# LC-PUFA Supplementation in Phenylketonuria Patients

Subjects: Nutrition & Dietetics

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Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism. The treatment of PKU consists of a phenylalanine-free diet, which limits the intake of natural proteins of high biological value.

arachidonic acid | cognitive function | docosahexaenoic acid | long-chain polyunsaturated fatty acids | phenylketonuria | visual function

## 1. Introduction

Phenylketonuria (PKU; OMIM 261600) is an inborn error of phenylalanine (Phe) metabolism caused by an inherited deficiency in L-phenylalanine-4-hydroxylase (PAH; EC 1.14.16.1) activity, leading to elevated levels of Phe in body fluids [1]. Of patients with high phenylalanine concentrations, 98% have a defect in PAH and 1–2% in tetrahydrobiopterin metabolism. Children with PKU diagnosed by newborn screening who begin dietary treatment during the neonatal period usually show normal neurological development [2][3]. However, these patients may have lower intelligence quotients [4] and exhibit mild neuropsychological disturbances including impaired motor skills, visual function, attention, inhibition, and memory [5][6], especially when compared with non-phenylketonuric siblings [7] and healthy individuals [8][9]. PKU treatment consists of lifelong restriction of Phe intake by limiting the amount of natural protein in the diet, combined with administration of a Phe-free amino-acid mixture [10]. More recently, a synthetic form of tetrahydrobiopterin (6R-BH4) has been used to treat selected patients who have moderate forms of PKU and respond to the BH4 loading test [11][12]. Owing to a tendency to exclude protein-rich animal food from their diet, micronutrient deficiencies are common in PKU patients [13][14][15].

Meat and fish are the main sources of long-chain polyunsaturated fatty acids (LC-PUFA) in humans, and although they are produced endogenously, dietary intake is the key determinant of LC-PUFA levels [16]. Docosahexaenoic acid (DHA) and arachidonic acid (AA) are the most important LC-PUFAs of the *n*-3 and *n*-6 series, respectively [17]. Both are structural components of cell membranes and influence their biological functions, including enzymatic activity, transport through ion channels, and signal transduction [18], especially in the nervous system and the retina [19]. Incorporation of DHA and AA in these tissues during the pre- and postnatal periods has been correlated with visual, cognitive, and motor functions in humans [20][21][22].

The low-Phe diet of PKU patients has been linked to insufficient blood levels of LC-PUFAs, which may contribute to the mild neurological, cognitive, and visual alterations described in these patients [23]. However, to date no

conclusive evidence supports a link between the PKU diet, the LC-PUFA profile and the clinical status of PKU patients [24].

## 2. Current Insights on LC-PUFA Supplementation in Phenylketonuria Patients

This systematic review of controlled trials regarding LC-PUFA supplementation in children and adults with PKU reveals that the addition of DHA at doses ≥10 mg/kg/day to the patient's Phe-restricted diet decreases VEP latencies. However, no conclusive evidence supports a relationship between LC-PUFA supplementation and neurocognitive outcomes in these patients.

DHA and AA are the most important LC-PUFAs of the *n*-3 and *n*-6 series, respectively. These key structural components of neuronal cell membranes are of crucial importance for brain development and retinal function [25]. In randomized clinical trials, LC-PUFA supplementation is associated with improved visual and cognitive maturation in full-term and, in particular, preterm infants [26][27][28]. These outcomes in preterm infants may be linked to the greater predisposition of these children to LC-PUFA deficiency due to fetal accretion of DHA (which usually occurs during the third trimester), an inability to convert precursor fatty acids to DHA, and low postnatal DHA intake [29].

PKU patients are another population at risk of LC-PUFA deficiency; the typical Phe-restricted diets of these patients provide low amounts of animal products, which are the main source of LC-PUFAs [30][31]. Moreover, excess Phe is catabolized to phenylpyruvate and phenyllactate, which are reported to inhibit endogenous synthesis of DHA and AA [32]. A 2013 systematic review and meta-analysis of nine case control studies and six randomized controlled trials concluded that PKU patients have significantly lower levels of both DHA and AA in all biomarkers studied than healthy controls [24]. In line with this suboptimal LC-PUFA status in PKU patients, studies of children with amino acid metabolism disorders have described reduced LC-PUFA intake (a consequence of dietary protein restriction) and lower plasma and erythrocyte membrane concentrations of DHA than healthy controls [33][34][35]. The results of studies of AA status in these patients are inconclusive (ranging from normal to reduced), suggesting that endogenous synthesis may be sufficient to ensure adequate AA status in some cases [36].

The findings of this systematic review indicate that DHA supplementation in PKU patients significantly increases DHA levels in plasma and/or erythrocyte membranes [37][38][39][40][41][42][43][44][45]. It should be noted that erythrocyte fatty acid composition yields more information regarding long-term LC-PUFA status and is less influenced by fasting, appearing to be a more valuable biomarker [46][47]. While the most commonly administered dose of DHA was 10–15 mg/kg/day, significant increases in DHA levels were observed even with lower doses (0.1–7 mg/kg/day) [37]. There are insufficient data to define an optimal LC-PUFA supplementation dose for PKU patients of different age groups, and optimal DHA intake in infants and children remains a topic of debate according to both the ESPGHAN Committee on Nutrition and The European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies (NDA). Despite the lack of appropriate data on which to base dietary reference values for pediatric patients, the aforementioned organizations have proposed an intake of 100 mg/day for patients aged 6–24 months and 250 mg/day for those aged 2 years and older [48].

VEP testing was conducted to assess central nervous system (CNS) function in four of the studies included in this review [37][41][43][44]. VEP is widely used in studies of neural maturation as it provides a sensitive means of assessing the function of a major CNS pathway. P100 wave latency is considered the most reliable clinical indicator, as is the variable least affected by technical factors and the degree of patient cooperation [49]. Longer VEP latencies, which are observed in PKU patients not receiving LC-PUFA supplementation [49], indicate a lower speed of information processing from the retina to the visual cortex. It should be noted that the controlled trials (CTs) and randomized controlled trials (RCTs) in which shorter P100 wave latencies were observed after intervention were those in which the patients received higher doses of DHA (10–15 mg/kg/day) [43][44]. In the two RCTs [37][41] that reported no differences in VEP latencies after LC-PUFA supplementation, patients received lower (0.1–7 mg/kg/day) or uncontrolled doses (i.e., a LC-PUFA-supplemented, Phe-free formula) of DHA. In the latter study [41], higher levels of DHA in erythrocyte membranes were significantly correlated with a shorter P100 wave latency after adjustment for age. This observation suggests that the LC-PUFA intake of these patients was irregular and, in many cases, insufficient to alter the clinical outcome.

None of the studies included in this review specifically evaluated retinal function. However, a 2013 study [50] assessed visual function in PKU patients using a comprehensive ophthalmological test battery. Electroretinography (ERG), which allows for objective measurement of retinal function, revealed that PKU patients showed abnormalities in scotopic and photopic ERG amplitudes and latencies not observed in healthy individuals. It should be noted that this pattern of ERG alterations has also been described in animal models of LC-PUFA depletion and is likely related to abnormal DHA metabolism in photoreceptor membranes [51][52][53].

Evidence suggests that LC-PUFA supplementation may improve neurocognitive function, including motor skills [39], in PKU patients. Children with early-treated PKU can present structural alterations in cerebral white matter myelin [54][55][56] that may be associated with high Phe levels, but also with low DHA concentrations. However, because beneficial effects were reported in only one CT [39], and given the considerable variability across the studies included in this review in terms of the dose used, form of supplementation, functional outcome measures, and neurocognitive scales used, the available evidence is inconclusive. Previous reviews that have assessed the effects of LC-PUFA supplementation on cognitive performance in children and adults without PKU [57][58][59][60] have reported similarly inconclusive findings, in large part due to the marked heterogeneity in the interventions and outcome measures used.

The duration of the intervention is another important variable to consider when examining the functional effects of LC-PUFA supplementation. In their study of the effects of DHA administration in pediatric PKU patients and healthy controls, Agostoni et al. [61] found that P100 wave latencies and DHA status, both of which had improved in the PKU group during the intervention, returned to baseline levels 3 years after treatment discontinuation.

When evaluating the risk of bias for each of the studies included in this systematic review, not all forms of bias should be considered equally important. For example, because LC-PUFA levels and VEP latencies are objective measures, the selected studies are less likely to be affected by performance bias. Besides that, the reporting bias

is unclear in all articles included, so the main forms of bias to consider in our review are selection bias, attrition bias, and detection bias.

Future studies should consider using standardized neurocognitive assessment scales and doses and durations of DHA supplementation in order to determine the tissue levels of DHA necessary to achieve significant homogenous clinical improvements. Moreover, data on the clinical course of patients who discontinue DHA supplementation could be particularly valuable, since the effects of DHA may disappear after discontinuation. Specifically, adjustment of these data for age would enable the identification of the most vulnerable stages of life and the optimum window of opportunity for intervention.

## 3. Conclusions

This entry supports the beneficial effects of DHA supplementation in PKU patients: deficient LC-PUFA status is corrected in patients from 2 weeks to 47 years of age, and P100 wave latency improves in children from 1 to 11 years old. However, evidence is inconclusive regarding the effect of DHA on neurocognitive function. Further research will be required to establish the optimal DHA dose and duration of intervention.

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