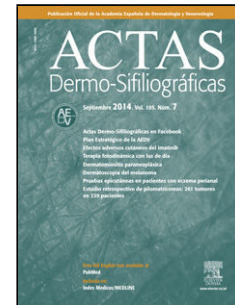


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Sección. Practical Dermatology

Hair graying update and review

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Abstract: Graying is a natural process, characterized by the loss of pigment in the hair, and is considered a sign of aging in society; its onset and progression is closely correlated with age and occurs to varying degrees in all individuals, regardless of gender or race. However, premature graying has a psychological and social impact, affecting patients' self-esteem. The exact etiopathogenesis is still unknown, and it has been associated with multiple factors such as: oxidative stress, ultraviolet radiation, genetic factors, and lifestyle factors such as smoking, nutritional and emotional factors. All of this causes a decrease in the production of melanin by the melanocytes of the hair bulb. Despite the extensive molecular research being carried out to understand the pathogenesis of graying, there is a shortage of effective, evidence-based treatment options. Today, graying has become a cultural phenomenon, where many people opt for cosmetic treatments to cover gray hair.

Keywords: gray hair, premature graying, oxidative stress.

Palabras clave: canas, envejecimiento prematuro, estrés oxidativo.

Introduction

Hair graying—also known as gray hair, white hair, or achromotrichia—is considered one of the earliest normal signs of aging. It usually appears around 34 years of age in Caucasians and 43 years in individuals of African descent¹. However, it is defined as premature graying (PG) when at least 5 gray hairs appear before the age of 20 years in Europeans, 25 gray hairs in Asians, and before 30 years of age in Africans².

Hair symbolizes well-being and health and plays an important role in social communication, self-perception, self-esteem, and body image³. Recently, the treatment of premature graying has been increasingly studied due to its psychological consequences and its possible association with metabolic diseases^{4,5}.

Hair Follicle Melanogenesis

Hair follicle melanocytes are categorized into subpopulations according to their function, degree of differentiation, and location.

The first location is in the hair bulb during the anagen phase, in the upper region of the dermal papilla. Bulbar melanocytes are the only cells that contribute to hair pigmentation. They express active tyrosinase and dihydroxyphenylalanine (DOPA) and are considered part of the hair follicle pigmentary unit, along with keratinocytes⁶.

Melanogenesis occurs within specialized lysosomes called melanosomes, which are transferred to keratinocytes via dendrites and filopodia. This process occurs exclusively during the anagen phase, ceases during catagen, and remains inactive during telogen.

Melanosomes transfer melanin primarily to the hair cortex, to a lesser extent to the medulla, and only occasionally to the cuticle⁷.

Unlike epidermal melanocytes, the hair bulb contains approximately 1 melanocyte for every 5 keratinocytes, and hair follicle melanocytes have longer and more numerous dendrites⁸.

The second melanocyte location within the hair follicle is the bulge area. These melanocytes are immature and inactive, do not express melanogenic enzymes such as tyrosinase or tyrosinase-related protein 1 (TRP-1), and serve as precursor cells. They proliferate, mature, and migrate to the bulb during anagen⁹.

Melanocytes have also been identified in the infundibulum, similar to epidermal melanocytes, and in sebaceous glands⁶ (Table 1).

The Graying Process

The hair follicle pigmentary unit reaches its maximum melanin production during adolescence, followed by a gradual decline over the years.

Repigmentation and reconstruction of the pigmentary unit are lost with each hair cycle and can only be achieved for 7 to 15 cycles, corresponding to approximately 40–45 years of age, resulting in reduced pigment production. Another contributing factor is the prolongation of the telogen phase that occurs with aging¹⁰ (Figure 1).

Pigment loss in the hair shaft is associated with reduced melanin content and a decrease in bulbar melanocytes. When hair becomes gray, few melanocytes remain, but they still express tyrosinase and continue melanin transfer to keratinocytes. In contrast, white hair lacks melanocytes in the bulb altogether¹.

Etiopathogenesis

The exact etiopathogenesis of premature graying has not yet been fully elucidated. It may be associated with autosomal genetic disorders, premature aging syndromes such as progeria and pangeria, oxidative stress resulting from ultraviolet radiation, pollution, and emotional factors, as well as inflammatory causes. Several studies have also reported associations with deficiencies of vitamin B12, vitamin D, iron, calcium, ferritin, copper, and zinc, as well as with thyroid hormone deficiency and drugs that reduce melanogenesis².

Oxidative Stress

Oxidative stress plays a significant role in melanogenesis. Melanin synthesis generates hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxyl free radicals. Compared with keratinocytes, melanocytes are more vulnerable to oxidative stress¹¹.

Defense mechanisms against oxidative stress include antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). However, their activity

decreases with aging, creating an imbalance between oxidative damage and repair mechanisms¹².

Excessive accumulation of reactive oxygen species (ROS) within hair follicle melanocytes leads to cellular damage through lipid peroxidation, DNA strand breaks, mutations, and protein and enzyme denaturation. Damage to the cell membrane generates arachidonic acid, followed by the formation of aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal. MDA crosses the cell membrane into the extracellular compartment; therefore, its serum concentration represents a sensitive marker of oxidative stress. Collectively, this damage results in decreased melanocyte pigment-forming capacity and may even induce apoptosis through activation of inflammatory pathways such as the MAPK and p53 pathways¹³.

Saxena et al. evaluated serum levels of MDA, reduced glutathione, and SOD in patients with premature graying and found significantly higher MDA levels vs controls. SOD levels were also lower in premature graying cases, reinforcing the role of oxidative stress in PG¹⁴.

Genetic Factors

Numerous genes and signaling pathways involved in premature graying have been identified. Bian et al. reported reduced expression of genes responsible for melanin synthesis in the hair follicle—such as TYR, melan-A (MLANA), premelanosome protein (PMEL), TYRP1, SLC45A2, KIT, G protein-coupled receptor 143 (GPR143), and OCA2—in patients with premature graying¹⁵.

UV Radiation

UV radiation plays an important role in hair graying by stimulating the production of free radicals. UVA radiation can cause hair color changes by penetrating deeply into the cortex and inducing biochemical damage, whereas UVB radiation leads to protein depletion and structural damage to the cuticle^{16, 17}.

Tobacco Use

Smoking is associated with hair graying through increased free radical production. Shin et al. found a statistically significant association between smoking and premature graying, consistent with former studies^{18, 19}.

Stress

The mechanism linking graying and stress is not yet fully understood.

Animal studies suggest that stress can accelerate hair graying. Sharma et al. evaluated stress levels in patients with PG using the Perceived Stress Scale (PSS) and found significantly higher stress scores in patients with PG vs controls²⁰.

Zhang et al. demonstrated that acute stress can cause irreversible depletion of somatic stem cells via activation of the sympathetic nervous system, resulting in permanent tissue damage and hair graying²¹.

Hair follicles are innervated by sympathetic nerves; under stress conditions, they release norepinephrine, inducing proliferation of melanocyte stem cells that differentiate and migrate out of the bulge¹⁰. This leads to depletion of melanocyte stem cells without replacement. Without melanocytic cells to provide pigment during the next anagen phase, hair appears white^{10,22} (Figure 2).

Various stressors—including nociception-induced stress, chronic stress, and restraint stress—have been shown to cause melanocyte stem cell loss and hair graying through immunological mechanisms, corticosterone, and norepinephrine^{22,23}.

Melanocyte stem cells express β_2 -adrenergic receptors, which respond to norepinephrine. Loss of this receptor completely blocks stress-induced hair graying²³. Other stress-related mediators include calcitonin gene-related peptide, which maintains immune privilege and induces catagen while promoting melanogenesis; substance P, which downregulates growth, induces apoptosis, and increases free radical production; and vasoactive intestinal peptide, which prevents follicular collapse^{24,25}.

Adipose tissue surrounding hair follicles is rich in growth factors that regulate stem cell activation and regeneration and repress Wnt signaling^{22,24}.

Nutritional Factors

Hair may exhibit reversible hypopigmentation due to nutritional deficiencies. Daulatabad et al. found lower vitamin B12 levels in patients with PG vs controls, with greater deficiency associated with increased severity. They also found lower folic acid levels but no differences in biotin levels²⁶.

Sharma et al. reported lower serum calcium and ferritin, lower HDL cholesterol, and higher LDL cholesterol levels in patients with PG vs controls²⁰. Premature graying has been linked to early cardiovascular disease, and dyslipidemia may serve as a connecting factor⁵.

Furthermore, lower vitamin D levels have been reported in patients with PG, although without statistically significant associations^{20,27}. Regarding copper, lower levels have been observed in PG patients vs controls, but without statistical significance^{28,29}.

Comorbidities

Several studies have reported a higher prevalence of atopic diathesis in patients with PG^{20,26,30}. Das et al. conducted a study in patients with PG and found higher levels of blood pressure, glucose, insulin, C-reactive protein, and HOMA index, as well as elevated IL-6 levels, compared with controls. These findings suggest an increased cardiovascular risk, leading the authors to propose screening for cardiovascular risk factors in patients with PG⁵.

Chandran et al. measured thyroid hormone levels in patients with PG and found higher anti-thyroid peroxidase (TPO) antibody levels vs controls; however, no differences were observed in T3, T4, or TSH levels³¹.

An increased risk of osteopenia—up to fourfold higher—has been reported in patients with PG vs individuals without gray hair³². Nevertheless, more recent studies failed to confirm this association³³.

In cases of PG, a laboratory work-up may be necessary, including iron studies, vitamin B12, folic acid, 25-hydroxyvitamin D, thyroid profile, and antithyroid antibodies^{31–33}.

Clinical Features

Gray hair primarily results from an optical phenomenon. The pale yellow keratin of non-pigmented hair appears white due to light refraction or reflection³⁴. Compared with pigmented hair, gray hair is thicker, stiffer, and more difficult to manage, grows faster, and is more susceptible to UV radiation damage, requiring greater protection³⁵. Alterations in hair fiber make it more difficult to maintain artificial color, leading many individuals to undergo repeated dyeing procedures, which may result in toxicity from artificial hair dyes³⁶.

There are no sex-related differences in the prevalence of premature graying³⁷.

In women, gray hair usually begins along the hairline, whereas in men it typically starts in the temporal region and sideburns. Graying first affects the scalp, followed by the facial area, and finally body hair.

Classification

There is no standardized scale for classifying graying. Several have been proposed; one of the most widely used is the Hair Whitening Score (HWS), which is based on the percentage of affected hair³⁸:

- Trace: < 25%
- Mild: 25%–50%
- Moderate: 50%–75%
- Marked: 75%–100%
- Complete: 100%

Differential Diagnosis

It is necessary to distinguish graying from other conditions that cause localized or diffuse hair hypopigmentation (Table 2).

There are reports of abrupt overnight graying, known as sudden canities or Marie Antoinette syndrome, which is related to diffuse alopecia areata. In this condition, pigmented hair is preferentially shed, leaving only hypopigmented hair^{39, 40}.

Treatment

Despite extensive research into the pathophysiology of graying, no satisfactory treatments currently exist (Table 3). Due to high patient demand, vitamin supplements, antioxidants, and minerals such as biotin, zinc, copper, selenium, and calcium pantothenate are frequently used, although their efficacy has not been demonstrated. If deficiencies of vitamin B12, folic acid, vitamin D, or thyroid hormone abnormalities are detected, specific treatment is recommended.

1. Oral Treatment

Calcium pantothenate and para-aminobenzoic acid (PABA) have been used, showing temporary hair repigmentation. Pasricha et al. reported hair repigmentation in 2 patients with PG on 200 mg of calcium pantothenate daily⁴¹. In a subsequent study using the same dose combined with plucking of gray hair, a reduction in the number of gray hairs was observed at a 3-year follow-up⁴².

Conversely, a prospective study evaluating 100 mg of calcium pantothenate + 200 mg of PABA daily in 27 individuals with age-related graying and 6 with PG found that 6% (all with age-related graying) showed marked repigmentation and 21% showed slight improvement after 8 months. However, hair returned to gray after discontinuation of supplementation³⁴. No recent studies support the use of calcium pantothenate or PABA.

2. Topical Treatment

Palmitoyl tetrapeptide-20 and melitane are biomimetic peptides that act as agonists of α -melanocyte-stimulating hormone (α -MSH) and, together with its melanocortin-1 receptor (MC1R), regulate pigment production in hair. Palmitoyl tetrapeptide-20 has been studied in vitro and in 15 men with premature graying, inducing hair pigmentation after 3 months⁴⁴. The use of melitane plus oral supplements has been reported in a 14-year-old woman, with favorable results observed after 6 months⁴⁵.

Latanoprost has been studied in animal models, demonstrating increased follicular melanogenesis and hair growth⁴⁶.

3. Dyes and Colorants

Most patients resort to natural or artificial dyes. Natural dyes contain ingredients such as henna (*Lawsonia alba*), Indian gooseberry (*Emblica officinalis*), and false daisy (*Eclipta alba*), and are generally less irritating and allergenic⁴⁷.

Hair dyes are categorized as permanent, semi-permanent, and temporary (Table 4). Permanent dyes are the most widely used due to their durability and wide color range; however, some components have been associated with allergic reactions, toxicity, carcinogenesis, and hair fiber damage. Temporary dyes do not penetrate the cuticle and are removed with washing^{48, 49}.

4. Emerging Therapies

RT1640 is a compound consisting of cyclosporine A, minoxidil, and RT175, a non-immunosuppressive tacrolimus ligand with regenerative capacity. Cyclosporine A is a calcineurin inhibitor that modulates hair growth by prolonging the anagen phase, activating inactive melanocytes, and blocking catagen. Minoxidil promotes the transition from telogen to anagen, increasing the duration of anagen. Anderson et al. tested this compound in mice and found an 80% increase in melanocyte progenitor cells in the hair bulb, resulting in hair pigmentation even after shaving⁵⁰.

Saha et al. described the use of a placental extract rich in C18:0 sphingolipids, which activates the microphthalmia-associated transcription factor (MITF) to stimulate quiescent melanocyte stem cells in gray-haired mice, resulting in hair pigmentation and suggesting reactivation of melanocyte stem cells⁵¹.

5. Other Drugs

Numerous drugs used for other conditions have been identified as causing hair repigmentation. However, not all patients exposed to these drugs develop pigmentation, and hair color usually returns to baseline after drug discontinuation (Table 5)⁵².

Quality of Life

Hair disorders have a significant impact on quality of life, and PG is no exception. Daulatabad et al. assessed quality of life using the Dermatology Life Quality Index (DLQI) in 57 patients with PG, finding that 65,4% had a significant impact and 19,23% had an extremely significant impact, with high levels of guilt and mood changes⁵³. Mathias et al. reported that among 100 patients with PG, 49% had a significant impact and 22% an extremely significant impact on quality of life⁵⁴. Parihar et al. assessed body image in 295 patients with PG and found poor body image in 54%⁵⁵.

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

Es una revisión bibliográfica práctica sobre el encanecimiento

3. ¿Su trabajo incluye un ensayo clínico?:

No

No es un ensayo sino un trabajo de revisión y actualización

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:

Sí

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Figure 1. Etiopathogenic process of hair graying across phases.

Figure 2. Etiopathogenic mechanism of stress-induced hair graying.

Table 1. Key signaling pathways involved in melanogenesis

Signaling pathway	
Wnt/ β -catenin pathway	Increases transcription of the melanocyte-inducing transcription factor in melanocyte stem cells. <ul style="list-style-type: none"> Increases endothelin receptor type B signaling Promotes migration, proliferation, differentiation, and melanogenesis
MC1R	<ul style="list-style-type: none"> Melanogenesis and melanosome transfer Repair of UV radiation-induced DNA damage
KIT / SCF	Regulation of melanin production
EDN / EDNRB	Melanocyte proliferation and melanogenesis
PI3K / AKT	<ul style="list-style-type: none"> Extracellular release of melanin; prevention of oxidative stress, DNA damage, and reduced cell survival
TGF- β	Main regulator of melanocyte stem cells, causing cell cycle arrest and downregulation of MITF Differentiation of melanocyte stem cells.
MITF	<ul style="list-style-type: none"> Positive regulation of pigmentation Positive regulation of melanosomes Facilitates melanocyte proliferation Antiapoptotic Mitigates DNA damage

Table 2. Differential diagnosis of premature graying

Source: Adapted from Premature graying of hair: A comprehensive review and recent insights. Poonia K, Bhalla M. Indian Dermatol Online J. 2024;15:721–731.

Disease	Characteristics
Localized causes of gray/white hair	
Vitiligo	Achromic patches that may be accompanied by poliosis
Piebaldism	Congenital pigmentary disorder characterized by areas of leukoderma and poliosis, secondary to KIT gene mutation
Waardenburg syndrome	Autosomal dominant disorder characterized by sensorineural deafness, pigmentary abnormalities, and iris heterochromia
Diffuse gray/white hair causes	
Oculocutaneous albinism	Group of autosomal recessive disorders characterized by inability of melanocytes to produce pigment in skin, hair, and eyes
Chediak–Higashi syndrome	Partial oculocutaneous albinism, immunodeficiency, and recurrent bacterial infections
Hermansky–Pudlak syndrome	Oculocutaneous albinism, platelet dysfunction, and lysosomal storage defects
Griscelli syndrome	Partial albinism, photosensitivity, silvery-gray hair, and neurological disorders
Menkes syndrome	Copper metabolism disorder, hypopigmented, sparse, brittle hair with steel-wool appearance, associated with hair shaft abnormalities
Elejalde syndrome	Silvery hair, central nervous system dysfunction including seizures, hypotonia, and intellectual disability
Sudden graying	Alopecia areata, telogen effluvium, and vitiligo

Table 3. Level of evidence for treatments of graying

Treatment	Grade of recommendation	Quality of evidence	Studies
Calcium pantothenate	2A	B	41, 42, 43
PABA + calcium pantothenate	2A	B	43
Palmitoyl tetrapeptide-20	2B	C	44
Melitane 5%	2B	C	45

Table 4. Characteristics of hair dyes

Type of dye	Characteristics	Duration
Temporary	a. High-molecular-weight molecules that remain on the cuticle	Removed after the first washes

Type of dye	Characteristics	Duration
Semi-permanent	a. Small molecules that diffuse into the cortex without binding stably to proteins b. No ammonia or hydrogen peroxide c. Gray hair coverage < 30%	6–12 washes
Demi-permanent	a. Contains 3 agents: developer, coupler, and oxidant; contains ethanolamine or sodium carbonate instead of ammonia b. Hydrogen peroxide 2% c. Gray hair coverage up to 50%	20–25 washes
Permanent	a. Contains 3 agents: developer, coupler, and oxidant b. Penetrate deeply into the cortex, changing hair structure c. Use ammonia and hydrogen peroxide up to 6% d. 100% gray hair coverage	Color fades with washing; requires retouching of new hair growth

Table 5. Drugs causing hair hyper- or hypopigmentation

Depigmentation	Hyperpigmentation / gray hair pigmentation or depigmentation	Hyperpigmentation
Chloroquine	Imatinib	Cyclosporine
Interferon	Valproate	Indinavir
Tamoxifen	Cisplatin	Zidovudine
Hydroxychloroquine	Etretinate	Verapamil
Sunitinib	Acitretin	Para-aminobenzoic acid
Pazopanib		
Phenobarbital		
Phenytoin		
Dasatinib		

TRADUCCIÓN DE FIGURAS

Figura 1

Fase anágena

Fase catágena

Fase telógena

Anágeno temprana

Anagen phase

Catagen phase

Telogen phase

Early anagen

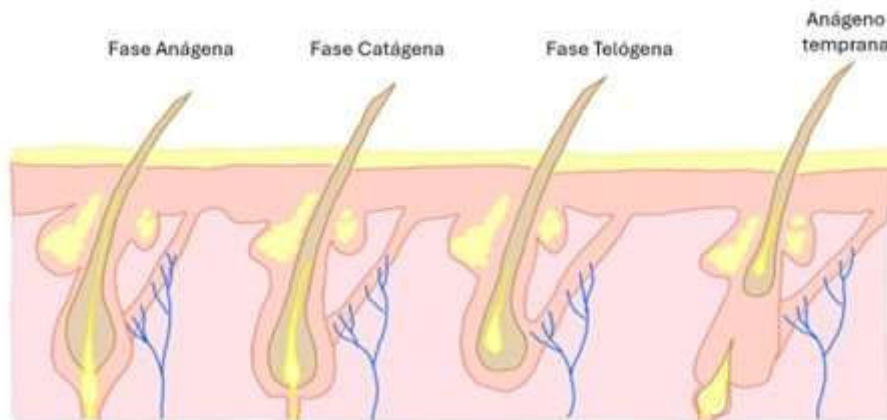


Figura 2

Fase anágena

Migración de células madre

Agotamiento de células madre de melanocitos

Estrés

Liberación de norepinefrina

Encanecimiento

Anagen phase

Migration of stem cells

Depletion of melanocyte stem cells

Stress

Norepinephrine release

Hair graying

