# *Phenylketonuria (Pku): Food Controlled Genetic Disease*

***Mine ERGÜVEN***[1]

**Abstract**
Phenylketonuria (PKU) is an autosomal recessive inborn disorder of the metabolism that occurs due to mutations in the gene that codifies enzyme called the phenylalanine hydroxylase (PAH) which is responsible for converting dietary phenylalanine (Phe) into tyrosine (Tyr) in the liver. This results in persistent elevated Phe blood and tissue concentrations, with potential toxic effects, particularly for the developmental brain. Although some new therapeutic approaches have been tested in order to improve the quality of life of PKU patients (as neutral amino acids, tetrahydrobiopterin, Phe ammonia lyase or gene therapy), dietary restriction throughout an individual's lifetime is a general consensus for the current standard of care and primary treatment for PKU. Nutritional guidelines and statements vary between countries, but low protein and Phe-restricted diet are common. However, PKU patients' individual tolerances are determinant for the treatment. The content of dietary treatment was protein substitutes (Phe-free AA mixtures) and a wide range of low protein products (like bread, biscuits, cereals, pasta, flour, the substitutes of milk, cheese and egg.. etc. ) and strictly controlled amounts of natural foods, essentially fruits, vegetables and other natural foods or food products with low protein content. Medicinal food are also included in the diet, however high tyr content, the lack of some diet substitutes make them unpreferred. The aim of this review was to discuss the some concerns about the dietary treatment of PKU.

***Keywords*** Phenylketonuria, Diet, Phenylalanine, Tyrosine, Medicinal Food

Phenylketonuria (PKU) was first described in 1934 by Asbörn Föling. It is an autosomal recessive inborn error of the metabolism that occurs due to mutations in the gene that codifies the phenylalanine hydroxylase (PAH) which is responsible for converting dietary phenylalanine (Phe) into tyrosine (Tyr) in the liver. The location and type of mutation within the gene determine the severity of the phenotype. A decrease of PAH concentration and/or lower enzyme activity results in persistent elevated Phe blood and tissue concentrations, with potential toxic effects, particularly for the developmental brain [1-3] Several studies have specifically examined the relationship between genotype and biochemical phenotype, and the corresponding dietary Phe tolerance and genotype–phenotype correlations have been examined in different populations [4]. For some ethnic populations, informative mutations have been collected and further classified into the four categories of classical, moderate, mild PKU, or mild hyperphenylalaninemia (HPA) using blood Phe concentrations. In addition, several reports classify PKU based on individuals' reported dietary Phe intake [4].

Typical target blood Phe levels of 120–360 μmol/L. There is no evidence that blood

[1] *Istanbul Aydın University, Faculty of Engineering, Department of Food Engineering, mineerguven@aydin.edu.tr*

Phe control in adolescents and adults can be relaxed, especially for women of childbearing age. Tyr levels are also routinely measured and should be between 50 and 100 μmol/L. Because low plasma Tyr concentrations have been determined in some individuals with PKU, not only tyr but alo other amino acid concentrations should also be in the normal range [4].

Early diagnosis in the neonatal period, with a screening program and prompt dietary treatment are essential to prevent severe mental retardation and to achieve a good patient prognosis [5]. Indeed, patients with late diagnose and/or poor metabolic control tend to evidence signs of cognitive dysfunction, namely, developmental delay, progressive intellectual impairment, seizures, attention deficit/hyperactivity disorder, decreased autonomy, behavioral problems, such as aggression, anxiety or social isolation [6]. Other clinical signs such as a mousy odour, eczema, reduced pigmentation, reduced growth and microcephaly were also been determined [7].
Although some new therapeutic approaches have been studied in order to improve the quality of life of PKU patients (as neutral amino acids, glycomacropeptide, tetrahydrobiopterin, Phe ammonia lyase or gene therapy) [8], dietary restriction throughout an individual's lifetime is a general consensus for the current standard of care and primary treatment for PKU [4, 5].
Nutritional guidelines and statements are not same between countries [6], but low protein and Phe-restricted diet is unchangeable rule as well as the need to continue the treatment throughout life. Individuals with PKU need to be individually assessed to provide recommendations to meet total energy needs. Adequate energy must be provided for individuals with PKU during illness to limit catabolism resulting in elevated blood Phe concentrations [4]. In order to limit the intake of Phe, dietary management of PKU patients restrict natural-protein food [9]. Therefore, based on nutritional recommendations due to gender, age, weight, family history and on PKU patients' individual tolerances, dietary treatment includes protein substitutes (Phe-free AA mixtures) and a wide range of low protein products (like bread, biscuits, cereals, pasta, flour, milk substitutes, cheese substitutes, egg substitutes, soups, candies, amongst others) to make up the energy needs of the PKU patients. In addition to these, the diet also consists of strictly controlled amounts of natural foods, essentially fruits, vegetables and other natural foods or food products with low protein content [6, 9,10].

Dietary treatment for PKU also includes the consumption of medical foods. These foods include Phe-free amino acid-based formulas that also contain energy, vitamins, and minerals; products that use GMP (a protein derived from whey) as the protein source; and specialized products that have been modified to be low in protein. Products modified to be low in protein are necessary to provide adequate energy, satiety, and variety beyond that provided by amino acid-based medical foods [4,11-13].

Medical food formulation based on requirements has focused on improving palatability, packaging, and product type (e.g., sport drinks ). Products with lower volume or caloric density modular products using amino acids without added fat, carbohydrates, or micronutrients, and newer products utilizing intact protein sources naturally low in Phe have been developed. Although these products focus on suplying energy and growth development, some are nutritionally incomplete, which could compromise nutritional status if not correctly utilized. For example GMP, a natural

protein source that contains minimal Phe, has insufficient amounts of histidine, leucine, tryptophan. In addition, thr and isoleucine content is two to three times higher than in other natural protein sources [4, 11-13] , which can result in the collapse of PKU. The balance in content of all proteins is necassary .In addition, their content of additives (eg. sweeteners, some sugar..etc) also make them dangerous that other diseases as diabetes mellitus can be occured, PKU patient who use them should be regularly monitorized.

In order to increase the quality of life is to eat more normal sources of protein. The targets of dietary treatment protocols used to determine Phe tolerance are to ascertain how much natural protein can be increased in the diet, if and how much medical food may be decreased, and whether the use of foods modified to be low in protein is still needed. The best approach for determining increased dietary Phe tolerance is to add incrementally a natural protein (e.g., powdered milk) that can be easily calculated, measured, and adjusted without significantly affecting the patient's usual diet. This can then be converted to dietary protein if the Phe levels remain in the target range [4, 8, 9, 12]. A computer-based diet analysis tool for use by metabolic dietitians is available at Genetic Metabolic Dietitians International web site as http://GMDI.org which can be used in conjunction with blood Phe levels to adjust Phe and Tyr intake, macro- and micronutrients, fluids, and meal pattern.

In conclusion individualized treatment is necessary to maximize nutritional status, cognitive outcomes, behavior, mood, and quality of life. Regular monitoring of blood Phe and Tyr and nutritional biomarkers to evaluate treatment adequacy and adherence is very necessary. Blood Phe concentrations along with assessment of corresponding actual Phe intake is critical to determine Phe tolerance. Phe tolerance and genotype can lead to the design of effective treatment strategies. Additional treatment options should be individually evaluated, especially for "off-diet" individuals or others who do not adhere to treatment.

**Conflict of interest**

None decleared.

## REFERENCES

[1] Dokoupil K, Gokmen-Ozel H, Lammardo AM, Motzfeldt K, Robert M, Rocha JC, van Rijn M, Ahring K, Bélanger-Quintana A, MacDonald A., "Optimising growth in phenylketonuria: current state of the clinical evidence base.", Clin Nutr. vol. 31, pp.16-21, 2012.

[2] Bélanger-Quintana A, Burlina A, Harding CO, Muntau AC, "Up to date knowledge on different treatment strategies for phenylketonuria.", Mol Genet Metab. Vol 104 Suppl:S, pp. 19-25, 2011.

[3] Belanger-Quintana A, Dokoupil K, Gokmen-Ozel H, Lammardo AM, MacDonald A, Motzfeldt K, Nowacka M, Robert M, van Rijn M, Ahring K. "Diet in phenylketonuria: a snapshot of special dietary costs and reimbursement systems in 10 international centers.", Mol Genet Metab.,vol 105, pp 390-4, 2012

[4] Camp KM, Parisi MA, Acosta PB, Berry GT, Bilder DA, Blau N, Bodamer OA, Brosco JP, Brown CS, Burlina AB, et al. Phenylketonuria

Scientific Review Conference: state of the science and future research needs. Mol Genet Metab. vol 112, pp 87-122, 2014.

[5] Pimentel FB, Alves RC, Costa AS, Torres D, Almeida MF, Oliveira MB, "Phenylketonuria: protein content and amino acids profile of dishes for phenylketonuric patients. The relevance of phenylalanine.", Food Chem. vol 149, pp.144-50, 2014.

[6] Demirkol M, Giżewska M, Giovannini M, Walter J, "Follow up of phenylketonuria patients.", Mol Genet Metab., vol 104 Suppl:S, pp 31-9, 2011.

[7] Rocha JC, Martel F, "Large neutral amino acids supplementation in phenylketonuric patients.", J Inherit Metab Dis. vol 32, pp. 472-80, 2009.

[8] Blau N, van Spronsen FJ, Levy HL, "Phenylketonuria", Lancet, vol 376, pp.1417-27, 2010.

[9] Feillet F, Agostoni C, "Nutritional issues in treating phenylketonuria", J Inherit Metab Dis., vol 33, pp. 659-64, 2010.

[10] Weetch E, Macdonald A, "The determination of phenylalanine content of foods suitable for phenylketonuria.", J Hum Nutr Diet.,vol 19, pp. 229-36, 2006.

[11] Zannini E, "Technological challenges and strategies for developing low-protein/protein-free cereal foods for the dietotherapic treatment.", G Ital Nefrol., vol 31, pp. pii: gin/31.2.15, 2014.

[12] Ney DM, Blank RD, Hansen KE, "Advances in the nutritional and pharmacological management of phenylketonuria.", Curr Opin Clin Nutr Metab Care., vol 17, pp. 61-8, 2014.

[13] van Calcar SC, Ney DM, "Food products made with glycomacropeptide, a low-phenylalanine whey protein, provide a new alternative to amino Acid-based medical foods for nutrition management of phenylketonuria." J Acad Nutr Diet., vol. 112, pp. 1201-10, 2012