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DIETARY MANAGEMENT PRACTICES IN PHENYLKETONURIA: RESULTS OF AN ITALIAN MULTICENTRIC SURVEY AND COMPARISON WITH THE EUROPEAN GUIDELINES

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***ABSTRACT* – Objective:** Phenilalanine (Phe)-restricted diet is the cornerstone of treatment of phenylketonuria (PKU). Dietary management remains heterogeneous in Europe despite the publication of the PKU European Guidelines (EG) in 2017. We conducted a multicentric survey on PKU dietary management in Italy to investigate the current situation.

Materials and methods: From February to March 2023, a survey on PKU dietary management in Italy was conducted after the publication of the PKU EG. The survey, encompassing the timing of initiation of therapy, ideal Phe concentration, protein requirements, dietary Phe management, and use of protein substitutes, was administered to Italian metabolic dietitians from 13 clinical centers.

Results: The survey showed that 61% of dietitians changed their practice after the publication of EG. In particular dietary approach was simplified, allowing free intake of food with phe <75 mg/100 g. Moreover, according to EG, dietary treatment was anticipated within 10 days of life in 85% of cases. The target Phe concentration was in line with EG, while the EG range in pregnancy (120–360 µmol/l) was achieved in 54% of cases. Regarding the total protein prescriptions, dietitians suggested the appropriate for general population or a 20–40% increase in 23% and 67%, respectively. All centers prescribed glycomacropeptide-containing substitutes, including in PKU pregnancies (54%). Large-neutral amino acids were used in 61% of centers. In sports activities, 77% of centers reported specific adaptations. During intercurrent illnesses, 61% of centers reduced or discontinued natural protein intake.

Conclusions: This study adds new insights into dietary management of PKU in Italy, fostering shared management for treatment personalization in PKU.

Keywords: Dietetic practices, Dietitian, Phenylketonuria, PKU, European PKU guidelines.

INTRODUCTION

Phenylketonuria (PKU) is an inherited disorder of amino acid metabolism caused by mutations in the gene encoding the enzyme phenylalanine hydroxylase, responsible for converting phenylalanine (Phe) to tyrosine[1]. These mutations lead to Phe accumulation in the blood and central nervous system, resulting in neurological damage and developmental delays associated with behavioral disorders. Currently, the cornerstone of PKU treatment, aimed at preventing central nervous system damage and promoting appropriate psychomotor development, is a low-Phe diet[2]. The national newborn screening (NBS) program has enabled the early identification of patients with PKU, allowing timely access to treatment.

Reducing Phe intake is achieved through a lifelong strict dietary restriction of natural proteins (e.g., meat, eggs, fish, cheese, etc.) to maintain plasma Phe levels within the therapeutic target range while providing the necessary macro and micronutrients for proper growth and development[3]. To cover these nutritional requirements, the diet must be supplemented with low or Phe-free protein substitutes consisting of synthetically derived amino acids or glycomacropeptide from casein (C-GMP) and foods for special medical purposes with a low protein content (e.g., bread, flour, pasta, etc.)[4,5].

The management of PKU through dietary intervention remains heterogeneous in Europe despite shared treatment goals[6,7]. The publication of the first "European guidelines" (EG) for PKU management in 2017, addressing diagnosis, treatment, and care for patients of all ages with PKU, provided an essential reference tool to reduce treatment disparities and establish clear standards for the care of patients with PKU[8].

However, many aspects of dietary management still vary among centers, particularly concerning the timing of treatment initiation, optimal plasma Phe levels in different age groups and during pregnancy, protein requirements, and the use of protein substitutes[9].

The EG recommend initiating treatment within the first 10 days of life, but this cannot always be guaranteed by all centers[8].

Plasma Phe levels serve as the primary indicator for guiding, monitoring, and assessing metabolic control in patients with PKU[8].

This is particularly crucial in the early stages of life when elevated plasma Phe levels significantly impact brain and neurological development[10]. However, it is now known that chronically elevated Phe levels can also impact cognitive abilities in adulthood[11,12]. Concerning the safety ranges for plasma Phe concentrations, there is still a considerable discrepancy in international practices, especially regarding the optimal Phe target for adult patients with PKU[13]. However, the EG indicate a maximum Phe level of 360 µmol/L for children under 12 years and 600 µmol/L for patients aged 12 years and above[8].

The level of natural protein restriction depends on individual tolerance[14], influenced by patient phenotype, age, growth, additional therapies, and the amount of protein equivalents from protein substitutes[4,14]. In clinical practice, the allocation of daily Phe is approached in various methods[15]. Some centers prefer to prescribe a daily amount of Phe/proteins from all consumed foods, while others use a method based on a known Phe exchange system[4,16].

The EG recommend that total protein intake provides 40% more than the safe levels for protein intake established by FAO/WHO/UNU. They also suggest that fruits and vegetables containing Phe ≤75 mg/100 g (excluding potatoes) can be administered without weighing the food in a low-Phe diet. This simplified diet has demonstrated comparable metabolic control to patients on a traditional diet in which all foods are counted and measured, encouraging greater adherence to diet[17].

Although NBS for PKU has been conducted in Italy for more than 30 years, this is, to our knowledge, the first study investigating the dietary practices of Italian dietitians hitherto unexplored. Dietary practices, early treatment delivery, and nutritional education for patients with PKU must be as consistent and shared across centers as possible to provide patients and their caregivers with reliable and uniform therapeutic strategies aligned with guideline recommendations. This ensures equitable care standards, which are necessary to effectively improve the quality of life for patients with PKU in Italy. On behalf of the dietetics group of the Italian Society for the Study of Inherited Metabolic Diseases and Newborn Screening (SIMMESN), we conducted a survey on the dietary management of PKU in Italian centers to assess current practices and changes since the publication of the PKU EG.

MATERIALS AND METHODS

A cross-sectional questionnaire was sent to all dietitians and nutritionists belonging to the dietetics group of SIMMESN. The questionnaire was distributed digitally using the Google Form® platform; it consisted of 28 questions, some with structured multiple-choice questions and others with open-ended questions to ensure greater freedom of expression and reduce investigator bias.

Responses were collected over a month, from February 3 to March 3, 2023. The questionnaire was in Italian, and the primary author (SG) made themselves available to clarify any interpretative doubts of the respondents.

Each clinical center was allowed one response, and professionals were invited to answer each question based on their general clinical practice. The investigated themes included:

- Dietary management after NBS: timing of initiating dietary therapy following a positive NBS result and infant's preferred feeding method;
- Metabolic control: blood Phe concentrations are considered indicative of good metabolic control in different age groups and during pregnancy;
- Protein requirement: the bibliographic sources used to determine the ideal total protein intake at different life stages;
- Dietary Phe management: practical management of counting and exchanging foods to determine adequate dietary Phe intake;
- Protein substitutes other than standard amino acid supplements: use of C-GMP and large neutral amino acids (LNAAs);
- Particular conditions: dietary management under special conditions such as physical activity or during concurrent illnesses;
- Impact of the EG: subjective perception of how the publication of the EG[8] may have influenced changes in dietary management practices for patients with PKU.
- Responses to the questionnaire were analyzed using statistical analysis with qualitative parameters, including percentages (%) and absolute numbers (n).

RESULTS

Responses were collected from 13 metabolic centers: six from northern Italy, four from central Italy, and three from southern Italy. In some cases, more than one professional was present in the same center, resulting in a total of 20 professionals.

Newborn screening dietary management

The average time to initiate PKU dietary therapy was investigated in newborns who tested positive for NBS. The results showed that ≤10 days was reported in 85% (*n*=11/13) of cases, 10–14 days in 8% (*n*=1/3), and 14–21 days in the remaining 8% (*n*=1/13).

In the first 6 months of a patient's life, 54% (*n*=7/13) of the centers reported a preference for breastfeeding, allowing the baby to breastfeed *ad libitum* after a calculated amount of Phe-free protein substitute administered by bottle; 23% (*n*=3/13) of the centers mainly prescribed alternating breastfeeding and Phe-free protein substitute, while the remaining 23% (*n*=3/13) primarily recommended breastmilk expression to allow calculated amounts to be bottle-fed along with Phe-free protein substitute.

Metabolic control

There was a reasonably homogeneous result across the centers regarding blood Phe values considered indicative of good metabolic control by age group. All metabolic centers (*n*=13/13) considered Phe concentrations <360 µmol/L to be indicative of good metabolic control in children up to 12 years old. In patients aged ≥12 years, 77% (*n*=10/13) of the centers set or considered acceptable a maximum limit of up to 600 µmol/L, while 23% (*n*=3/13) of the centers chose lower values. Professionals were also asked to identify the ideal Phe concentration during pregnancy. In this regard, 54% (*n*=7/13) of the centers aimed for or found tolerable blood concentrations between 120 and 360 µmol/L, while the remaining 46% (*n*=6/13) considered it more protective to maintain lower upper limits, i.e., 240 µmol/L (Table I).

Table 1. Range of blood Phe values considered indicative of good metabolic control at different ages and during pregnancy, represented by single centers.

Centers	Patients <12 years (µmol/L)	Patients ≥12 years (µmol/L)	Pregnancy (µmol/L)
Center 1	120–360	120–360	120–240
Center 2	120–360	120–600	120–240
Center 3	120–360	120–600	120–360
Center 4	120–360	120–360 (420)	120–240
Center 5	120–360	120–360 (600)	120–240 (360)
Center 6	100–360	100–600	100–300
Center 7	NA–360	NA–600	NA–250 (300)
Center 8	120–360	120–600	120–300
Center 9	120–360	NA–600	120–360
Center 10	120–360	120–360	120–240 (360)
Center 11	120–360	120–600	120–360
Center 12	120–360	120–600	120–360
Center 13	90–360	120–600	90–360

() = tolerated value, even if not the primary target value. NA = not available.

Protein requirement

We asked all centers for the references used to define patients' ideal total protein intake (protein equivalents from Phe-free protein substitute plus natural protein). The data gathered showed that 85% (*n*=11/13) of the centers, although not homogeneous on the bibliographic source used, either refer to the general population indications by increasing the needs with a variable share of 20–40% or employ pathology-specific tables. Only 15% (*n*=2/13) reported relying on recommendations equivalent to those for the general population without additional proteins.

Detailed data for each center are presented in Table II.

Dietary Phe allocation in the diet

Centers described their preferred method of prescribing the dietary Phe allocation and which foods they consider as "exchange-free":

- 46% (*n*=6/13) of the centers reported using food exchange lists, specifying all foods to be limited as portions in grams already calculated for the day, based on the patient's daily tolerance (e.g., 100 mL of cow's milk for breakfast; 80 g potatoes for lunch, 40 g ricotta cheese for dinner; this will provide 378 mg/day of Phe and the patient has limited choice of food alternatives calculated by the center);

Table 2. References used to define ideal total protein intake in patients with PKU.

Centers	Source
Center 1	*P:* UK MRC 1993[31] *A:* WHO/FAO/UNU 2007[32] safe levels +40%
Center 2	LARN[33] 1996 +20–30%
Center 3	*P:* UK MRC[31] *A:* WHO/FAO/UNU 2007[32] safe levels +40%
Center 4	LARN 2014[34] +20%
Center 5	LARN 2014[34]
Center 6	LARN 2014[34] +20%
Center 7	WHO/FAO/UNU 2007[32] safe levels
Center 8	LARN 2014[34] +40%
Center 9	LARN 2014[34] +20%
Center 10	UK MRC 1993[31] 1993
Center 11	LARN 2014[34] +20–40%
Center 12	*P:* UK MRC 1993[31] *A:* LARN 2014[34] +20%
Center 13	WHO/FAO/UNU 2007[32] safe levels +20–40%

A = data for adolescent and adult population with PKU; P = data for pediatric population with PKU.

- 46% (*n*=6/13) reported employing the exchange system, teaching the patient to calculate the final portion from lists of foods with a fixed Phe content (e.g., 56 g potatoes = 1 exchange of 50 mg of Phe; if a patient wants to eat 2 exchanges for lunch, they will multiply 56 g potatoes by 2);
- 8% (*n*=1/13) indicated using the counting of Phe in mg/day by giving the Phe content of foods for 100 g and teaching the patient how to calculate portions for a daily amount of Phe.

Among the six centers using the exchange system, 50% (*n*=3/6) use exchanges of 50 mg of Phe, 33% (*n*=2/6) use exchanges of 20 mg, and 17% (*n*=1/6) use exchanges of 10 mg. The data are summarized in Figure 1.

Regarding allowing patients to consume certain low-Phe vegetables without counting them, 46% (*n*=6/13) considered foods with a content <75 mg/100 g as unrestricted, and 38% (*n*=5/13) instructed patients to count all foods, even those with low-Phe content. One center set the limit at 50 mg/100 g of Phe, and another allowed unlimited intake of all fruits and vegetables, regardless of protein or Phe content.

Finally, the study investigated the professional figures involved in the dietary titration process based on patient tolerance. Overall, 85% (*n*=11/13) of centers stated that dietary Phe intake is determined by collaborative teamwork involving both physicians and dietitians, 8% (*n*=1/13) reported that guidance is provided solely by the physician, and 8% (*n*=1/13) mentioned that the decision-making process is exclusive to the dietitian.

Protein substitutes other than standard amino acids supplements: casein glycomacropeptide (C-GMP) and large neutral amino acids (LNAAs)

We investigated the use of protein substitutes with C-GMP and LNAAs. The hypothetical limitations of C-GMP prescription included the phenotype of patients with PKU (classic/non-classic) and maternal PKU, given the residual amount of Phe and the scarce evidence for these patients. All centers declared that they would prescribe C-GMP-containing protein substitutes regardless of the patient's phenotype, including severe forms such as classic PKU; 54% (*n*=7/13) of the centers reported using C-GMP formulas

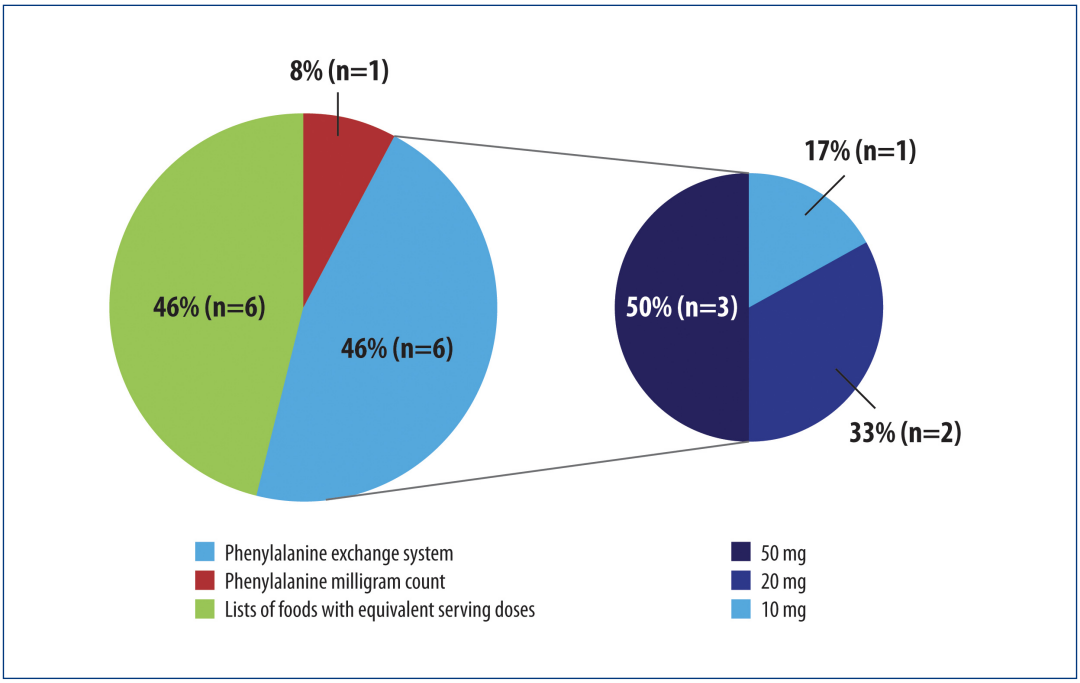

Figure 1. Different approaches in Italian clinical centers for the administration of dietary phenylalanine allocation.

even during pregnancy in patients with PKU, while 38% (*n*=5/13) would not prescribe them in pregnancy. Additionally, 8% (*n*=1/13) of the centers stated that they did not use C-GMP as their first choice during the gestational period but considered them a possible alternative if the patient did not accept the traditional amino acid-based substitute.

Overall, 61% (*n*=8/13) of the centers reported exclusively prescribing LNAA formulations in an adolescent-adult population with poor metabolic control. In contrast, 38% (*n*=5/13) stated they do not use them mainly due to insufficient evidence and unclear indications for use or lack of patients ideally eligible for treatment (e.g., one center exclusively follows the pediatric population).

Specific situations

We investigated dietary practices in two specific situations that can increase energy demands or induce the body into catabolic states, namely intense sports activities and intercurrent illnesses. For sports activities, 77% (*n*=10/13) of the centers reported providing specific guidance for athletes or individuals engaged in intense sports activities. Among the 10 centers, five specified the proposed intervention: two suggested variations in the timing of protein substitute intake; two centers adjusted the timing of protein substitute and carbohydrate intake where recommended; one center increased the total protein intake in addition to changing the timing of administration.

Regarding dietary management during intercurrent Illnesses, approximately 61% (*n*=8/13) of the centers reported changing dietary intervention during illnesses, such as infections or fever, as a temporary reduction or discontinuation of natural protein intake and fluid and carbohydrate supplementation, or just one of the two options. The data are presented in Figure 2.

Impact of the PKU EG on Italian dietary practices

Finally, we asked dietitians/nutritionists whether the publication of the 2017 guidelines[8] had practical implications for the management of patients with PKU. Among the centers, 61% (*n*=8/13) reported that they had, to some extent, adapted their clinical practices following the publication of guidelines. Two main aspects were emphasized. The first is the method used to estimate and calculate the protein

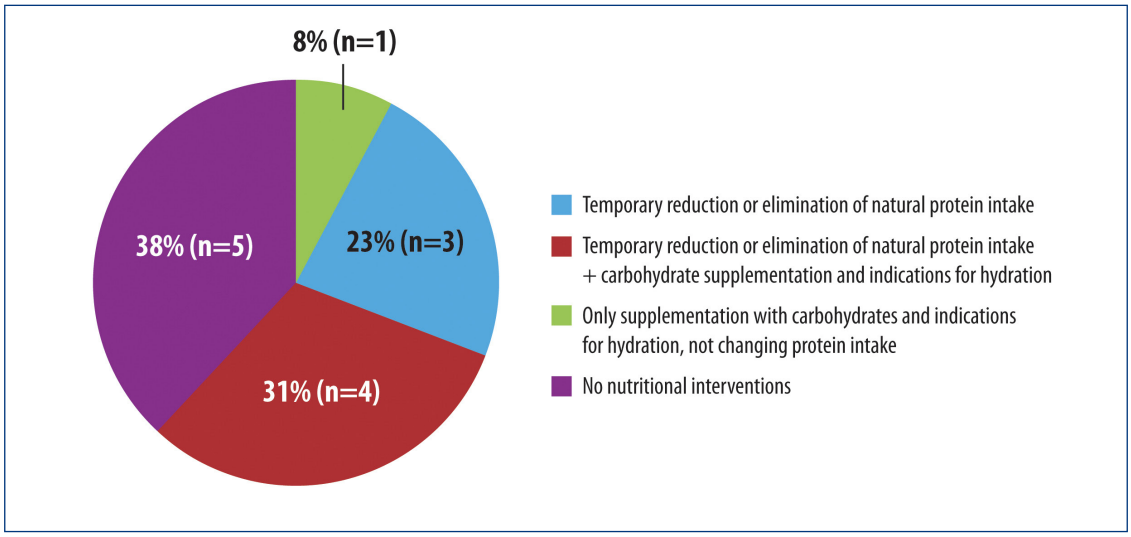

Figure 2. Dietary approaches to intercurrent illnesses in patients with phenylketonuria.

requirements of patients with PKU, which was modified by 38% of the centers (*n*=5/13). The second is the recommendation to consider foods with Phe content <75 mg/100 g as "unrestricted exchange", as declared by 23% of the centers (*n*=3/13), thus making dietary recommendations less stringent.

DISCUSSION

About 30 years after the introduction of screening for PKU in Italy, Italian dietitians/nutritionists wanted to investigate the dietary practices for PKU nationwide to analyze variations among centers and lay the foundation for future multicenter observational studies. The publication of the EG for PKU in 2017 represented an important moment of discussion among international centers, comparing dietary practices for patients with PKU[19,20].

In this study, we investigated dietary management practices and assessed the impact of the PKU EG on centers' dietary approaches. To this end, we analyzed data from a questionnaire sent to Italian dietitians and nutritionists experienced in PKU management to assess various aspects related to the treatment of the condition after the publication of the EG.

The study surveyed 20 dietitians/nutritionists from 13 centers currently managing Italian patients with PKU, estimated to be around 35 new patients each year (incidence of 1:11,300)[21].

For the first time, the collected data investigated the attitudes of dietitians/nutritionists experienced in PKU dietary management regarding various aspects. The study showed that most Italian centers are able to comply with the EG[8] on the timing of patient management for those who tested positive for NBS.

In addition to the treatment initiation, a practical aspect of managing newborns in the first months of life was indicated. More than half of the centers (54%) declared that, when breastmilk is available, the primary method of feeding the infant is to give an amount of Phe-free formula before breastfeeding until satiety, followed by those who prefer to alternate breastfeeding with Phe-free formula in 23% of cases. These results confirm our approaches similar to those previously underlined by Pinto et al[22] from other European centers.

A general consensus was demonstrated among Italian dietitians/nutritionists experienced in PKU regarding the blood Phe range levels for dietary management of different age groups and during pregnancy. In all cases, the values considered indicative of good control align with the EG for children <12 years old, while for older patients, only 77% of centers conform to guidelines.

Differences are also observed for maternal PKU, considering that 46% of centers reported maintaining more cautious limits of blood Phe level (e.g., upper limit of 240 µmol/L). This discrepancy is justified by the possibility that the fetus may be exposed to higher Phe concentrations during intrauterine life than those measurable in maternal blood. Although there is no scientific evidence regarding fetal outcomes, it is known that the placenta tends to concentrate Phe more in fetal blood than in maternal blood[23]. Therefore, Italian dietitians display an attitude of great caution in the management of pregnant patients with PKU.

An interesting finding of our study concerns current practices for protein requirements in patients with PKU. Most centers prescribe an increased daily intake of total protein (natural protein plus Phe-free protein equivalents) compared with the protein requirements of the general population. This aligns with the observation of the lower bioavailability of Phe-free amino acid-based protein substitutes for PKU and their variable induction of metabolic response *in vivo*[24]. Higher doses of Phe-free amino acid-based protein substitutes are also known to be associated with better blood Phe values in patients with PKU[25].

Although the formulation suggested by the EG for calculating total protein requirements has not been universally adopted, it is likely to have stimulated a general discussion among centers about current recommendations for protein intake in diet-treated patients with PKU. A few months after guideline publication, another investigation on dietary practices was conducted in Italy, and comparing results with those of the present study, the percentage of centers using recommendations for the general population and not specific for PKU decreased from 30% to 15%[26]. This indicates that more Italian centers are now distinguishing the protein requirements of patients with PKU from those of the general population, particularly by increasing the amount to 20–40% to correct protein quality and bioavailability.

To overcome the lower bioavailability of synthetic amino acid-based protein substitutes, formulations containing C-GMP, a natural protein extremely low in Phe and therefore suitable for PKU therapy, have been available for some years[27]. While C-GMP-based formulations may have advantages in terms of palatability, bone health, and body composition, they have raised concerns, especially for use in classic forms of PKU, because they contain a minimal amount of residual Phe that may impact blood Phe levels[28].

Our study found that using C-GMP as a protein substitute for PKU in Italy was consistently employed across different PKU phenotypes. Interestingly, approximately half of the centers reported using C-GMP even during pregnancy, although not recommended by guidelines due to a lack of literature data. However, it should be noted that the first case report describing its use in pregnancy was published later[29], and although data remain limited to date, confidence in these protein substitutes has increased.

LNAA-based formulations are protein substitutes containing mainly histidine, isoleucine, methionine, leucine, threonine, tryptophan, tyrosine, and valine at higher doses to compete with Phe in the LAT1 transporter and to lower blood Phe level. In the present study, we found that slightly more than half of the centers use LNAA-based formulations. Survey participants expressed concerns about the robustness of supporting studies for LNAA-based formulations, the difficulty of not having a clear marker to assess effectiveness, and the scarcity of data on ideal therapeutic dosages, as also expressed by the authors of guidelines[8].

Eight out of 13 centers declared providing specific recommendations to support intercurrent illnesses, intending to manage the moment of reduced tolerance to dietary Phe/increased Phe release from tissues, associated with increased energy demand and often reduced nutrient intake. Most Italian centers suggest that patients supplement carbohydrates (e.g., maltodextrins) with adequate hydration, as indicated by the EG[8]. No reduction in dietary Phe intake is recommended by guideline, as illness often leads to decreased appetite, which can significantly limit natural protein intake. It may be interesting to evaluate how these practices may affect the blood Phe levels of patients with PKU during illnesses.

As the average age of patients in follow-up increases, their nutritional needs are becoming different from childhood. Recently, physical activity management in patients with PKU has become a relevant aspect to consider in terms of its impact on metabolic control and optimization of sports performance. Most Italian centers (77%) reported addressing this aspect by adjusting the dietary regimen according to the type of physical activity practiced, focusing particularly on protein and carbohydrate intake timing. This intervention is an adaptation of recommendations for the general population, as also suggested in the practical supplement by the EG[4], since there is no specific evidence for sport and exercise nutrition in the population with PKU.

It has also been observed that, since the publication of the EG, among Italian dietitians/nutritionists, dietary practices for PKU have become less stringent, allowing unrestricted intake of fruits and vegetables (i.e., foods with Phe content <75 mg/100 g), with possible long-term prognosis benefits in terms of adherence and psychological impact[30]. Additionally, about half of the centers reported successfully using the "food exchange'' system, which theoretically allows for further diversification of natural protein-containing foods and, thus, greater variety in the PKU diet. There is a lack of studies on the different methods of allocating Phe in the diet, so it might be interesting to evaluate their impact on the family organization, dietary adherence, and food variety of patients with PKU.

Finally, 85% of the centers stated that managing prescribed Phe intake and its titrations over time is a shared responsibility between the physician and dietitian, demonstrating a model of integration between two professional figures.

CONCLUSIONS

The present study highlights how the publication of the PKU EG has stimulated a review of dietary practices for PKU in Italy, encouraging discussions among dietitians/nutritionists aimed at tailoring nutritional interventions. Such discussions within SIMMESN may lead to a future harmonization of practices for treatment personalization, even on topics not fully defined in the EG. We also believe that, with shared practices, it will be easier to compare patient outcomes in future observational studies, develop national educational materials for patients, and streamline the training of dietitians/professionals dedicated to PKU.

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Author Contribution:
SG developed the questionnaire, interpreted data, and analyzed data. SG, MG, S Par, wrote the first draft of the manuscript. All the remaining authors were involved in data collection, interpretation of data, critical revision of the paper for important intellectual content, and final approval of the version before publication. Supervision by AB and S. Pac.

Conflicts of Interest:
The authors declare no conflict of interest.

Data availability statement:
The datasets generated and/or analyzed during the ongoing study, as well as the original questionnaire used, are available from the corresponding author upon reasonable request.

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REFERENCES

1. Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier DM, Mitchell J, Smith WE, Thompson BH, Berry SA; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med 2014; 16: 188-200.
2. Singh RH, Rohr F, Frazier D, Cunningham A, Mofidi S, Ogata B, Splett PL, Moseley K, Huntington K, Acosta PB, Vockley J, Van Calcar SC. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. Genet Med 2014; 16: 121-131.
3. MacDonald A. Inborn errors in metabolism. In: Paediatric Nutrition in Practice, 2nd Edition. Koletzko B (Ed.). Karger: Basel, Switzerland, 2015; 226-233.
4. MacDonald A, van Wegberg AMJ, Ahring K, Beblo S, Bélanger-Quintana A, Burlina A, Campistol J, Coşkun T, Feillet F, Giżewska M, Huijbregts SC, Leuzzi V, Maillot F, Muntau AC, Rocha JC, Romani C, Trefz F, van Spronsen FJ. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis 2020; 15: 171.
5. MacDonald A, Rocha JC, van Rijn M, Feillet F. Nutrition in phenylketonuria. Mol Genet Metab 2011; 104 Suppl: S10-S18.
6. [Ahring K, Bélanger-Quintana A, Dokoupil K, Gokmen Ozel H, Lammardo AM, MacDonald A, Motzfeldt K, Nowacka M, Robert M, van Rijn M. Dietary management practices in phenylketonuria across European centres. Clin Nutr 2009; 28: 231-236.
7. Pinto A, Adams S, Ahring K, Allen H, Almeida MF, Garcia-Arenas D, Arslan N, Assoun M, Atik Altınok Y, Barrio-Carreras D, Belanger Quintana A, Bernabei SM, Bontemps C, Boyle F, Bruni G, Bueno-Delgado M, Caine G, Carvalho R, Chrobot A, Chyż K, Cochrane B, Correia C, Corthouts K, Daly A, De Leo S, Desloovere A, De Meyer A, De Theux A, Didycz B, Dijsselhof ME, Dokoupil K, Drabik J, Dunlop C, Eberle-Pelloth W, Eftring K, Ekengren J, Errekalde I, Evans S, Foucart A, Fokkema L, François L, French M, Forssell E, Gingell C, Gonçalves C, Gökmen Özel H, Grimsley A, Gugelmo G, Gyüre E, Heller C, Hensler R, Jardim I, Joost C, Jörg-Streller M, Jouault C, Jung A, Kanthe M, Koç N, Kok IL, Kozanoğlu T, Kumru B, Lang F, Lang K, Liegeois I, Liguori A, Lilje R, Ļubina O, Manta-Vogli P, Mayr D, Meneses C, Newby C, Meyer U, Mexia S, Nicol C, Och U, Olivas SM, Pedrón-Giner C, Pereira R, Plutowska-Hoffmann K, Purves J, Re Dionigi A, Reinson K, Robert M, Robertson L, Rocha JC, Rohde C, Rosenbaum-Fabian S, Rossi A, Ruiz M, Saligova J, Gutiérrez-Sánchez A, Schlune A, Schulpis K, Serrano-Nieto J, Skarpalezou A, Skeath R, Slabbert A, Straczek K, Giżewska M, Terry A, Thom R, Tooke A, Tuokkola J, van Dam E, van den Hurk TAM, van der Ploeg EMC, Vande Kerckhove K, Van Driessche M, van Wegberg AMJ, van Wyk K, Vasconcelos C, Velez García V, Wildgoose J, Winkler T, Żółkowska J, Zuvadelli J, MacDonald A. Weaning practices in phenylketonuria vary between health professionals in Europe. Mol Genet Metab Rep 2018; 18: 39-44.

8. van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 2017; 12: 162.
9. Burlina A, Leuzzi V, Spada M, Carbone MT, Paci S, Tummolo A. The management of phenylketonuria in adult patients in Italy: a survey of six specialist metabolic centers. Curr Med Res Opin 2021; 37: 411-421.
10. Kanufre V, Almeida MF, Barbosa CS, Carmona C, Bandeira A, Martins E, Rocha S, Guimas A, Ribeiro R, MacDonald A, Pinto A, Rocha JC. Metabolic control of patients with phenylketonuria in a portuguese metabolic centre comparing three different recommendations. Nutrients 2021; 13: 3118.
11. Jahja R, Huijbregts SCJ, de Sonneville LMJ, van der Meere JJ, Legemaat AM, Bosch AM, Hollak CEM, Rubio-Gozalbo ME, Brouwers MCGJ, Hofstede FC, de Vries MC, Janssen MCH, van der Ploeg AT, Langendonk JG, van Spronsen FJ. Cognitive profile and mental health in adult phenylketonuria: A PKU-COBESO study. Neuropsychology 2017; 31: 437-447.
12. Romani C, Palermo L, MacDonald A, Limback E, Hall SK, Geberhiwot T. The impact of phenylalanine levels on cognitive outcomes in adults with phenylketonuria: Effects across tasks and developmental stages. Neuropsychology 2017; 31: 242-254.
13. Burgard P, Ullrich K, Ballhausen D, Hennermann JB, Hollak CEM, Langeveld M, Karall D, Konstantopoulou V, Maier EM, Lang F, Lachmann R, Murphy E, Garbade S, Hoffmann GF, Kölker S, Lindner M, Zschocke J. Issues with European guidelines for phenylketonuria. Lancet Diabetes Endocrinol 2017; 5: 681-683.
14. Pinto A, Ilgaz F, Evans S, van Dam E, Rocha JC, Karabulut E, Hickson M, Daly A, MacDonald A. Phenylalanine tolerance over time in phenylketonuria: a systematic review and meta-analysis. Nutrients 2023; 15: 3506.
15. Evans S, Adam S, Adams S, Allen H, Ashmore C, Bailey S, Banks J, Churchill H, Cochrane B, Cook J, Dale C, Daly A, Dixon M, Dunlop C, Ellerton C, Emm A, Firman S, Ford S, French M, Gribben J, Grimsley A, Herlihy I, Hill M, Judd S, Lang K, Males J, McDonald J, McStravick N, Millington C, Newby C, Noble C, Pereira R, Pinto A, Robertson L, Robotham A, Ross K, Singleton K, Skeath R, Terry A, Van Wyk K, White F, White L, Wildgoose J, Woodall A, MacDonald A. Uniformity of Food Protein Interpretation Amongst Dietitians for Patients with Phenylketonuria (PKU): 2020 UK National Consensus Statements. Nutrients 2020; 12: 2205.
16. Bernstein L, Burns C, Sailer-Hammons M, Kurtz A, Rohr F. Multiclinic Observations on the Simplified Diet in PKU. J Nutr Metab 2017; 2017: 4083293.
17. MacDonald A, Rylance G, Davies P, Asplin D, Hall SK, Booth IW. Free use of fruits and vegetables in phenylketonuria. J Inherit Metab Dis 2003; 26: 327-338.
18. Law No. 104 of February 5, 1992, Article 6. Legge-quadro per l'assistenza, l'integrazione sociale e i diritti delle persone handicappate. https://www.gazzettaufficiale.it/eli/id/1992/02/17/092G0108/sg
19. Gomes M, Almeida MF, Barbosa CS, Gama MI, Peres M, Pinto É, MacDonald A, Rocha JC. Total Protein Intake in Patients with PKU: Adequacy Evaluation According to the European PKU Guidelines from 2017. Nutrients 2023; 15: 4883.
20. Chiesa A, Spécola N, Poubel M, Vela-Amieva M, Jurecki E, Vilela DR, Mesojedovas D, Carneiro GC, Eiroa H, Nakamura KH, de Almeida ML, Cunha RB, Amorim T, Schwartz IVD. Adherence to PKU guidelines among patients with phenylketonuria: A cross-sectional national multicenter survey-based study in Argentina, Brazil, and Mexico. Mol Genet Metab Rep 2023; 38: 101026.
21. SIMMESN technical report 2022. www.simmesn.it/it/documenti/rapporti-tecnici-screening-neonatale.html. (accessed 20 January 2024).
22. Pinto A, Adams S, Ahring K, Allen H, Almeida MF, Garcia-Arenas D, Arslan N, Assoun M, Atik Altınok Y, Barrio-Carreras D, Belanger Quintana A, Bernabei SM, Bontemps C, Boyle F, Bruni G, Bueno-Delgado M, Caine G, Carvalho R, Chrobot A, Chyż K, Cochrane B, Correia C, Corthouts K, Daly A, De Leo S, Desloovere A, De Meyer A, De Theux A, Didycz B, Dijsselhof ME, Dokoupil K, Drabik J, Dunlop C, Eberle-Pelloth W, Eftring K, Ekengren J, Errekalde I, Evans S, Foucart A, Fokkema L, François L, French M, Forssell E, Gingell C, Gonçalves C, Gökmen Özel H, Grimsley A, Gugelmo G, Gyüre E, Heller C, Hensler R, Jardim I, Joost C, Jörg-Streller M, Jouault C, Jung A, Kanthe M, Koç N, Kok IL, Kozanoğlu T, Kumru B, Lang F, Lang K, Liegeois I, Liguori A, Lilje R, Ļubina O, Manta-Vogli P, Mayr D, Meneses C, Newby C, Meyer U, Mexia S, Nicol C, Och U, Olivas SM, Pedrón-Giner C, Pereira R, Plutowska-Hoffmann K, Purves J, Re Dionigi A, Reinson K, Robert M, Robertson L, Rocha JC, Rohde C, Rosenbaum-Fabian S, Rossi A, Ruiz M, Saligova J, Gutiérrez-Sánchez A, Schlune A, Schulpis K, Serrano-Nieto J, Skarpalezou A, Skeath R, Slabbert A, Straczek K, Giżewska M, Terry A, Thom R, Tooke A, Tuokkola J, van Dam E, van den Hurk TAM, van der Ploeg EMC, Vande Kerckhove K, Van Driessche M, van Wegberg AMJ, van Wyk K, Vasconcelos C, Velez García V, Wildgoose J, Winkler T, Żółkowska J, Zuvadelli J, MacDonald A. Early feeding practices in infants with phenylketonuria across Europe. Mol Genet Metab Rep 2018; 16: 82-89.
23. Zaugg J, Ziegler F, Nuoffer JM, Moser-Hässig R, Albrecht C. Counter-directed leucine gradient promotes amino acid transfer across the human placenta. J Nutr Biochem 2021; 96: 108760.
24. Giarratana N, Giardino L, Bighinati A, Reiner G, Rocha JC. In Vivo Metabolic Responses to Different Formulations of Amino Acid Mixtures for the Treatment of Phenylketonuria (PKU). Int J Mol Sci 2022; 23: 2227.
25. MacDonald A, Chakrapani A, Hendriksz C, Daly A, Davies P, Asplin D, Hall K, Booth IW. Protein substitute dosage in PU: how much do young patients need? Arch Dis Child 2006; 91: 588-593.
26. Gestione dietetica della fenilchetonuria (PKU) in italia: cosa è cambiato dopo le Linee Guida europee. https://congressosimmesn.it/abstract_list.php (accessed 20 January 2024).
27. Daly A, Evans S, Chahal S, Santra S, Pinto A, Jackson R, Gingell C, Rocha J, Van Spronsen FJ, MacDonald A. Glycomacropeptide: long-term use and impact on blood phenylalanine, growth and nutritional status in children with PKU. Orphanet J Rare Dis 2019; 14: 44.
28. Daly A, Pinto A, Evans S, MacDonald A. Glycomacropeptide in PKU-Does It Live Up to Its Potential? Nutrients 2022; 14: 807.
29. Pinto A, Almeida MF, Cunha A, Carmona C, Rocha S, Guimas A, Ribeiro R, Mota CR, Martins E, MacDonald A, Rocha JC. Dietary management of maternal phenylketonuria with glycomacropeptide and amino acids supplements: A case report. Mol Genet Metab Rep 2017; 13: 105-110.
30. Huemer M, Huemer C, Möslinger D, Huter D, Stöckler-Ipsiroglu S. Growth and body composition in children with classical phenylketonuria: results in 34 patients and review of the literature. J Inherit Metab Dis 2007; 30: 694-699.

31. Recommendations on the dietary management of phenylketonuria. Report of Medical Research Council Working Party on Phenylketonuria. Arch Dis Child 1993; 68: 426-427.
32. Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser 2007; 935: 1-265.
33. Nutrizione Umana, Società Italiana (SINU) "Livelli di assunzione raccomandati di energia e nutrienti per la popolazione Italiana." LARN (Daily Assumption of Nutrient Levels for the Italian Population) (1996).
34. Società Italiana di Nutrizione Umana (SINU). LARN: Livelli di Assunzione di Riferimento di Nutrienti ed Energia, 4th ed.