ion exchange^[5].

Hair Follicle Pigmentation Process.

The hair follicle, a complex organ comprising melanocytes and keratinocytes, undergoes periodic cycles of growth, degeneration, and

regeneration, governed by hormonal and local signaling molecules.

Human hair displays a remarkable spectrum of colors, from black to blonde and red, due to the production of melanin pigment by melanocytes, derived from neural crest cells .

Human hair follicles contain **two melanin types** – **Eumelanin** (black-brown) and **Pheomelanin** (reddish-brown)

- whose varying quantities and ratios create diverse hair colors.

Lower pH values progressively inhibit tyrosinase, shifting melanin production towards pheomelanin, causing hair to appear reddish or blonde.

Normal hair follicles experience a 3-stage life cycle, consisting of :



Telogen ends with hair shedding, new growth begin The hair follicle-melanin unit, comprising one melanocyte and five keratinocytes, orchestrates melanin production in concert with the hair cycle stages. Melanocytes, with neural crest origins, migrate and establish residence on

the basement membrane, forming the boundary between the epidermis and dermis.

Melanocytes produce and supply melanin to keratinocytes within the hair follicle. Melanin synthesis happens within membrane-enclosed melanosomes

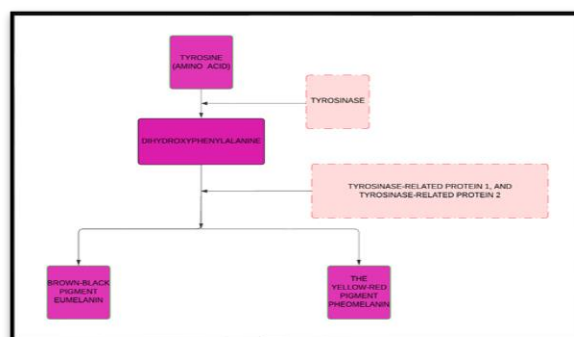


Fig: Biochemical synthesis of melanin

Melanin synthesis takes place solely during the anagen phase within melanocytes of the hair bulb. Melanocytes located in the outer part of the hair follicle can function as stem cells, capable of self-renewal and generating new melanocytes., replenishing melanogenic melanocytes in the hair bulb after telogen-phase apoptosis.^[6,7] Stem cell maturation into melanin-producing melanocytes depends on stem cell factor, released by dermal papilla, which activates c-kit receptor tyrosine kinase, promoting melanocyte proliferation and melanogenesis. Various neuroendocrine factors, specifically adrenocorticotrophic hormone (ACTH), beta-endorphin, thyrotropin-releasing hormone (TRH), alpha-melanocyte-stimulating hormone (alpha-MSH), and thyroid hormones triiodothyronine (T3) and levorotatory thyroxine (T4), have been shown to influence hair color by stimulating the production of melanin..

Normal Aging Process-Induced Hair Graying

As individuals age, hair follicle melanogenesis declines due to decreased melanocyte numbers and diminished enzyme activity, leading to progressive graying and whitening.^[10,11,12,13] With age, hair follicle stem cells aberrantly differentiate into melanogenic melanocytes, disrupting the normal follicular development process. As stem cells are lost, the hair follicle's ability to replace

melanocytes after programmed cell death (apoptosis) is compromised, leading to decreased melanocyte density and subsequent pigment reduction^[11,12]. The accumulation of endogenous and exogenous reactive oxygen species (ROS) with age contributes to the ectopic differentiation of stem cells in hair follicles^[10,13,14]. Oxidative stress not only promotes ectopic differentiation of stem cells but also triggers premature apoptosis of melanogenic melanocytes in the hair bulb, further substantiating the free radical theory of hair graying^[15].

Histopathology Of Canities

The bulb of the hair follicle is compartmentalized into two regions: a lower region of stem cell-like, undifferentiated cells and an upper region characterized by cellular differentiation, giving rise to the inner root sheath and hair. Beneath the Auber line lies the follicular matrix, characterized by high mitotic activity, and the dermal papilla, from which cells migrate upward into the bulb, undergoing significant volume increase and vertical elongation. The upper region of the hair follicle bulb displays residual mitotic activity, but this is restricted to a small population of cells, making its contribution to hair growth relatively negligible.

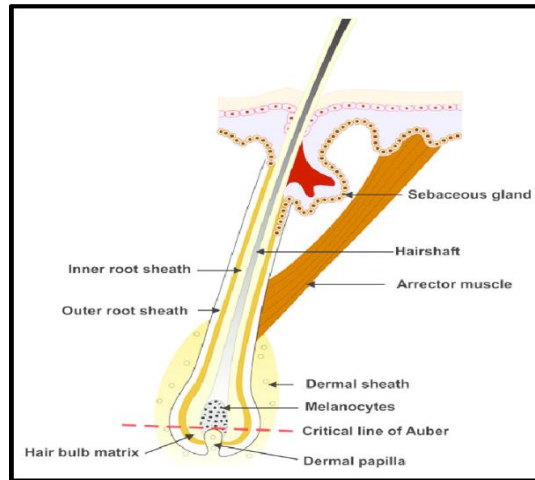


Fig: Melanin Production Unit: Dermal Papillae, Hair Follicle, and Auber's Line

The pigmentary unit, situated at the tip of the dermal papilla, is a specialized, pear-shaped entity where melanocytes converge to produce pigment in pigmented hair follicles. Below Auber's line, the hair bulb contains a population of melanocyte stem cells that are unpigmented and have not undergone differentiation into mature, pigment-producing melanocytes. Gray hair is distinguished by disruptions in the pigmentary unit, manifesting as fuzziness, reduced melanocyte counts, and the presence of oligodendritic melanocytes in the proximal hair bulb. Graying of hair is caused by a decrease in the number of melanogenically active melanocytes in the hair bulb, disrupting normal melanin production and resulting in characteristic pigment loss.

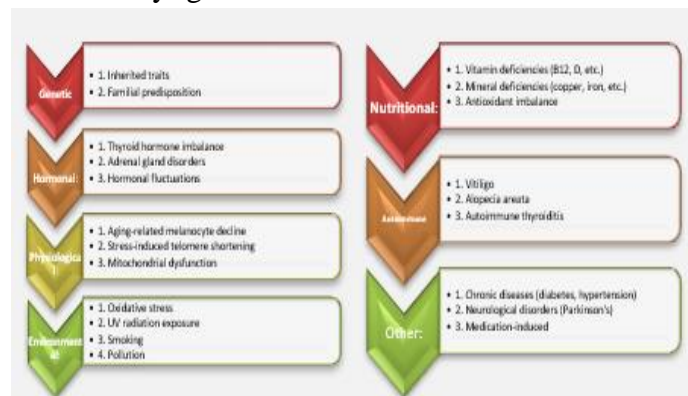
Multifactorial Pathogenesis Of Hair Graying

The precise mechanisms behind hair graying are still not fully understood. Primary generalized

hypopigmentation (PGH) can occur as an autosomal dominant condition. Additionally, graying may be associated with premature aging disorders like progeria and pangeria. There are also reported links to atopic diathesis and autoimmune diseases.

A significant area of research has focused on the impact of reactive oxygen species (ROS) on hair graying. During the anagen phase, when hair is actively growing, melanogenesis takes place within the hair follicles. This process includes the hydroxylation of tyrosine and the oxidation of dihydroxyphenylalanine into melanin, resulting in considerable oxidative stress. If the body doesn't have enough antioxidants to protect itself, oxidative stress can damage the cells that produce hair color (melanocytes), resulting in lighter hair.

Possible Etiopathogenetic Factors:



Oxidative stress may be triggered by various factors, including ultraviolet (UV) radiation, pollution, emotional stress, and inflammation. Research conducted on mice has shown that UV exposure can lead to oxidative damage in hair follicles, contributing to hair graying. Moreover, a heightened oxidative load associated with psychological stress indicates that emotional factors can also play a role in the development of premature graying.^[18,19] Primary generalized hypopigmentation (PGH) is closely associated with factors that induce oxidative stress, including emotional stress, alcohol consumption, and chronic illnesses in individuals with a genetic predisposition. Vitiligo, a condition that causes patches of skin to lose pigment, can also contribute to premature graying. People with vitiligo have melanocytes that are more easily damaged by oxidative stress. This damage, caused by reactive oxygen species (ROS), can disrupt the function of stem cells and lead to the death of mature pigment-producing cells. Additionally, vitamin B12 deficiency is linked to PGH through mechanisms that are not fully understood. Approximately 55% of individuals with pernicious anemia experience graying before the age of 50, compared to 30% in the control group. A decrease in thyroid hormones can also result in premature graying, alopecia, and changes in hair structure. Thyroid hormones T3 and T4 directly stimulate melanogenesis in hair follicles.^[21,22] Certain chemotherapy drugs and antimalarials are known to contribute to PGH as well. These medications are thought to block a specific protein receptor (c-kit) in melanocytes, which in turn reduces the production of melanin. For instance, chloroquine is thought to selectively decrease pheomelanin production through mechanisms that remain unclear.^[23,24,25,26] Smoking has been identified as a potential cause of early-onset achromotrichia. Research has shown a significant link between smoking and premature hair graying, likely due to the

prooxidant effects of smoking, which increases reactive oxygen species (ROS) damage to the melanocytes in hair follicles. Studies in young Indian populations have found lower levels of certain nutrients, including iron, calcium, vitamin D, and vitamin B12, in individuals prone to premature graying (PGH). These studies also suggest a link between PGH and lower levels of "good" cholesterol (HDL-C)..

Hair Graying Patterns

In a case-control study by Sharma et al., the average age of onset for premature hair graying (PHG) was set up to be 13.8 ± 4.68 years, with a range from 2 to 22 years; the formost recorded onset was at age 2. Also, Daulatabad et al. reported an average onset age of 11.6 ± 3.6 years, ranging from 3 to 18 years, with the youngest case being 3 years old.^[27] The start and advancement of hair turning gray nearly align with the natural aging process, with at least some gray hair present in all individuals by the age of 60, regardless of gender or race. The appearance of white hair is attributed to an optical illusion; the pale yellow of keratin reflects or refracts light, making it seem white. Gray hair contains some color due to sparsely distributed melanosomes, while white hair has no melanosomes or color and typically occurs only on the scalp. A widely accepted observation is that by the age of 50, about half of the population will have roughly half of their hair turn gray. In men, graying typically begins at the temples and sides of the face, gradually spreading to the top of the head and the rest of the scalp. In women, graying often starts around the hairline. The speed at which hair grays is influenced by inherited factors and can vary significantly not only across different parts of the head but also on other areas of the body. Beard and body hair tend to gray later, with chest, pubic, and axillary hair often remaining pigmented well into old age. Jo et al. found that the temporal and occipital regions are more frequently affected in men than in women, with graying



typically starting in the temporal area for men and in the frontal area for women. Additionally, the initial areas affected can differ based on the age of onset; for those with early-onset graying, the parietal or occipital regions may be more involved initially, while those with late-onset graying often see the frontal area affected first.

Distinctive Traits Of Gray Or White Hair

Gray hair tends to be coarser, stiffer, and more challenging to manage compared to darker hair. Its growth rate and thickness can be significantly higher than that of pigmented hair, with gray beard hair potentially growing up to four times faster. Additionally, gray hair is more vulnerable to environmental damage and UV radiation, requiring enhanced protection from sunlight. It is also less likely to retain artificial color due to structural changes in the hair fibers^[29].

Physical Characteristics

1. **Loss of Melanin Pigment:** Hair may become gray or white.
2. **Reduced Hair Diameter:** Thinning hair strands can occur.
3. **Increased Brittleness:** Hair becomes more fragile and prone to breakage.
4. **Dryness and Rough Texture:** Hair may feel coarse and lack moisture.
5. **Decreased Elasticity:** Hair is less able to stretch and bounce back.
6. **Changed Hair Growth Pattern:** Growth may become uneven or slower.
7. **Uneven Color Distribution:** Color may not be uniform, leading to patches of different shades.

Optical Characteristics

1. **Reflectivity and Shine Reduction:** Hair appears duller and less vibrant.
2. **Increased Transparency:** Thinning can lead to more see-through strands.
3. **Shift from Yellow to Blue/White Hue:** Older or damaged hair may take on a cooler tone.
4. **Reduced Hair Color Intensity:** Overall color may appear faded or less rich.

Early Graying: A Possible Predictor Of Age-Related Health Risks

Several studies have explored the link between premature graying of hair (PGH) and other health conditions. A few of these studies found that graying hair before the age of 40 can be a significant indicator of low bone density and osteopenia^[30,31].

On the other hand, studies indicate that premature hair graying is less common in racial groups that typically exhibit higher bone density. In contrast, Morton et al. reported no correlation between premature hair graying and low bone mineral density. Premature graying may be linked to other autoimmune conditions, such as vitiligo, Addison's disease, Graves' disease, and certain hormonal deficiencies. Some studies have suggested a possible connection between premature graying and an increased risk of heart attacks in men. However, other research has not found such a link. One study found that premature graying, especially among smokers, may significantly increase the risk of heart disease.

A recent study investigated the link between hearing loss and premature hair graying (PGH). It found that patients with PGH exhibited hearing impairment at higher frequencies. The researchers suggested that PGH could be a significant risk factor for hearing loss, indicating that these connections warrant more detailed investigation.

Evaluations For Premature Canities

Assessing premature graying of hair is primarily a clinical diagnosis. However, in cases where it occurs at a young age without a family history, certain tests, such as serum levels of vitamin B12, folic acid, and a thyroid profile, may be necessary.

Diagnostic Considerations For Premature Graying

Premature graying needs to be differentiated from other conditions that also cause hair to lose its color.



- **Albinism:** This condition can cause white hair due to the lack of melanin production.
- **Neurocutaneous disorders:** Conditions like Griscelli, Chediak-Higashi, and Elejalde syndromes, which affect both the nervous system and the skin, can also cause white hair in children.
- **Other genetic disorders:** Conditions such as Angelman syndrome, Prader-Willi syndrome, and Cross syndrome may also lead to gray hair in childhood.
- **Metabolic disorders:** Some metabolic problems can also cause hair to become lighter in color.
- **Vitiligo and poliosis:** Vitiligo, a condition that causes white patches on the skin, can also lead to patches of white hair (poliosis). Poliosis can also occur in other conditions that affect skin pigmentation.
- **Canities subita:** This is a rare condition where hair suddenly grays. It can be linked to vitiligo, hair loss conditions, and emotional stress.

Management Strategies For Premature Canities

Currently, there isn't a universally accepted scoring system to evaluate the severity of premature graying of hair (PGH). Various attempts have been made to categorize graying into mild, moderate, and severe based on factors such as the percentage of hair affected, the number of gray strands, or the extent of graying in different areas of the scalp. These classification methods typically rely on questionnaires and clinical examinations to gauge severity.^[45,46,47,48,49]

Treatment for PGH should focus on addressing the underlying causes. For instance, deficiencies in vitamin B12 and conditions like hypothyroidism can be managed with appropriate vitamin and hormone therapies. For individuals with less than 10% of their scalp affected, plucking gray hairs can be a simple solution.^[50]

Hair colours

Many people turn to hair colorants to restore their natural hair color^[51]. These colorants can be derived from natural sources or created synthetically, and they come in both temporary and permanent forms. Common natural hair dyes include Natural dyes, such as those derived from Indian gooseberry, false daisy, lotus tree, and henna, are generally considered hypoallergenic and non-toxic Permanent hair dyes are particularly popular in the market, but they can pose a risk of damage to the hair shaft due to oxidation. In contrast, temporary hair dyes do not penetrate the hair cuticle and can be easily washed out with shampoo^[53]. Hair dyes not only help conceal gray hair but also offer protection against photodamage^[54]. However, some individuals may experience irritant dermatitis, often caused by p-phenylenediamine, as well as hair loss from coloring treatments.^[55]

Vitamins and minerals

Despite the prescription of various vitamins and minerals like biotin, calcium pantothenate, zinc, copper, and selenium, the outcomes have generally been unsatisfactory. Calcium pantothenate is frequently recommended for treating premature graying of hair (PGH). Pasricha documented successful treatments in two adolescent girls who received 200 mg of calcium pantothenate daily. Further research involving 39 patients indicated that this high dosage (200 mg/day) was effective for PGH. Additionally, combining this treatment with gray hair avulsion therapy produced improved results, with some of the avulsed gray hairs not regrowing as gray.^[56]

P-aminobenzoic acid (PABA).

P-aminobenzoic acid (PABA) has been associated with anecdotal reports of temporary hair darkening^[57]. Sieve administered 200 mg of PABA to 30 patients over a two-month period, and all subjects experienced some degree of repigmentation. Similarly, Zarafontes noted that patients receiving PABA for various conditions



also showed repigmentation of gray hair. However, the authors do not endorse the use of PABA solely for the purpose of darkening hair.

Psoralen and UVA (PUVA)-

Psoralen and UVA (PUVA) therapy has been reported to be effective for treating premature graying of hair (PGH) in one study, as it stimulates melanocytes to promote pigmentation. However, subsequent experiments did not consistently produce the same positive outcomes.^[58]

Latanoprost

Bellandi et al. documented cases of gray hair repigmentation after approximately three years of using latanoprost, a PGF2 alpha eye drop^[60]. The repigmentation began at the roots and the proximal portion of the hair, gradually extending along the entire length.^[62]

Prostaglandins

Prostaglandins are among the most powerful stimulators of melanocyte growth and the process of melanogenesis.^[63,64] Recent developments include the incorporation of antioxidants like vitamins C and E into shampoos, though their effectiveness has been questioned due to the short duration of contact with the scalp. Additionally, compounds such as green tea extract, selenium, copper, phytoestrogens, and melatonin are being explored as potential topical anti-aging agents. Research on recombinant human growth hormone has shown it can enhance hair thickness, growth, and even darken hair^[63]. Skulachev et al. discussed their findings on preventing cellular aging, highlighting a new class of compounds called SkQs, which include plastoquinone. These antioxidants have demonstrated the ability to inhibit age-related changes like graying, hair loss, retinopathy, and cataracts, making them a promising option for addressing senescence and age-related conditions^[69]. The concept of delivering drugs via the hair follicle route is also being investigated. Current research is focusing on the targeted delivery of liposomes to melanin,

genes, and proteins within hair follicles. Using liposomal delivery to introduce melanin into hair follicles has led to darkening of the hair. Liposomes could serve as a means to selectively target hair follicles in molecular and gene therapy aimed at restoring hair color.^[70] In some cases, certain medications, such as defibrotide, cyclosporine, corticosteroids, and others, have been observed to cause hair darkening as a side effect. However, confirming that the medication was the cause of the hair darkening can be challenging. This is because most patients continue taking the medication, making it difficult to determine if the hair color would return to normal if the medication were stopped.

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HOW TO CITE: Prachiti Sahane*, Gauri Mahajan, Dr. Manisha Nangude, Sakshi Bhosale, Kalyani Shelar, Ayurvedic Baby Wipes: A Natural Approach to Infant Care, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 12, 3138-3149. <https://doi.org/10.5281/zenodo.14511959>