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Alkaptonuria: pathogenesis, clinical manifestations, and management perspectives

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ABSTRACT

Alkaptonuria (AKU) is a rare autosomal recessive disorder caused by mutations in the HGD gene, leading to deficiency of homogentisate 1,2-dioxygenase and accumulation of homogentisic acid (HGA). Oxidized HGA forms ochronotic pigment that deposits in connective tissues, producing progressive damage. The earliest sign is urine darkening. Over time, bluish-brown discoloration of cartilage, spinal stiffness, large-joint arthritis, tendon ruptures, aortic valve disease, and renal calculi may develop. The global prevalence ranges from 1 in 25,000 to 1 in 1,000,000 births, with higher incidence in Slovakia, the Dominican Republic, India, and Jordan. Diagnosis is confirmed by urinary HGA measurement via high-performance liquid chromatography, HGD mutation analysis, and imaging such as MRI, CT, or DEXA. Treatment is mainly supportive, including analgesics, physiotherapy, and surgery for severe joint involvement. Nitisinone therapy significantly reduces urinary HGA and may slow disease progression but requires monitoring of plasma tyrosine levels. Although AKU rarely reduces lifespan, it causes substantial morbidity, highlighting the importance of early detection, multidisciplinary management, and further research into disease-modifying therapies.

Keywords: Arthropathy; Alkaptonuria; Homogentisic acid; Ochronosis; Nitisinone.

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INTRODUCTION

Alkaptonuria (AKU) is an uncommon monogenic autosomal-recessive condition [1]. It results from a deficiency of homogentisate 1,2-dioxygenase (HGD) activity, leading to an inborn error of metabolism [2]. The lack of HGD causes an accumulation of homogentisic acid (HGA), an intermediate in the degradation of tyrosine and phenylalanine. Excess HGA deposits in connective tissues and darkens urine, ultimately causing severe arthritis in affected individuals [1]. Deposition of HGA in collagenous tissues leads to ochronosis and ochronotic osteoarthropathy [3].

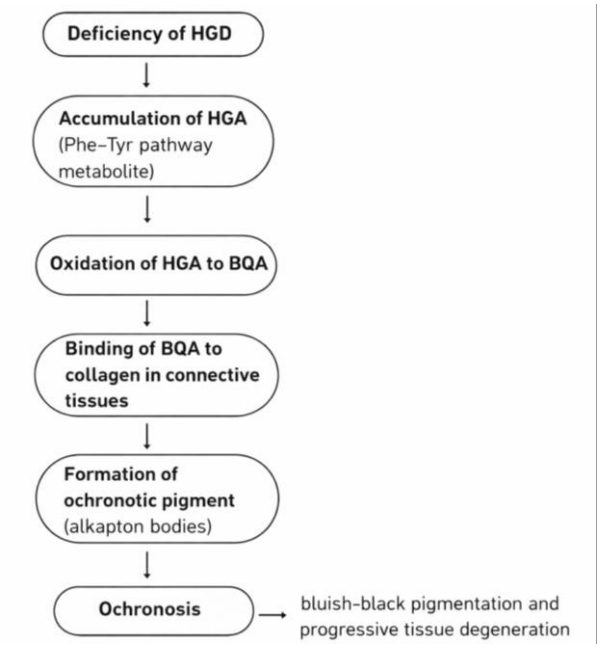
Clinical manifestations are irreversible and have a substantial impact on quality of life, typically appearing from the third decade of life [4]. The pathogenesis and complications of AKU such as spondyloarthropathy, rupture of ligaments, muscles, and tendons, valvular heart disease (including aortic stenosis), and renal stones are primarily due to HGA accumulation [5]. Management includes supportive and palliative measures such as joint replacement, physiotherapy, and analgesics [4]. Although life

expectancy is generally not reduced, the disease significantly impairs quality of life [6].

Epidemiology: Globally, the estimated prevalence of AKU ranges from 1 in 25,000 to 1 in 1,000,000 live births [7]. To date, 950 patients have been identified across 40 countries, with higher prevalence reported in Slovakia, the Dominican Republic, India, and Jordan [8]. Slovakia has the highest documented prevalence approximately 1 in 19,000 based on a national screening program involving over 611,000 residents (including 509,000 newborns), which identified 208 patients, of whom 110 were children [9].

Etiology: AKU is caused by mutations in the *HGD* gene, which disrupt tyrosine metabolism and lead to a deficiency of homogentisate 1,2-dioxygenase (HGD) activity [10]. This deficiency results in the accumulation of homogentisic acid (HGA), which undergoes oxidation to form a polymeric ochronotic pigment [11]. Deposition of this pigment in various tissues causes the systemic manifestations of the disease. AKU is a chronic, progressive metabolic disorder [12].

Pathophysiology: Alkaptonuria (AKU) is a rare autosomal recessive disorder caused by a deficiency of homogentisate 1,2-dioxygenase (HGD) activity [13]. This enzyme defect leads to elevated levels of homogentisic acid (HGA) and its oxidized product, benzoquinone acetic acid (BQA) [13,14]. HGA is a byproduct of the phenylalanine–tyrosine (Phe–Tyr) degradation pathway. In the absence of sufficient HGD activity, the following sequence occurs in **Figure 1.**



HGD – Homogentisate 1,2-dioxygenase**; HGA –** Homogentisic acid**; Phe–Tyr –** Phenylalanine–Tyrosine**; BQA –** Benzoquinone acetic acid

Figure 1: Pathophysiology of Alkaptonuria

The accumulation of ochronotic pigment within collagen-rich tissues, such as cartilage, tendons, and cardiac valves, leads to the characteristic clinical manifestations of AKU [14].

Symptoms: The earliest and most common clinical feature of alkaptonuria is dark brown or black urine, caused by excessive excretion of homogentisic acid (HGA) [15]. Over time, oxidation of HGA leads to the deposition of bluish-brown pigment in connective tissues, a hallmark known as *ochronosis*, which typically affects the spine, large joints, and cartilage [16]. The musculoskeletal manifestation of ochronosis is termed *ochronotic arthropathy* [17].

Chronic accumulation of these abnormal metabolites can result in severe spondylosis, peripheral arthropathy, tendon ruptures, osteoporosis, aortic valve stenosis, and skin discoloration [15]. Cardiovascular ochronosis may present with significant complications such as aortic valve calcification and stenosis, while genitourinary involvement can cause urinary tract obstruction due to ochronotic calculi [18]. Schematic representation of symptoms of alkaptonuria is depicted in **Figure 2.**

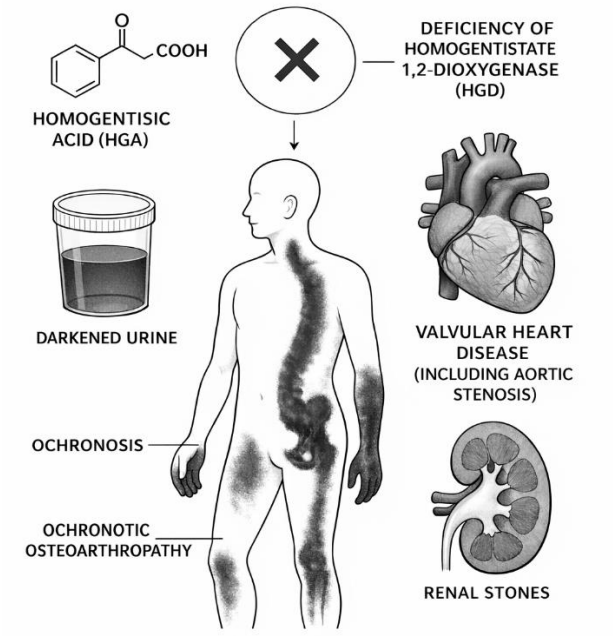


Figure 2: Symptoms of Alkaptonuria

Diagnostic evaluation: The diagnosis of alkaptonuria can be confirmed by quantitative assessment of homogentisic acid (HGA) in urine and *HGD* gene mutation analysis [19]. The following investigations are used in diagnostic evaluation:

DEXA (Dual-energy X-ray absorptiometry) and **CT (Computed Tomography) densitometry** at the femoral neck (FN) and lumbar spine (LS) to assess bone mineral density [20].

High-performance liquid chromatography (HPLC) for sensitive and specific quantification of homogentisic acid in biological fluids [21].

Alkalinization test: Urine is made highly alkaline using potassium or sodium hydroxide and then dropped onto regulation-sensitized photographic paper, which turns coal black upon contact due to rapid oxidation of HGA [22].

Isotope bone scan: Commonly used to assess bone involvement in malignant conditions, but also increasingly applied to evaluate the extent of arthropathy in degenerative diseases such as rheumatoid arthritis and osteoarthritis [23].

Magnetic Resonance Imaging (MRI) of the hip to assess cartilage damage and joint involvement [24].

Treatment:

Pharmacolical treatment: Therapeutic strategies in AKU aim to minimize the damaging effects of the underlying metabolic defect on articular cartilage.

Antioxidant therapy: Vitamin E and N-acetylcysteine (NAC) have been explored for their ability to scavenge free radicals, thereby limiting oxidative damage to joint tissues [24].

Combination antioxidants: NAC in combination with ascorbic acid (ASC) has been investigated as a novel therapeutic approach [25].

Nitisinone therapy: Nitisinone, administered at 10 mg daily, has been shown to be well tolerated and effective in reducing urinary excretion of HGA. Treatment with nitisinone decreases ochronosis and improves clinical signs, indicating slower disease progression [26].

Anti-inflammatory and antioxidant combination: Low-dose methotrexate (MTX), a commonly used anti-inflammatory drug, combined with antioxidant molecules, has demonstrated the ability to reduce ochronotic pigment deposition and amyloid fibril formation [27].

Monitoring parameter: Monitoring of the tyrosine metabolic pathway including measurement of plasma metabolites such as tyrosine is essential to assess efficacy, detect potential toxicity, and ensure safety during and after nitisinone therapy [28].

Surgical procedure: In cases of ochronotic arthropathy with advanced degenerative changes, surgical intervention may be required. Bilateral total shoulder arthroplasty has been successfully performed to manage severe joint involvement in AKU patients [29].

CONCLUSION

Alkaptonuria (AKU) is a rare, autosomal recessive metabolic disorder resulting from homogentisate 1,2-dioxygenase deficiency, leading to progressive accumulation of homogentisic acid and subsequent ochronotic pigment deposition in connective tissues. Although life expectancy is generally unaffected, the disease imposes a substantial burden through irreversible musculoskeletal, cardiovascular, and renal complications that significantly impair quality of life. Early recognition through biochemical assays and genetic testing is crucial for timely intervention. While current management remains largely supportive, emerging therapies such as nitisinone and antioxidant combinations offer promise in slowing disease progression. Continued research, long-term monitoring, and multidisciplinary care are essential to optimize outcomes and improve quality of life for individuals affected by AKU.

Future research perspectives

Recent advances in biomedical science suggest that the future management of rare metabolic disorders such as alkaptonuria may benefit from innovations in immunology, precision medicine, regenerative therapies, and digital health technologies. Emerging approaches that integrate molecular diagnostics, targeted therapies, and patient-specific treatment strategies are increasingly transforming the management of complex chronic diseases. These advancements have already demonstrated promising outcomes in immune-mediated and inflammatory disorders, where personalized therapeutic approaches allow for improved treatment efficacy and safety profiles [30].

Continued investigation into molecular pathways involved in metabolic diseases will further facilitate the development of disease-modifying therapies and precision-based treatment strategies.

Rare inherited metabolic disorders share several common molecular mechanisms involving enzyme deficiencies, metabolite accumulation, and progressive multisystem complications. Insights gained from research in other metabolic diseases have contributed to improved understanding of disease mechanisms and the development of targeted therapeutic strategies, which may also inform future management approaches for alkaptonuria [31]. Furthermore, multidisciplinary management approaches incorporating pharmacological innovations, digital health monitoring, and personalized medicine frameworks are expected to improve long-term clinical outcomes in patients with rare disorders. Such integrated strategies have already shown significant potential in the management of chronic respiratory and inflammatory diseases, highlighting their possible relevance in future therapeutic models for alkaptonuria and related metabolic conditions [32]. Insights obtained from studies on other genetic skeletal disorders have improved understanding of disease mechanisms, clinical progression, and long-term management strategies. Comparative research in hereditary musculoskeletal conditions may contribute to improved therapeutic approaches and multidisciplinary management strategies for patients with alkaptonuria [33].

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All authors contributed equally in this research work.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this work.

Ethical Approval

Ethical approval was not required for this study, as it is a systematic review based exclusively on previously published data.

Informed Consent

Informed consent was not applicable, as no individual patient data were collected or analyzed in this study.

Data Availability Statement

All data analyzed in this study are included in the published articles identified through the systematic review and are available within the manuscript and its supplementary materials.

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