

DIET IN PATIENTS WITH PHENYLKETONURIA TREATED WITH PEGVALIASIASE: A NARRATIVE REVIEW ON THE STATE-OF-THE-ART AND CHALLENGES

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ABSTRACT – The aim of this narrative review is to investigate dietary management in patients with phenylketonuria (PKU) treated with pegvaliasia, focusing on clinical and psychological impacts, nutritional challenges, and best practices. Due to the recent introduction of pegvaliasia, patient attitudes and dietary management, as well as the clinical and psychological effects of nutritional changes, remain underexplored.

A PubMed search using terms such as “pegvaliasia,” “phenylketonuria,” and “diet/nutrition changes” included studies on humans published in English over the past 20 years. Relevant data on dietary adjustments, psychological outcomes, and adherence were analyzed.

Effective pegvaliasia management requires dietary adjustments consistent with dose adjustments, aiming to achieve adequate phenylalanine (Phe) levels. Micronutrients (e.g., zinc, selenium, vitamins D and B12) and nutritional status are mandatory variables to be taken into consideration, focusing on the patient’s overall health. Pegvaliasia enables increased natural protein intake, reduced reliance on medical protein substitutes, and dietary liberalization, enhancing nutritional adequacy and quality of life. However, psychological challenges, including anxiety and food-related neophobia, can complicate the management of the diet and, therefore, therapy.

Multidisciplinary care, combined with education for patients and caregivers, is vital to achieving sustainable clinical and psychological outcomes in pegvaliasia-treated PKU patients. Long-term studies are needed to refine guidelines and establish high standards of care.

KEYWORDS: Phenylketonuria, Pegvaliasia, Enzyme replacement therapy, Diet, Nutrition.

ABBREVIATIONS: BMI: Body Mass Index; DRI: Dietary Reference Intake; FAO/WHO/UNU: Food and Agriculture Organization/World Health Organization/United Nations University; GMP: Glycomacropeptide; LNAA: Large Neutral Amino Acids; PAH: Phenylalanine Hydroxylase; Phe: Phenylalanine; PKU: Phenylketonuria; QoL: Quality of Life.

INTRODUCTION

Phenylketonuria (PKU) is the most common autosomal recessive disorder impacting amino acid metabolism caused by mutations in the *PAH* gene. These mutations lead to phenylalanine hydroxylase (PAH) deficiency (gene/locus MIM number 612349)¹, which, if not properly treated, can result in neurological damage, cognitive impairment, and behavioral disorders².

Dietary management remains the primary approach for PKU worldwide, involving a low-protein diet supplemented with low-Phe amino acid protein substitutes (PS) and Special Low Protein Foods (SLPFs)³.

This phenylalanine-restricted diet is crucial for reducing blood phenylalanine (Phe) levels, requiring patients to abolish or strongly limit protein sources. Protein requirement is tailored based on many fac-

tors, including individual age, sex and weight, and the severity of the disease. Classic PKU usually only tolerates between 200 and 500 mg Phe/day. Patients with a milder form of PKU (untreated blood Phe concentrations less than 1,000-1,200 $\mu\text{mol/l}$), usually tolerate ≥ 500 mg/day of dietary Phe. By comparison, in non-PKU, the third US National Health and Nutrition Examination Survey (NHANES III)⁴ demonstrated that mean daily dietary Phe intakes for all life stages and gender groups were as high as 3,400 mg/day. Phe tolerance is responsible for the ratio between natural and synthetic proteins in the prescribed diet. Most fruits and vegetables are naturally low in Phe (<75 mg Phe/100 g of product) and generally do not impact blood Phe levels⁴. Food for special medical purposes (FSMPs), including Phe-free amino acid formulas and low-protein commercial products, provide necessary calories, fats, amino acids, and micronutrients. However, these may be costly and are often not covered by insurance, creating financial burdens for families in some countries but not in Italy⁵. Glycomacropeptide (GMP), a protein derived from cheese whey, is a low-Phe option and a protein substitute⁶. Supplementation with large neutral amino acids (LNAAs) is beneficial in reducing neurological symptoms, especially for adolescents and adults⁷. Overall, the diet must ensure a balanced intake of essential nutrients, vitamins, and minerals, which are often industrially included in protein substitutes or provided as separate supplements⁸.

The first pharmacological treatment for PKU includes sapropterin dihydrochloride, a synthetic form of tetrahydrobiopterin, a cofactor for the PAH enzyme⁹. Recently, pegvaliasse, a pegylated recombinant enzyme derived from *Anabaena variabilis* has been available. Pegvaliasse lowers blood Phe levels by replacing the deficit PAH activity and converting Phe into ammonium and trans-cinnamic acid¹⁰. Approved by the USA in 2018, in Europe in 2019, and in Italy in 2021 for patients aged over 16 with Phe levels >600 $\mu\text{mol/L}$ despite the prescription of dietary therapy, pegvaliasse is administered in three phases – induction, titration, and maintenance – beginning at 2.5 mg per week and increasing to a maintenance dose of up to 60 mg daily, depending on tolerance and efficacy¹¹. Pegvaliasse notably enables dietary protein intake at levels comparable to general dietary guidelines, allowing for greater dietary flexibility¹².

Comprehensive dietary management is essential for optimizing pegvaliasse therapy, including protein intake adjustments aligned with dosage based on regular Phe level monitoring. This can be challenging for patients, with lifestyle factors also playing a crucial role in disease management¹³.

Patient attitudes and dietary management, as well as the clinical and psychological effects of nutritional changes, remain underexplored due to the recent introduction of pegvaliasse. Further research is needed to understand its impact on metabolic outcomes, psychological well-being, and quality of life.

This narrative review aims to provide insights into the nutritional management of patients treated with pegvaliasse, capturing state-of-the-art theoretical and practical recommendations; additionally, this narrative review will focus on the attitudes of patients towards dietary adjustments and the changes from a clinical and psychological perspective.

METHODS

For this narrative review, a PubMed search led to the identification of 125 papers, using the following keywords and combinations: “pegvaliasse”, “phenylketonuria”, “diet/nutrition changes”, “dietary management”, and “nutritional status”. Only studies on humans published in English within the last 20 years were considered. Based on their relevance to the topic, 18 articles were screened by the authors, using a full-text or abstract review.

Relevant information was extracted from each study for analysis. The focus was on current practices and recommendations for dietary management and nutritional status assessment of patients under pegvaliasse treatment, along with evidence regarding patient attitudes and adherence to dietary changes and the clinical and psychological impacts of pegvaliasse-related dietary modifications.

CLINICAL PRACTICES AND RECOMMENDATIONS FOR DIETARY MANAGEMENT OF PATIENTS WITH PKU UNDER ENZYME REPLACEMENT THERAPY

Eight articles^{9,14-20} were identified as relevant for this analysis. A broad consensus exists on managing the introduction of pegvaliasse, which generally calls for a multidisciplinary team. This team typically includes a physician specialized in metabolic diseases who performs initial assessments, educates patients on pegvaliasse treatment, prescribes and adjusts pegvaliasse dosage, monitors adverse events, and manages concomitant medications; a dietitian who participates in the assessment of nutritional status, adjusts dietary plans according to pegvaliasse dosage and counsels patients on dietary management with

pegvaliasse; a psychologist who assesses neurocognitive and psychosocial status, quality of life (QoL), and provides counseling and who supports both the patient and the family. Close coordination with the laboratory is also mandatory during pegvaliasse treatment¹⁴.

Moreover, German centers¹⁵ have reported strong consensus on the essential role of field nurses as primary contacts for pegvaliasse-related inquiries. Field nurses in these centers provide first-line support throughout treatment phases, manage mild adverse events, and promptly communicate with the metabolic clinic. Additional responsibilities include coordinating prescription requests (for pegvaliasse and other medications), sharing blood Phe test results, consulting with patients on dosage adjustments, and evaluating injection hygiene (e.g., regular rotation of the injection site). As reported by Cunningham et al¹⁶, some metabolic centers have included metabolic geneticists within their multidisciplinary teams.

Blood Phe level is the primary biomarker and minimum requirement for assessing metabolic control. During maintenance, blood Phe level should be monitored monthly through the dried blood spot (DBS) or biweekly if it falls below 30 $\mu\text{mol/L}$ (based on two consecutive readings). Regarding the target blood Phe level to be achieved in treatment with pegvaliasse, no outcome studies have been conducted, nor is there a consensus. It is worth noting the suggestion of Longo et al¹², who, in 2019, proposed a more ambitious target of Phe (120 $\mu\text{mol/L}$), compared to the 360 $\mu\text{mol/L}$ established by the American guidelines⁷ for patients with PKU, not specific to enzyme therapy.

In addition to the guidance on performing DBS mentioned above, a general agreement is reported on managing patients on pegvaliasse treatment, which may require more frequent and consistent monitoring compared to what is indicated by the guidelines for PKU care to address drug-related issues, adjusting the dosage, or prescribing diet changes¹⁷.

To keep up with the necessity of timely adjustments and the potential need to address adverse events, rapid communication systems, including home monitoring and telemedicine, are considered essential¹⁷. According to Krämer et al¹⁵, 24/7 emergency phone or email access has been effective for promptly reporting and managing adverse events.

European experts⁴ recommend that nutritional status assessment carefully integrate dietary management, particularly protein intake and pegvaliasse dosage, to ensure optimal outcomes.

Assessment frequency should be tailored at the discretion of the metabolic team, taking into account the treatment phase and the degree of dietary freedom¹⁴.

In pegvaliasse management, significant importance has been given to training caregivers and educating patients by providing a wide range of tools, such as videos and a demonstrative kit. However, less specific and detailed indications on how to convey to patients the importance of proper nutrition have been reported^{14,17}. Cunningham et al¹⁶ also highlighted the importance of building strong provider-patient relationships to support long-term adherence, promote healthy eating, and monitor nutritional status and protein intake adequacy.

Minimal nutritional assessments, recommended every six months, should include anthropometric evaluations [body mass index (BMI), height, and waist circumference] and assessments of nutritional intake using tools such as the Food Frequency Questionnaire, 24-hour recall records, 3-day food records; also, the Food Neophobia Questionnaire has been proposed¹⁴. This aligns with findings from a Delphi survey by Cunningham et al¹⁶, which reported 100% agreement on the importance of evaluating individual food behaviors and attitudes. In this context, nutritional assessments should encompass discussions of taste or texture aversions, fears or phobias of previously restricted foods, and preferences for new foods as the diet becomes more liberalized¹⁶. Metabolic dietitians are recommended to assess nutrient intake and adequacy, particularly protein quality, and to counsel patients on incorporating high-protein foods into their diet, including guidance on portion sizes, food safety, and cooking methods¹². For proper assessment, blood analysis is strongly recommended to include a full amino acid profile and other micronutrients (selenium, zinc, iron, calcium, vitamin D, vitamin B12), which should be monitored annually¹⁴. Disordered or atypical eating behaviors are common in individuals who have consistently followed a restricted PKU diet, and they may require support to adjust their emotional response to a more liberalized diet, including previously “forbidden” foods⁹. Some individuals may experience anxiety when implementing new dietary goals, as well as guilt related to increasing their intake of high-protein foods and trying new foods¹⁸.

Regarding the evaluation of food patterns, the dietary reference intake (DRI) for protein is 0.8 g/kg/day, derived from a combination of animal and plant proteins¹⁹. For vegan patients, a 20% higher intake, or 1 g/kg/day, is generally recommended²⁰. To achieve the DRI while maintaining blood Phe levels below 240 $\mu\text{mol/L}$, natural protein intake should be gradually increased by 10-20 g per day, with tolerance monitored before further increments. Conversely, protein substitutes should be proportionally reduced to accommodate this adjustment¹⁴.

Monitoring of blood pressure, insulin resistance, and lipid profile is also recommended to screen for comorbidities typical of adults, such as hypertension, hyperlipidemia, and cardiovascular disease. Quality of life (QoL) questionnaires are also suggested to assess the physical, emotional, and social well-being of PKU patients undergoing pegvaliasse treatment¹⁴.

EVIDENCE OF DIETARY MANAGEMENT IN PKU PATIENTS UNDER PEGVALIASSE TREATMENT - CLINICAL AND PSYCHOLOGICAL IMPACT

Regarding the evidence on nutritional assessment and clinical and psychological outcomes of PKU patients treated with pegvaliasse, we identified ten studies^{11,17,21-28} relevant to this analysis, whose information is summarized in Tables 1 and 2.

Patients treated with pegvaliasse generally showed increased tolerance for natural protein intake and decreased reliance on medical protein formulas. Scala et al¹⁷ reported an increase in natural protein intake from an average of 45 g/day to 61 g/day, along with a reduction in FSMP intake from 35 g/day to 14 g/day at the final follow-up¹⁷. Similarly, Sacharow et al²¹ reported a median increase of 50% in intact protein intake and a 25% decrease in medical food protein. In three cases reported by Bernstein et al²², two patients demonstrated a significant increase in intact protein intake (Case #1 from 7 g/day to over 80 g/day and Case #2 to over 100 g/day after therapy initiation), while all three patients eliminated FSMPs entirely. Viau et al²³ also reported an increase in natural protein intake and a decrease in protein equivalent intake among both responders and partial responders to a Phe-restricted diet, with or without FSMPs. Burton et al²⁴ and Zori et al¹¹ also reported an increase in intact protein intake, while Rohr et al²⁵ documented a reduction in medical product use. Among patients initially relying on medical products for >75% of their protein intake, 36.6% reduced this reliance (to 0-75%), and 34.1% eliminated FSMPs entirely. Among those initially consuming 0-75% medical protein, 49.1% reported no medical protein intake at their last assessment²⁵.

Most studies reported significant reductions in blood Phe concentrations with pegvaliasse. Sacharow et al²¹ observed a decrease from a baseline of 1,031±385 µmol/L to 654±509 µmol/L after 1 year, with 69% of patients achieving at least a 50% reduction. In the study by Rohr et al²⁵, 50% of patients achieved Phe concentrations ≤600 µmol/L within 8 months, with a subset reaching ≤120 µmol/L by 15 months. Bernstein et al²² also reported Phe reductions in case studies. In Case #1, Phe levels decreased from 394 µmol/L to below 120 µmol/L within 6 months of pegvaliasse initiation at a dose of 20 mg/day. Cases #2 and #3 achieved normal Phe levels, with both experiencing a rapid decrease to <30 µmol/L through increased protein intake and/or pegvaliasse dose adjustments²².

Micronutrient intake remained a concern despite increased dietary flexibility. Viau et al²³ reported decreases in vitamin D and E intake as patients reduced their reliance on medical protein, necessitating supplementation in some cases.

Recently, intake deficiencies in several vitamins and minerals, such as zinc, selenium and thiamine, have been reported in patients treated with pegvaliasse and inadequate iron intake in the female population, despite good adherence to the Mediterranean diet²⁶. Interestingly, our study observed that the dietary habits of patients who underwent counseling align closely with those reported in the general Italian population, suggesting that dietary counseling is effective in guiding dietary choices²⁶.

Changes in BMI varied across studies and were generally modest. Sacharow et al¹⁷ observed minimal BMI fluctuation (0.14±1.1 kg/m²), with significant weight changes in only five patients, four of whom showed improved BMI. Viau et al²³ documented varied BMI responses, with changes ranging from -6.4% to +16.8% in pegvaliasse Phe-restricted diet responders and from -4.8% to +2.4% in partial responders²³. Rohr et al²⁵ noted general stability in weight and BMI over time, with a slight BMI increase, which was more evident among patients who eliminated medical proteins from their diet.

In several studies, patients reported challenges in adjusting to a higher-protein diet as well as socioeconomic difficulties, including economic or food insecurity, challenging living or care arrangements, and legal issues²⁷. Viau et al²⁸ reported that 53% of participants self-identified as having moderate (*n*=6) to high (*n*=3) food neophobia. Conversely, other studies reported successful diet liberalization among patients, with positive psychosocial impacts on quality of life. Viau et al²³ described reduced patient anxiety and food-related neophobia, along with a self-reported increase in food enjoyment. Patients expressed feeling freer to appreciate and explore a broader range of foods, which had previously been restricted under a low-protein, Phe-restricted diet²³. In Scala et al¹⁷, one patient benefited from nutritional counseling, while another experienced significant improvement in anxiety and attentional functions, and two patients reported enhanced social and relational outcomes, contributing to an overall improvement in quality of life.

Table 1. Patients' characteristics and nutrient intake from retrieved cases.

Study	Patients (n)	Age (years)	Macronutrients intake	Micronutrients intake
Stecchi et al ²⁶ 2024	7 patients (5 males, 2 females)	18-42 years	<p>During follow-up:</p> <ul style="list-style-type: none"> • Median caloric intake of 51% calories from carbohydrates, 16% from proteins, and 34% from lipids • Protein consumption 1 g/kg; animal protein median (min-max): 39 (37-54) g/day; vegetal protein median (min-max): 28 (16-49) g/day • Percentage of calories provided by simple sugars: 13% of the total caloric intake, • Percentage of calories provided by saturated fats: 9% of the total caloric intake 	Unsatisfactory zinc, selenium, thiamine, riboflavin, and folate; iron inadequate for women.
Scala et al ¹⁷ 2024	18 patients (11 males, 7 females)	17-43 years	<ul style="list-style-type: none"> • Natural protein intake before the treatment: average of 45 g/day (range 6-120 g/day); at the last follow-up, an average of 61 g/day • Phe-free protein intake before treatment 35 g/day; at the last follow-up: 14 g/day 	
Bernstein et al ²² 2021	Case #1: A Female Case #2: A Female Case #3: A Male	Case #1: 35 years Case #2: 30 years Case #3: 34 years	<p>Case #1</p> <ul style="list-style-type: none"> • Prescribed: 152 g Phenyl-Free[®] 2 + 38 g Phenylade[®] MTE AA Blend, 63 g Phe-free protein equivalents, none at follow-up • Total protein intake: about 70 g (1.5 g/kg/day) at baseline • Natural protein intake (g/day): 7 at baseline, >80 at follow-up <p>Case #2</p> <ul style="list-style-type: none"> • Prescribed: PKU sphere[®] (2 packets, 40 g Phe-free protein) at baseline, none at the 12-month follow-up • Total protein intake was 74 g (0.9 g/kg protein/day) • Natural protein intake (g/day): 34 at baseline, >100 at follow-up <p>Case #3</p> <ul style="list-style-type: none"> • Prescribed: PheBLOC[®], 27 tablets/day, 14.5 g Phe-free protein at baseline, none at follow-up • Natural protein intake (g/day): 110 (1.6 g/kg) at baseline, 100-120 at follow-up 	Case #1 Serum amino acids, prealbumin, and vitamin D in the normal range at baseline

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Table 1. Patients' characteristics and nutrient intake from retrieved cases.

Study	Patients (n)	Age (years)	Macronutrients intake	Micronutrients intake
Sacharow et al ²¹ 2020	26 patients	35.9±10.5 years (range 19.1-55.4)	At pegvaliasie initiation, the majority of patients (16/26) consumed a Phe-restricted diet with Phe-free food (protein substitutes), 8/26 consumed a moderate protein restriction with inadequate Phe-free food (≤50% of prescribed) and 2/26 had discontinued all dietary treatment. Of the 18 patients with a blood Phe response, 50% tolerated a natural protein intake (≥0.8 g/kg/day) with no Phe-free food. At the time of data collection, patients with ongoing diet modifications (n=9) had a median of a 50% increase in natural protein and 25% decrease in Phe-free food protein	
Viau et al ²⁸ 2021	18 patients (61% female)	38.2±8.8 years	At >1-year follow-up: mean of 73.2±17.6 g protein/d (1.0±0.3 g/kg/d). Intakes of sodium, saturated fat, and added sugars exceeded recommendations for healthy adults, though mean diet quality was comparable to a US adult reference population	Micronutrient and Essential Fatty Acids (EFA) concentrations were normal except for mildly low vitamin D (<30 ng/mL, n=12).
Rohr et al ²⁵ 2024	<p>Participants consuming no protein intake from Phe-free food</p> <ul style="list-style-type: none"> • 101 patients, 53 females (52.5%) <p>Participants consuming some protein intake from Phe-free food (0-75%)</p> <ul style="list-style-type: none"> • 108 patients, 47 females (43.5%) <p>Participants consuming protein intake from Phe-free food (>75%)</p> <ul style="list-style-type: none"> • 41 patients, 23 females (56.1%) 	<p>No Phe-free protein consumers</p> <ul style="list-style-type: none"> • Mean (SD): 30.9 (8.39) years <p>Some Phe-free proteins (0-75%) consumers</p> <ul style="list-style-type: none"> • Mean (SD): 28.6 (8.32) years <p>Phe-free protein (>75%) consumers:</p> <ul style="list-style-type: none"> • Mean (SD): 26.0 (9.40) years 	<p>Participants consuming no Phe-free protein at baseline</p> <ul style="list-style-type: none"> • 91.1% were not consuming Phe-free protein • 7.9% consumed some Phe-free protein • 1% consumed >75% Phe-free protein at the last assessment <p>Participants consuming some Phe-free proteins (0-75%) at base line</p> <ul style="list-style-type: none"> • 49.1% were consuming no Phe-free protein • 48.1% consumed some Phe-free protein • 2.8% consumed >75% Phe-free protein at the last assessment <p>Participants consuming >75% Phe-free protein at baseline</p> <ul style="list-style-type: none"> • 34.1% consumed no Phe-free protein • 36.6% consumed some Phe-free protein • 29.3% consumed >75% Phe-free protein at the last assessment <p>In participants eligible for diet changes due to protocol-defined HypoPhe, natural protein intake increased and Phe-free protein intake decreased in both groups consuming Phe-free protein</p>	

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Table 1. Patients' characteristics and nutrient intake from retrieved cases.

Study	Patients (n)	Age (years)	Macronutrients intake	Micronutrients intake
Burton et al ²⁴ 2024	183 patients • 88 (48.1%) females	Age (years), mean (SD): 30.0 (8.9)	Natural protein intake (total protein intake - Phe-free protein intake) • Baseline (mean±SD): 39.2±27.9 g/day (n=176/183) • 3-year follow-up (mean±SD): 63.3±27.8 g/day (n=146/183)	
Adams et al ²⁷ 2021	15 patients	18-53 years	11 (73%) were following a Phe-restricted diet and were using Phe-free foods at baseline. Natural protein intake in these patients ranged from 20 to 100 g/day (mean 69.8 g/day), and total protein intake ranged from 55 to 100 g/day (mean 76.2 g/day) at the last follow-up	
Zori et al ¹¹ 2019	Pegvaliasse vs. "sapropterin + diet" • 64 patients, 38 (59%) females vs. 64 patients, 37 (58%) females Pegvaliasse vs. "diet-alone" • 125 patients, 56 (45%) females vs. 125 patients, 56 (45%) females	Pegvaliasse vs. "sapropterin + diet" • Mean (SD): 32 (9) years vs. 33 (10) years Pegvaliasse vs. "diet-alone" • Mean (SD): 30 (8) vs. 31 (11) years	Pegvaliasse vs. "sapropterin + diet" Natural protein intake, mean (SD) • at baseline: 33 (19) vs. 36 (31) g/day • at 2-year follow-up: 57 (29) vs. 28 (18) g/day Pegvaliasse vs. "diet-alone" Natural protein intake, mean (SD) • at baseline: 34 (24) vs. 25 (19) g/day • at 2-year follow-up 57 (26) vs. 22(16) g/day	

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Table 1. Patients' characteristics and nutrient intake from retrieved cases.

Study	Patients (n)	Age (years)	Macronutrients intake	Micronutrients intake
Viau et al ²³ 2023	12 patients (7 females) 6 responders followed a Phe-restricted diet with or without Phe-free food (i.e., natural protein intake), the rest partial responders had a decrease in blood Phe with a concomitant increase in natural protein after self-liberalizing their diets over the study	19.5-52.9	<p>Responders (mean±SD)</p> <p>At baseline</p> <ul style="list-style-type: none"> • Energy: 1,830±468 kcal/day • Energy/kg: 24.4±8.7 • Total protein: 90.1±23.8 g/day • Total protein/kg: 1.19±0.35 • Natural protein: 22.5±12.6 g/day • Natural protein/kg: 0.3±0.2 • Protein equivalents: 67.6±29.9 g/day • Protein equivalents/kg: 0.9±0.4 • Total protein: 20.6±7.3% kcal • Carbohydrate: 52.9±2.4% kcal • Fat 26.5±8.2% kcal • Fiber: 19.2±9.3 g/day <p>At month 15</p> <p>unrestricted diet and decreased Phe-free</p> <ul style="list-style-type: none"> • Energy: 1,897±747 kcal/day • Energy/kg: 26.3±12.4 • Total protein: 79.0±23.1 g/day • Total protein/kg: 1.08±0.36 • Natural protein: 72.0±23.7 g/day • Natural protein/kg: 1.0±0.4 • Protein equivalents: 7.05±17.2 • Protein equivalents/kg: 0.1±0.2 • Total protein 17.1±4.2% kcal • Carbohydrate 49.1±4.8% kcal • Fat 33.9±3.0% kcal • Fiber: 17.8±8.5 g/day 	<p>At baseline, median dietary intakes of most vitamins and minerals assessed were adequate (≥100% of DRI):</p> <ul style="list-style-type: none"> • Vitamin A 154% (IQR 74–197%) • Vitamin B12 163% (IQR 100–321%) • Calcium 123% (IQR 58–186%) • Folic acid 162% (IQR 92–203%) • Iron 160% (IQR 66–226%) • Magnesium 100% (IQR 66–188%) • Selenium 183% (IQR 110–253%) • Zinc 125% (IQR 91–282%) <p>Median intakes of Vitamin D 47% (IQR 27–147%) and Vitamin E 77% (IQR 41–129%) were less than the DRI at baseline. As the pegvaliase responders transitioned to an unrestricted diet and decreased Phe-free food intake, median micronutrient intakes decreased, with iron and vitamins E and D being below the DRI.</p> <p>Eight participants reported taking a multivitamin and mineral supplement, four reported a vitamin D supplement, three reported a B12 supplement, two reported a fish oil/omega 3 supplement, one reported a calcium supplement, and one reported an iron supplement (in response to low serum iron)</p>

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Table 1. Patients' characteristics and nutrient intake from retrieved cases.

Study	Patients (n)	Age (years)	Macronutrients intake	Micronutrients intake
			Partial responders (mean±SD) At baseline <ul style="list-style-type: none"> • Energy: 1,963±493 kcal/day • Energy/kg: 25.8±4.1 • Total protein, 62.6±40.2 g/day • Total protein/kg: 0.81±0.47 • Natural protein: 34.2±20.2 g/day • Natural protein/kg: 0.4±0.3 • Protein equivalents: 28.4±45.1 • Protein equivalents/kg: 0.4±0.5 • Total protein: 11.7±5.3% kcal • Carbohydrate 57.7±4.3% kcal • Fat 30.6±6.2% kcal • Fiber: 16.1±3.4 g/day At month 15 <ul style="list-style-type: none"> • Energy: 1,909±534 kcal/day • Energy/kg: 26.7±7.8 • Total protein: 76.1±34.5 g/day • Total protein/kg: 1.07±0.50 • Natural protein: 60.9±44.0 g/day • Natural protein/kg: 0.9±0.7 • Protein equivalents: 15.2±34.0 • Protein equivalents/kg: 0.2±0.4 • Total protein 15.0±3.6% kcal • Carbohydrate 50.7±6.7% kcal • Fat 34.3±4.8% kcal • Fiber 13.8±5.4 g/day 	

Table 2. Patients' outcomes and diet adherence.

Study	Phe levels	Anthropometric measurements and metabolic phenotype	Diet (pre)-pegvaliasie adherence and perceptions, QoL and well-being
Stecchi et al ²⁶ 2024		<ul style="list-style-type: none"> • Normal weight • Glycometabolic parameters clinically normal • No insulin resistance • Normal blood iron and vitamin levels, thyroid function 	High alcohol consumption in one case. Median adherence to Mediterranean diet: 49.1%
Scala et al ¹⁷ 2024	Before treatment: average of 1,084 µmol/l; at last follow-up, average: 617 µmol/l	BMIs ranged from 17.3 to 36.4 kg/m ² ; one patient lost weight	<p>12 were on a restricted diet. 10/12 referred difficulties in maintaining dietary regimen.</p> <ul style="list-style-type: none"> • One patient benefited from nutritional counselling • One patient experienced a significant improvement in anxiety symptoms and attentional functions • Two patients achieved better social and relational outcomes, improving their overall quality of life.
Bernstein et al ²² 2021	<p>Case #1</p> <ul style="list-style-type: none"> • 394 µmol/L baseline; <120 µmol/L (about 6 months after dose increase to 20 mg/day) <p>Case #2</p> <ul style="list-style-type: none"> • <30 µmol/ with 10 mg/day dose and difficulty to increase natural protein intake, increased Phe levels with 10 mg every second day. • After monitoring normalized Phe levels from 3 times weekly to 5-7 times weekly, she went back to 10 mg daily and her Phe concentrations were more consistent; in the meantime, she increased her natural protein intake <p>Case #3</p> <ul style="list-style-type: none"> • Above 1,000 µmol/L before treatment • <30 µmol/L at 1 month, 20 mg/day • <30 µmol/L, although addition of high-protein foods, including chicken, fish, pork, eggs. • Dose was titrated down from 20 to 10 mg daily. Blood Phe increased slightly but remained below goal range, then further down to 10 mg three-times week, and blood Phe was in the target range. 	<p>Weight (baseline)</p> <ul style="list-style-type: none"> • Case #1: 45.2 kg • Case #2: 80 kg • Case #3: 70.9 kg <p>BMI (baseline)</p> <ul style="list-style-type: none"> • Case #1: 16.5 • Case #2: 32.1 • Case #3: 27.8 	<p>Case #1</p> <ul style="list-style-type: none"> • Not eating any high-quality protein foods, such as meat or dairy at baseline. Over time, she carried out a diet liberalization to include beans, eggs, nut butters, and eventually chicken and pork. • Overall, the patient is extremely happy with her current diet. <p>Case #2</p> <ul style="list-style-type: none"> • At baseline (higher-protein foods, such as cheese, yogurt and salami; the portion sizes were very small). • Initial difficulties to increase natural protein intake, currently consuming over 100 g of protein/day and loves meat and other high-protein food <p>Case #3</p> <ul style="list-style-type: none"> • Primarily vegetarian diet, including regular grains, fruits, and vegetables, as well as limited consumption of higher-protein foods, such as eggs and dairy. He also consumed meat occasionally, never having difficulty adding these high protein foods as he was excited to be able to eat an unrestricted diet

Continued

Table 2. Patients' outcomes and diet adherence.

Study	Phe levels	Anthropometric measurements and metabolic phenotype	Diet (pre)-pegvaliase adherence and perceptions, QoL and well-being
Sacharow et al ²¹ 2020	Mean blood Phe decreased from 1,031±385 µmol/L at baseline (n=26) to 654±509 µmol/L at 12 months of therapy (n=9). Nearly all patients (24/26) had a ≥30% decrease in Phe from baseline with an average decrease of 56±30%. 18 patients (69%) had a ≥50% decrease in Phe, corresponding to at least one blood Phe concentration <360 µmol/L, while on 10 mg (3/18), 20 mg (8/18), 40 mg (5/18) and 60 mg (2/18) pegvaliase/day at an average of 13±10.5 weeks, 16.1±7.7 weeks, 36.4±2.9 weeks and 58±5.7 weeks after starting pegvaliase therapy	Minor fluctuation in BMI (0.14±1.1 kg/m ²) after starting pegvaliase. 5/26 experienced >5% weight change that corresponded to an improvement in BMI in 4/5	
Viau et al ²⁸ 2021	11/18 low blood Phe (<30 µmol/L) with adequate protein intake and normal indices of protein status	Mean BMI of 29.2±4.1 kg/m ² at baseline	Lower food neophobia scores correlated with an increased aesthetic appreciation of food. However, 53% of participants self-reported having moderate (n=6) to high (n=3) food neophobia.
Rohr et al ²⁵ 2024	At baseline (mean ± SD): <ul style="list-style-type: none"> No Phe-free protein group: 1,480.7±337.1 µmol/L Some Phe-free protein (0-75%) group: 1,136.5±326.2 µmol/L >75% Phe-free protein group: 901.2±266.2 µmol/L 50% of the entire cohort achieved blood Phe ≤600, ≤360, and ≤120 µmol/L in 8, 11 and 15 months, respectively, after starting treatment 	At baseline: BMI (kg/m ²), mean (SD) <ul style="list-style-type: none"> No Phe-free protein group: 30.0 (6.98) Some Phe-free protein (0-75%) group: 27.8 (6.37) >75% Phe-free protein group: 26.3 (6.32) Weight and BMI were generally stable over time, with slight increases most notable in participants consuming no Phe-free protein 	
Burton et al ²⁴ 2024	<ul style="list-style-type: none"> At baseline (mean ± SD): 1,258.0±365.3 µmol/L At 3-year follow-up (mean ± SD): 396.9 (463.6) µmol/L (n=153/183) 		

Continued

Table 2. Patients' outcomes and diet adherence.

Study	Phe levels	Anthropometric measurements and metabolic phenotype	Diet (pre)-pegvaliasse adherence and perceptions, QoL and well-being
Adams et al ²⁷ 2021	<ul style="list-style-type: none"> At baseline: Range 262-1,474 $\mu\text{mol/L}$ At last follow-up: range 0-321 $\mu\text{mol/L}$ (mean 72 $\mu\text{mol/L}$) 		<p>Four of 15 patients reported significant socioeconomic challenges, including economic and/or food insecurity, difficult living and/or care arrangements, and ongoing legal challenges.</p> <p>Some patients experienced difficulty adjusting to a new diet with higher protein intake; however, two patients reaching efficacy were no longer on Phe-free food supplementation</p>
Zori et al ¹¹ 2019	<p>Pegvaliasse vs. "sapropterin + diet" (mean \pm SD)</p> <ul style="list-style-type: none"> At baseline: 1,172 (329) vs. 1,176 (383) $\mu\text{mol/L}$ At 2-year follow-up: 427 (527) vs. 891 (381) $\mu\text{mol/L}$ <p>Pegvaliasse vs. "diet-alone" (mean \pm SD)</p> <ul style="list-style-type: none"> At baseline: 1,085\pm294 vs. 1,089 (302) $\mu\text{mol/L}$ At 2-year follow-up: 302 (392) vs. 965 (359) $\mu\text{mol/L}$ 		
Viau et al ²³ 2023	At baseline, mean blood Phe was 547 \pm 324 $\mu\text{mol/L}$ in responders and 1,140 \pm 218 $\mu\text{mol/L}$ in partial responders	<p>Percentage change from baseline to month 15:</p> <p>Responders:</p> <ul style="list-style-type: none"> BMI: -6.4 to +16.8% FMI: -9.1% to 20.3% LMI: -6.4% to 11.4% <p>Partial responders</p> <ul style="list-style-type: none"> BMI: -4.8 to +2.4% LMI: <5% difference FMI: - 12.6% to 2.6% <p>All participants had an increased android:gynoid ratio at baseline and month 15 indicating abdominal obesity</p>	Over 15 months of pegvaliasse treatment: a decrease in food neophobia (FNS score increased by 8.6 \pm 6.7; range: 2-18), increase in Epicurean eating tendencies score (increased by 8.8 \pm 11.1; range: -4-26), decrease in uncontrolled eating (TFEQ-18 uncontrolled eating sub-score decreased by -5 \pm 3.6; range: -9 to -2), and decrease in emotional eating (TFEQ-18 emotional eating sub-score decreased by -0.8 \pm 1.6; range: -3-1; and EEQ score decreased by -5.2 \pm 7.2; range: -16-4)

BMI: Body Mass Index; LMI: Lean Mass Index; FMI: Fat Mass Index.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

This narrative review examines the interplay between dietary management and pharmacological therapy in phenylketonuria (PKU) patients treated with pegvaliase, providing insights into the current state-of-the-art and ongoing challenges, including the clinical and psychological impacts of these interventions.

Pegvaliase allows most patients with PKU to maintain an adequate blood Phe level while freeing their diet and moving away from prescriptive diets based on medical protein substitutes (Table 3).

Table 3. Blood phenylalanine monitoring and nutritional interventions in pegvaliase-treated PKU.

Clinical scenario/ treatment phase	Blood Phe monitoring indications	Nutritional intervention strategies
Initiation of pegvaliase (induction phase)	<ul style="list-style-type: none"> • Monitor blood Phe before starting therapy • Frequency of monitoring guided by clinical team (typically weekly or biweekly) 	<ul style="list-style-type: none"> • Maintain current protein substitute intake unless Phe drops too low
Dose titration phase	<ul style="list-style-type: none"> • Weekly or biweekly blood Phe levels to guide dosage • Increase monitoring if symptoms of hypoPhe occur 	<ul style="list-style-type: none"> • Gradually introduce natural proteins (10-20 g increments/day)* • Start reducing protein substitutes proportionally*
Maintenance phase	<ul style="list-style-type: none"> • Monthly monitoring if Phe is stable • Biweekly if blood Phe <30 $\mu\text{mol/L}$ for two consecutive readings 	<ul style="list-style-type: none"> • Progressive liberalization of the diet, based on Phe values • Progressive reduction of FSMPs based on natural protein intake* • When Phe values are at target, promote adherence to a healthy diet with a protein intake according to national nutritional guidelines

*If patients are not on a free diet before starting the therapy.

A unified target for blood phenylalanine (Phe) concentrations in pegvaliase-treated patients has not been established yet. While American guidelines⁷ recommend maintaining Phe levels below 360 $\mu\text{mol/L}$, some authors (e.g., Longo et al¹²) have proposed more stringent targets (e.g., 120 $\mu\text{mol/L}$) for patients under enzyme replacement therapy. European centers often rely on institution-specific targets guided by national or regional consensus. Therefore, tailoring pegvaliase dosing to the Phe targets established by each center, in accordance with local or international guidelines, is needed.

Studies^{11,17,21-28} consistently report improved natural protein tolerance and reduced reliance on FSMPs, leading to better quality of life. Individualized adjustment of natural protein intake with gradual reintroduction should be aligned with the patient's biochemical response and metabolic tolerance.

Indeed, pegvaliase raises two critical points that remain to be fully addressed: dietary freedom and the psychological implications of the therapy. Concerning diet, a consensus has yet to be reached on how to support patients in adopting healthy eating habits, and the literature remains scarce on the challenges patients face in terms of the adequacy of micro- and macronutrients. In addition to a standardized approach, regular nutritional assessments enable the early detection of potential problems, including deficiencies and metabolic derangements associated with excess body weight, as recommended by the European PKU guidelines⁴.

Concerning psychological challenges during pegvaliasse treatment, the reintroduction of previously restricted foods is a critical moment. Common issues include anxiety, guilt, and food neophobia, which may affect adherence to dietary adjustments and increase the risk of clinical complications and negative quality of life.

A standardized approach to evaluate, early detect and act upon these new psychological challenges has yet to be reached.

Patient education programs should encompass nutritional aspects of pegvaliasse therapy, empowering individuals to manage dietary changes effectively. Training for caregivers can also enhance awareness of current recommendations, improve adherence, and ensure high-quality care.

A recent survey²⁹ of Italian metabolic centers revealed that 61% had adopted the European guideline framework. However, heterogeneity in practices persists, particularly regarding the use of protein substitutes, protein calculations, and dietary liberalization strategies. For instance, encouraging the unrestricted intake of low-Phe fruits and vegetables has improved dietary flexibility, potentially enhancing patient adherence and quality of life.

Collaboration among centers treating patients with PKU is critical, as only through it can a consensus on best practices for dietary liberalization be reached, taking into account the eating habits peculiar to each country and strategies to address the psychological challenges associated with diet liberalization.

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