JRSSEM 2025, Vol. 05, No. 04
E-ISSN: 2807 - 6311, P-ISSN: 2807 - 6494

Molecular and Nutritional Review of Phenylketonuria: Implications for Clinical Management

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Abstract.
Phenylketonuria (*PKU*) is an autosomal recessive inborn error of metabolism caused by mutations in the phenylalanine hydroxylase (*PAH*) gene, disrupting the conversion of phenylalanine to tyrosine and leading to the accumulation of neurotoxic metabolites. This review aims to synthesize the molecular genetics, clinical consequences, and comprehensive management strategies of *PKU*, with a specific focus on implications for improving clinical practice and public health policy, particularly in underserved regions like Indonesia. Employing comprehensive literature review methodology, we analyzed recent scientific publications, clinical guidelines, and meta-analyses to consolidate current evidence. The results delineate that the cornerstone of management remains a lifelong, low-phenylalanine diet, supported by phenylalanine-free medical formulas and an evolving landscape of pharmacological therapies, including BH4 supplementation for responsive patients and novel options like pegvaliase. Crucially, the findings highlight a critical gap in epidemiological data and clinical infrastructure in Indonesia, underscoring the urgent need for the implementation of newborn screening programs and the development of locally relevant, evidence-based guidelines. This review concludes that integrating systematic screening, expanding local genetic research, and optimizing combined nutritional and molecular therapies are essential strategies to prevent irreversible neurological damage, improve long-term outcomes, and enhance the quality of life for individuals with *PKU* globally and in the Indonesian context.

Keywords: Phenylketonuria; Phenylalanine; Nutrition; Biomolecular.

INTRODUCTION

Phenylketonuria (PKU) is an inborn error of metabolism caused by mutations in the phenylalanine hydroxylase (PAH) gene (Vockley et al., 2014), which disrupts the conversion of phenylalanine to tyrosine (van Spronsen et al., 2021). This enzymatic deficiency leads to the accumulation of phenylalanine and its toxic metabolites in the blood and tissues (Longo, 2016), which, if left untreated, can lead to severe nervous system developmental disorders and systemic complications (Waisbren et al., 2018). Advances in molecular genetics and newborn screening have significantly improved early detection and management in many countries (Kremer et al., 2020), preventing irreversible neurological damage through appropriate nutritional and pharmacological interventions (Çakar et al., 2023; Gupta et al., 2022).

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism caused by mutations in the phenylalanine hydroxylase (PAH) gene (Bilen et al., 2022), which disrupts the conversion of phenylalanine to tyrosine (Hu et al., 2020). This enzymatic deficiency leads to the accumulation of phenylalanine and its toxic metabolites in the blood and tissues (Fiori et al., 2017). If left untreated, PKU can result in severe intellectual disability, neurological dysfunction, and systemic complications (Christ et al., 2020). Globally, PKU affects

approximately 1 in 10,000 to 1 in 24,000 live births, with significant regional variation (Hillert et al., 2017). In Europe, the prevalence is estimated at 1 in 10,000, while in Turkey, it can be as high as 1 in 4,000 due to high consanguinity rates (Çelik et al., 2021). In Asia, reported incidence ranges from 1 in 15,000 to 1 in 100,000 (Zhang et al., 2020). Despite these global figures, the epidemiological profile of PKU in Indonesia remains largely undefined due to the absence of a nationwide newborn screening program and limited molecular diagnostic capabilities (Kementerian Kesehatan RI, 2021). The lack of systematic data collection has resulted in an underestimation of the disease burden, hindering effective public health planning and resource allocation.

The absence of reliable national quantitative data on PKU in Indonesia represents a critical gap in both clinical and public health domains (Blau et al., 2018). Without local case studies or population-based genetic data, it is challenging to estimate the true prevalence, carrier frequency, or mutational spectrum of PKU in the Indonesian population (Narayanan et al., 2019). This data gap has profound implications for public policy, including the lack of integrated newborn screening (Therrell et al., 2017), insufficient training for healthcare providers (McCandless et al., 2020), and limited access to specialized nutritional and pharmacological therapies (van Wegberg et al., 2017). The failure to implement early detection and intervention strategies perpetuates preventable disabilities (Al Hafid & Christodoulou, 2015), increases long-term healthcare costs (Gentile et al., 2020), and exacerbates social and economic disparities for affected individuals and their families (Cazzorla et al., 2018).

Information on the epidemiological profile of PKU in Indonesia remains largely undefined (Limato et al., 2022; Syairaji et al., 2024). The absence of a newborn screening (NSSC) program and the limited availability of molecular diagnostic data contribute to underestimation of disease prevalence and hinder early therapeutic intervention. This data gap poses a critical challenge for public health planning, particularly given the lifelong nutritional and clinical management requirements of PKU. 3

The academic and practical urgency of addressing PKU in Indonesia cannot be overstated. From a clinical perspective, delayed diagnosis leads to irreversible neurological damage, placing a lifelong burden on individuals, families, and the healthcare system. From a public health standpoint, the absence of PKU in national health priorities reflects a broader neglect of rare genetic disorders, despite their cumulative impact on population health. Furthermore, the nutritional management of PKU requires lifelong adherence to a strict low-phenylalanine diet, which poses significant cultural, economic, and psychosocial challenges in the Indonesian context. There is an urgent need to develop culturally adapted dietary guidelines, affordable medical formulas, and sustainable care models tailored to local realities.

This review offers significant novelty by focusing specifically on the underexplored context of PKU in Indonesia. While extensive research has been conducted on PKU in Western populations, few studies have addressed the genetic, epidemiological, and clinical nuances of PKU in Southeast Asia, particularly in Indonesia. This review synthesizes global evidence while highlighting the critical gaps in local knowledge and infrastructure. It also proposes a framework for integrating PKU care into the Indonesian healthcare system, including the potential implementation of targeted newborn screening, the development of a local PAH variant database, and the formulation of context-specific nutritional and therapeutic guidelines.

The primary aim of this review is to provide a comprehensive analysis of the molecular

mechanisms, nutritional management, and evolving therapies for PKU, with a specific focus on implications for clinical practice and public health policy in Indonesia. By consolidating current evidence and identifying local research priorities, this review seeks to support the development of evidence-based strategies for early detection, lifelong management, and improved quality of life for individuals with PKU. Ultimately, this work aims to contribute to the establishment of a national PKU registry, inform policy decisions regarding newborn screening, and promote multidisciplinary collaboration among clinicians, researchers, and policymakers to address this neglected yet preventable cause of disability.

MATERIALS AND METHOD

The epidemiological profile of *PKU* in Indonesia remained unclear due to the absence of specific newborn screening and limited national data. While global estimates indicated a prevalence of approximately 1 in 24,000 live births, the exact figure for Indonesia was unknown. Given the significant consequences of intellectual disability caused by untreated *PKU*, this data gap compromised public health planning and underscored the urgent need to integrate *PKU* into newborn screening programs.

The *PAH* gene is located on the long arm of chromosome 12 (12q23.2) and spans approximately 90 kilobases of genomic DNA. It comprises 13 exons and 12 introns, encoding a polypeptide of 452 amino acids. Over 1,000 pathogenic variants in the *PAH* gene have been documented in the PAHvdb (PAH locus database). Typically, individuals with two severe mutations exhibited classic *PKU* with very high blood phenylalanine levels (>1,200 μmol/L), whereas those with at least one milder mutation displayed variant or mild forms of *PKU*. Mutations ranged from null types causing complete loss of function to those allowing residual enzyme activity.

PKU followed an autosomal recessive inheritance pattern, requiring both copies of the *PAH* gene—from each parent—to carry pathogenic variants for the disorder to manifest. Parents carrying one defective allele were asymptomatic carriers who could pass the mutation to offspring. When two carriers had a child, the probability of inheriting both defective alleles and developing *PKU* was 25%, a 50% chance existed the child would be a healthy carrier, and 25% the child would inherit two normal alleles.

The pathogenesis originated from mutations in the *PAH* gene causing partial or complete deficiency of enzyme activity. The *PAH* enzyme hydroxylated phenylalanine into tyrosine, which then served as a precursor for neurotransmitters (dopamine, norepinephrine, epinephrine) and melanin synthesis. The enzyme required tetrahydrobiopterin (BH_4) as a cofactor, oxygen (O_2), and iron (Fe^{2+}) for catalytic function. Mutations could impair any of these domains, reducing or eliminating enzyme activity. When *PAH* function was deficient, phenylalanine accumulated in the blood and tissues, with plasma levels exceeding 1,200 μmol/L—up to 20 times normal concentrations.

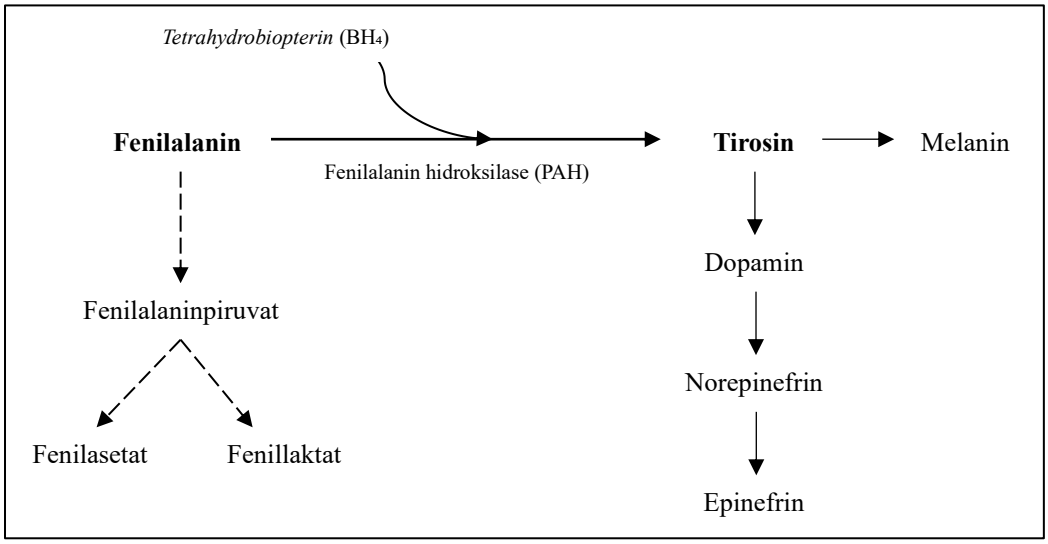
Reduced or lost *PAH* activity disrupted phenylalanine metabolism, leading excess phenylalanine to be transaminated to phenylpyruvate by aminotransferases using α-ketoglutarate as a co-substrate. Phenylpyruvate was further metabolized into phenyllactate and phenylacetate, collectively known as phenylketones. These metabolites accumulated in blood, cerebrospinal fluid, and urine, causing a characteristic “mousy” odor.

The metabolic imbalance also reduced downstream products; decreased tyrosine

synthesis impaired biosynthesis of catecholamine neurotransmitters and melanin. Lower dopamine and norepinephrine levels contributed to neurological dysfunction, while reduced melanin caused lighter hair, skin, and eye color in *PKU* individuals.

The brain absorbed phenylalanine and large neutral amino acids (LNAAs)—tyrosine, tryptophan, leucine, isoleucine, and valine—via the same transporter. Elevated plasma phenylalanine competitively inhibited LNAA brain uptake, reducing tyrosine and tryptophan availability, precursors for dopamine and serotonin. This led to deficient neurotransmitter synthesis, altered neuronal signaling, cognitive impairment, and emotional instability.

Though the central nervous system was most affected, *PKU* also impacted systemic metabolism. Studies linked it to lipid profile alterations, decreased bone density, and impaired endothelial function, likely due to chronic oxidative stress and reduced catecholamine levels. These systemic effects emphasized the necessity of lifelong metabolic control beyond early childhood.



RESULTS AND DISCUSSION

Early Diagnosis

With advances in molecular genetics, carrier detection has become a critical component of PKU prevention programs, especially in populations with a higher carrier frequency. Screening involves molecular examination of the PAH gene mutation in asymptomatic individuals with a family history of PKU. Prenatal diagnosis can be performed through non-invasive prenatal testing (NIPT) using cell-free fetal DNA in maternal plasma. Postnatal diagnosis is performed by newborn screening 24 to 72 hours after birth. Blood samples are obtained via heel prick and placed on special filter paper cards (Guthrie cards).

Clinical Nutrition and Current Therapy

Principles of Nutrition Therapy

The cornerstone of nutrition therapy for individuals with PKU is a low-phenylalanine diet, which should be initiated as soon as possible after diagnosis. This diet involves restricting natural protein intake, particularly from foods high in phenylalanine, such as meat, dairy products, nuts, and legumes. Supplementation with a phenylalanine-free medical formula

containing a balanced blend of essential amino acids, vitamins, and minerals is also necessary. Intake of fruits, vegetables, and special low-protein foods is controlled to maintain normal energy and micronutrient levels. Recommended target plasma phenylalanine levels range from 120–360 μmol/L in children and 120–600 μmol/L in adults, although specific targets may vary across international protocols.

Nutrition management, which requires lifelong adherence, presents a psychological challenge for individuals with PKU. Boredom with the taste of formula, limited food choices, and the high cost of low-phenylalanine foods often lead to discontinuation of nutrition therapy. Dietary behavioral counseling and supportive community involvement can maintain long-term adherence.

Macronutrient Distribution and Energy Requirements

Nutrition therapy should be tailored to monitoring plasma phenylalanine levels and regularly guided by a clinical nutritionist. Macronutrient distribution and energy requirements should be aligned with the average dietary reference values recommended for a healthy population. A balanced nutritional intake aims to avoid catabolism or deficiencies, while also preventing excess nutrients that can lead to overnutrition or toxicity.

Protein requirements generally range from 1.1–1.3 g/kg/day, depending on age, growth rate, and metabolic condition. Approximately 80–90% of total protein should come from phenylalanine-free or low-phenylalanine medical formulas, with the remainder coming from carefully calculated natural food sources. Infants and children require higher protein densities to support proper growth. The use of glycomacropeptide (GMP)-based protein substitutes, which naturally contain very low levels of phenylalanine, offers better palatability and satiety than synthetic amino acid formulas.

Carbohydrates should contribute approximately 45–60% of total daily energy intake, with a primary focus on complex carbohydrate sources such as fruits, vegetables, and specialty low-protein products to help maintain stable blood glucose levels and reduce the risk of muscle catabolism. Simple sugars such as sucrose or fructose can be added to improve food palatability, but intake should remain moderate to minimize the risk of hyperglycemia and excess weight gain.

Fat should account for approximately 25–35% of total caloric intake, with an emphasis on essential fatty acids such as linoleic acid and α-linolenic acid, as well as long-chain polyunsaturated fatty acids such as DHA and EPA to support neurological development and cardiovascular function. DHA supplementation is particularly important for children, pregnant women, and breastfeeding mothers on low-protein diets, as standard phenylalanine-free formulas generally contain limited lipid fractions and do not provide adequate amounts of PUFAs.

CONCLUSION

This review has successfully synthesized the molecular basis, clinical implications, and management strategies for Phenylketonuria (PKU), fulfilling its objective to consolidate global evidence for optimizing clinical care. The analysis confirms that successful PKU management hinges fundamentally on early diagnosis via newborn screening and lifelong adherence to a strict low-phenylalanine diet, supported by specialized nutritional formulas and evolving

pharmacological therapies. To achieve tangible progress in underserved regions such as Indonesia, a concerted effort is required to integrate PKU screening into national public health policy, expand local genetic epidemiological research to identify population-specific PAH mutations, and optimize combined nutritional and molecular therapeutic approaches. For future research, critical priorities include determining the national disease prevalence, developing culturally adapted and affordable dietary solutions, and evaluating the real-world applicability of novel therapies like pegvaliase and gene therapy within the local healthcare context. Addressing these goals is expected to significantly improve the quality of life for affected individuals, prevent long-term neurological and systemic sequelae, and alleviate the overall burden of PKU on families and the healthcare system.

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