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# SPECIAL LOW PROTEIN FOODS IN THE MANAGEMENT OF INBORN ERRORS OF METABOLISM: OVERVIEW ON AVAILABILITY, COMPOSITION AND COMPARISON WITH REGULAR FOODS IN ITALY

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***ABSTRACT* – Objective:** Special low-protein foods (SLPFs) are essential to achieving adequate caloric intake, improving dietary adherence, preventing catabolism and ensuring good metabolic control in patients with hereditary metabolic disease. This study aims to analyze the composition of SLPFs in Italy and compare them with similar regular foods (RFs).

**Materials and methods:** We collected data on the composition and ingredients of SLPFs distributed in Italy and on the composition of the corresponding RFs.

**Results:** A total of 177 SLPFs were identified and compared with 100 RFs from the same product categories. The average energy content was 326 kcal (range: 49.9–565.5 kcal) for all SLPFs and 329 kcal (range: 48.7–543 kcal) for all RFs. The amount of phenylalanine (Phe) was declared on 81% of SLPFs (143/177 products); for 54% of SLPFs (*n*=77/143), the Phe content was ≤25 mg per 100 g; for 7% of SLPFs (*n*=10/143), the Phe content was ≥100 mg per 100 g. Total carbohydrate content was higher in 51.8% (14/27) of SLPF subgroups than in RFs; sugars were higher in 33.3% (9/27) of SLPF subgroups than in RFs; 51.8% (14/27) of SLPF subgroups had higher total fat content than RFs, while 37% (10/27) of SLPF subgroups had lower total fat content than RFs. The fiber amount was >0 in 85% (*n*=151/177) of SLPFs, while 76% (*n*=135/177) of SLPFs contained added fiber.

**Conclusions:** SLPFs provide an important part of the energy requirements in the diet of patients with hereditary metabolic diseases; since these patients must follow the diet for life, improving the nutritional quality of these products is mandatory to ensure metabolic compensation and maintenance of good health in adulthood.

**Keywords:** Hereditary metabolic diseases, Low-protein diet, Special low-protein foods, Regular foods.

## INTRODUCTION

The management of hereditary metabolic diseases involving protein or specific amino acid metabolism (e.g., urea cycle defects, UCD, or amino acidopathies) focuses on a low-protein diet, which is essential to prevent irreversible neurological damage.

Some conditions, such as maple syrup urine disease (MSUD) or phenylketonuria (PKU), require a very low intake of natural proteins with the addition of amino acid supplements devoid of those involved in the deficiency. In other conditions (such as UCD), a low-protein diet is prescribed without necessarily adding special amino acid mixtures; the extent of protein restriction depends on the severity of the condition, which can range from asymptomatic to life-threatening[1-3].

In both cases, special low-protein foods (SLPFs) are essential to achieve adequate caloric intake to optimize growth and satisfy satiety; they offer the greatest possible variety and help replicate some normality in a lifelong restricted diet, improving dietary adherence. Both conditions are fundamental to prevent catabolism and ensure good metabolic control[3,4].

SLPFs are processed foods that replicate basic food, such as pasta, bread and cookies; they have limited protein content, and their composition is mainly based on fats and carbohydrates[4]. They are included in "Foods for Special Medical Purposes" (FSMPs), which are foods expressly developed for the dietary management of patients; they are used under medical supervision for complete or partial feeding of patients with limited ability to take, digest, absorb, metabolize or eliminate RFs or specific nutrients or metabolites and whose management cannot be accomplished solely by modifications of the normal diet. SLPFs are regulated by EU Regulation of the European Parliament n.609/2013[5], supplemented by the EU Commission Delegated Regulation 2016/128. In Italy, they must comply with the Ministry of Health guidelines on FSMPs (the last revision was in September 2023)[6]. According to these guidelines, SLPFs can be defined as substitutes for staple foods, such as bread, pasta and baked goods, with a protein residue not exceeding 1% or substitutes for protein-rich beverages, such as milk, with a protein residue not exceeding 0.5%. Substitutes for these foods with a protein residue between 1% and 2% can be defined as "hypoproteic".

The Italian Ministry of Health has developed a national registry of FSMPs. It was established by Article 7 of the Ministerial Decree of 8 June 2001, as amended by the Ministerial Decree of 17 May 2016[7]. This registry is divided into three sections, each by product and company and is updated monthly; it lists FSMPs that are reimbursable by the National Health Service to patients with specific pathological conditions, including hereditary metabolic diseases[7].

SLPFs are used in a variety of other pathological conditions (e.g., chronic kidney failure, Parkinson's disease), but in hereditary metabolic diseases their use is expected to be lifelong. Furthermore, due to low protein tolerance, SLPFs make an important contribution to daily energy intake in subjects with hereditary metabolic diseases; in severe PKU, with natural protein tolerance of less than 10 g/day, they may provide up to 50% of energy requirements[8,9]. Daly et al[4], analyzing SLPF contribution to the macronutrient intake in children with early-treated PKU, showed an average energy intake of 33% provided by SLPFs. Garcia-Arenas et al[10] found a similar average energy intake of 29% provided by SLPF consumption in children with hereditary metabolic disease, including conditions other than PKU.

In addition, in recent years, the number of adults suffering from hereditary metabolic diseases has increased significantly (improved neonatal survival, availability of expanded newborn screening) and prevention of cardiovascular risk has become an important part of treatment. In the review by Verduci et al[11], children with PKU did not show a different cardiovascular risk than healthy children. Similarly, Rodrigues et al[12], in their review, found no differences between patients with PKU and healthy controls in body mass index (BMI), except for a subgroup of patients with classical PKU that had a significantly higher BMI than healthy controls. Other studies in adult patients with PKU suggested potential cardiovascular risk due to low HDL cholesterol levels, elevated homocysteine levels[13] and increased markers of inflammation and oxidative stress[14]. Brambilla et al[15] found increased blood pressure, waist-to-height ratio and dyslipidemia associated with reduced resting energy expenditure (REE) measured by indirect calorimetry in patients with argininosuccinic aciduria. Although a higher prevalence of cardiovascular risk factors in the population with hereditary metabolic diseases is unclear, adult-related problems seem to emerge even in this group of patients, as in the general population (metabolic syndrome, hypertension, hypercholesterolemia and overweight). Therefore, other aspects of nutrition should be considered besides the anabolic effect of SLPFs and their role in metabolic control. For these reasons, the complete nutritional profile of SLPFs (e.g., fat quality, sugar content, salt, fiber, micronutrients) must be considered.

This study aims to analyze the composition of SLPFs distributed in Italy and to compare some aspects with similar RFs.

## MATERIALS AND METHODS

The list of SLPFs was obtained by cross-referencing the data from the national registry of FSMPs in Italy with those provided directly by the companies. SLPFs were organized into groups and subgroups that included bread (bread, breading, piadina, pizza base, frozen ready-to-eat pizza), pasta (pasta/rice, frozen ready-to-eat pasta, risotto), flour and mixes (flour, cake mixes, pancake/waffle/muffin mixes), baked product for breakfast (breakfast cereals, rusks, crispbread/rice or corn cakes), sweet snacks (biscuits or cookies, fruit bars, cakes, chocolate, cocoa hazelnut spread), salty snacks (crackers/breadsticks/taralli/croutons, industrial potato chips), desserts (puddings, powdered dessert mixes, yogurt mixes), milk replacers (liquid and powdered), baby food (instead cereal blend), meat replacers, cheese (cheese replacers, cheese sauce) and egg replacers. The division into groups and subgroups was similar to Wood et al[16], with little differences related to the Italian food tradition.

Composition data were obtained from websites and fact sheets available to healthcare professionals and provided directly by the companies. Data were collected concerning 100 g or 100 ml for energy, proteins, phenylalanine (Phe), total fats, saturated fats, carbohydrates, sugars, fibers and salt. Data for powdered products were expressed as 100 g of powder and not as diluted products unless otherwise specified. The ingredient list was also examined and data on the type of added fats, sugars and fibers were collected. When data on the type of added sugars were collected, maltodextrins were not considered. All information was collected on an Excel spreadsheet. The mean and the range of values for each subgroup were calculated for each nutrient using an Excel spreadsheet.

Similar data (except for the type of ingredients) were collected for RFs, which were chosen among the same product category based on similar texture, recipe and function. These data were obtained from the Italian Food Composition Database for Epidemiological Studies[17] when available, otherwise from individual commercial products by consulting the food brand websites. The database reported Phe content for most of the products considered; when not available, the value was estimated by considering the average equivalence between protein and Phe intake (1 g:50 mg). Where possible, only regular products in the same format as SLPFs were considered, such as dried format or after preparation. The nutritional composition of SLPFs and the equivalent RFs were compared by subgroup and variations less than ±10% were considered comparable. Only the SLPF egg, meat and cheese substitutes were excluded from this comparison because they are very different in ingredients than RFs. The final list of SLPFs and composition data were updated to January 2024.

## RESULTS

Overall, 177 SLPFs distributed by 10 companies were identified and compared with 100 RFs from the same product categories. **Supplementary Table 1** reports the percentage difference between the mean values for calories, macronutrients, fibers and salt. **Supplementary Table 2** shows the nutritional composition data for low-protein substitutes of protein-rich food.

The analysis of the 177 items also includes 11 products currently available only for sale and notified to the Ministry of Health but not yet included in the national registry of FSMPs.

The imbalance between the numerical samples of SLPFs and RFs can be neutralized by considering that the RFs in the Italian Food Composition Database for Epidemiological Research (BDA) are often the result of averaging among several products (from three to six different brands for the same food).

### Energy

The mean energy content (per 100 g) for all SLPFs (*n*=177) was 326 kcal (range: 49.9–565.5 kcal) and for all RFs (*n*=100) was 329 kcal (range: 48.7–543 kcal). Energy content was comparable for 67% of the subgroups of products (*n*=18/27). For SLPFs, the mean energy values for low-protein hazelnut spread, piadina, risotto and industrial potato chips (crisps) were 14–36% lower than the regular varieties. Low-protein breading, frozen ready-to-eat pasta, fruit bars, puddings and dessert mixes contained 15–80% more energy than regular versions (**Supplementary Table 1**).

### Proteins and Phenylalanine

The amount of Phe was declared on 81% of SLPFs (143/177 products).

For 54% of SLPFs (*n*=77/143), the Phe content was ≤25 mg per 100 g.

For 27% of SLPFs (*n*=39/143), the Phe content was ≥50 mg per 100 g.

For 7% of SLPFs (*n*=10/143), the Phe content was ≥100 mg per 100 g.

All SLPF subgroups contained 23–100% less protein and 44–100% less Phe than RFs.

**Supplementary Table 1** displays the range for Phe content.

### Carbohydrates and Sugars

The total carbohydrate content was higher in 51.8% (14/27) of SLPF subgroups than in RFs; the largest difference was found in yogurt mixes, industrial potato chips and liquid milk replacers (63%, 56% and 51%, respectively). Considering the grams of carbohydrates in 100 g of food, the difference was 3.9 g, 28.6 g and 2.6 g, respectively (**Supplementary Table 1**).

Regarding sugar content, it was higher in 33.3% (9/27) of SLPF subgroups than in RFs; crispbread/rice or corn cakes and breakfast cereals contained 1 and 24% more total carbohydrates, respectively, than RF analogues, but 543 and 212% more sugars; in crispbread/rice or corn cakes, the difference was low (only 3.8 g of sugars on 100 g of product) while in breakfast cereals the difference was 22.1 g of sugars on 100 g of product (**Supplementary Table 1**).

The two SLPF subgroups of biscuits and cakes contained fewer sugars than the corresponding RFs (-34% and -47%, respectively); while the sample of SLPFs also included foods without added sugar (with artificial sweeteners), the sample of RFs did not; sweeteners were contained in 6/25 biscuits (24%) and in 6/10 cakes (60%); artificial sweeteners were used as the sole source of sweetener in 5/25 biscuits (20%) and in 4/10 cakes (40%). Considering only SLPFs that did not contain sweeteners, their content of simple sugars was still lower than that of RFs; however, the difference was less noticeable (-17.7% for biscuits and -15.3% for cakes, respectively). SLPFs with non-nutritive sweeteners (NNS) had lower calorie content than SLPFs with natural sugars; about -10% of calories were for cakes and -5% for biscuits.

About 79% of SLPFs (140/177) contained an added source of sugars (excluding products containing only artificial sweeteners and no natural sugars). About 10.7% of SLPFs (19/177) contained artificial sweeteners; 47% (9/19) of SLPFs were without natural sugars and 53% (10/19) together with natural sugars.

Figure 1 shows the sources of added sugars in SLPFs identified from the ingredient list; sucrose and brown sugar were together the main sources and were present in 56.5% of SLPFs (100/177); other sourc-

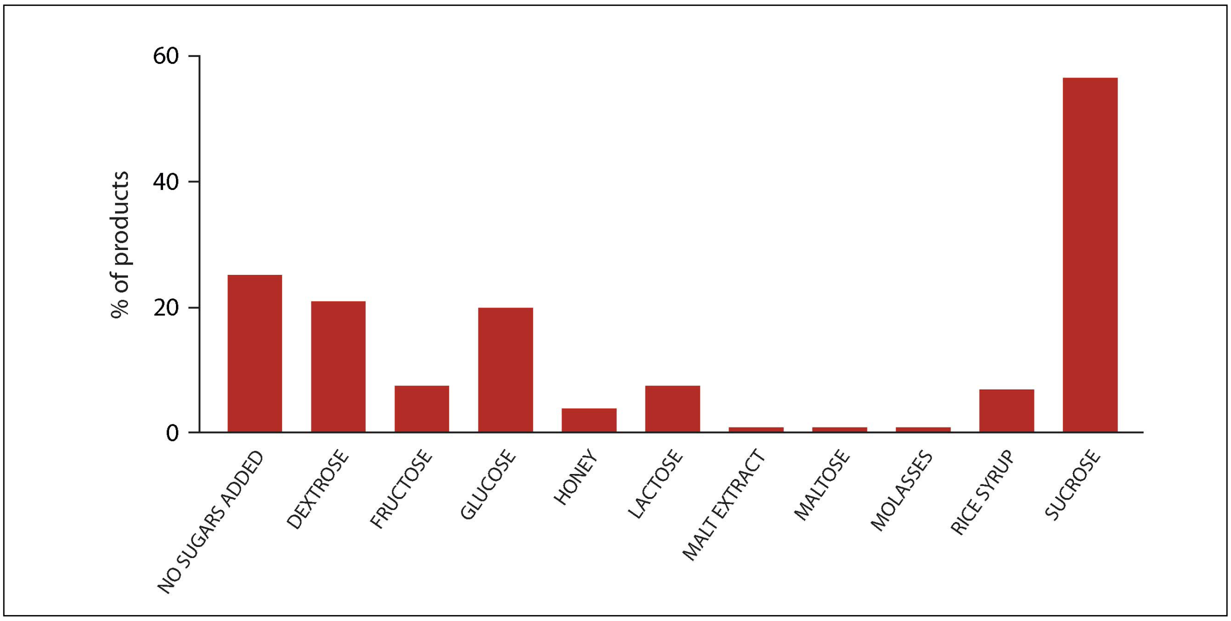


**Figure 1.** Sources of added sugars in SLPFs identified from the ingredient list.

es of added sugars were glucose and dextrose (both contained in 20% of SLPFs). Considering the pasta, bread, flour and mixes, salty snacks, meat and egg replacer groups (total 74 foods), sucrose and brown sugar were present in 64.8% of SLPFs (48/74).

Added sugars were found in 100% of baked products for breakfast, flour and mixes and milk replacers, in >90% of bread and in 80–90% of salty snacks, desserts and sweet snacks. Added sugars were present in 33% of meat replacers and in about 20% of pasta and egg replacers. Baby food and cheese did not contain added sugars (Figure 2).

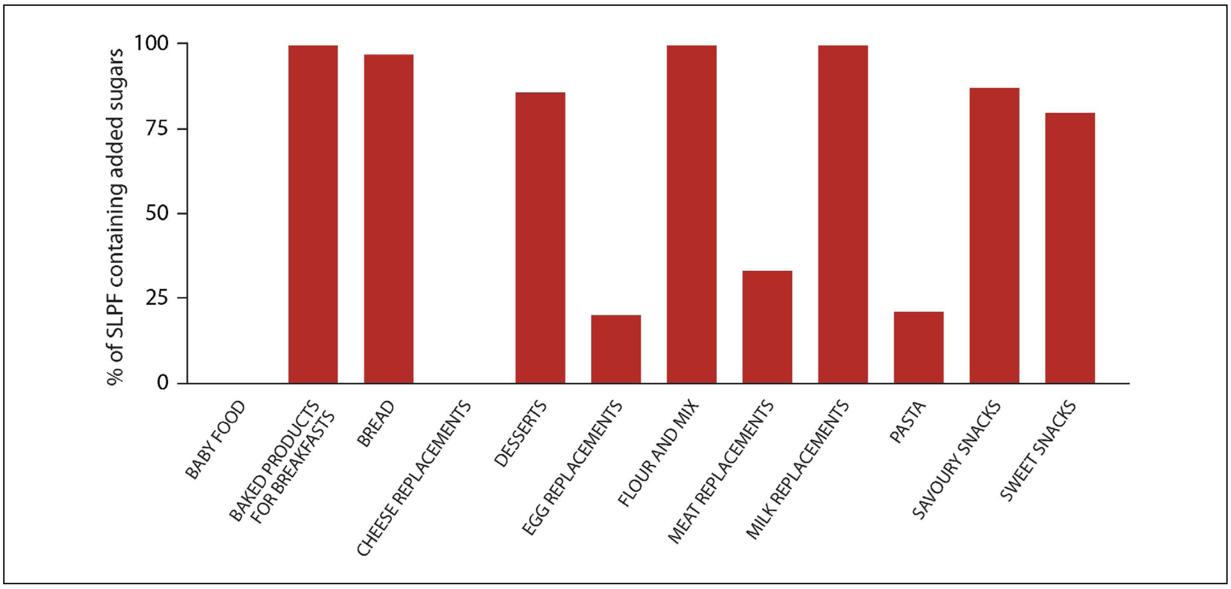


**Figure 2.** Percentage of SLPFS containing added sugars by groups.

## Total and Saturated Fats

In general, 51.8% (14/27) of SLPF subgroups had higher total fat content than RFs; the largest difference was found in dessert mixes, risotto and pancake/waffle/muffin mixes (1,989%, 614% and 544%, respectively). Considering the grams of fats in 100 g of food, the difference was 6 g, 4.3 g and 10.5 g, respectively.

Total fat content was lower in 37% (10/27) of SLPF subgroups than RFs; the largest difference was found in crispbread/rice or corn cakes, breakfast cereals and instant cereal blends (-74%, -73% and -72%, respectively). The difference between grams of fats in 100 g of food was -1.7 g, -3.4 g and -1.3 g, respectively.

The content of saturated fats was higher in 62.9% (17/27) of SLPF subgroups than in RFs; breading, cake mixes and dessert mixes contained 1,900%, 530% and 347% more saturated fats, respectively (4.7 g, 0.7 g and 1.5 g per 100 g of food, respectively).

Saturated fat content was lower in 33% (9/27) of SLPF subgroups than in RFs; the largest difference was found in piadina, infant cereal blend and industrial potato chips (-80%, -80% and -78%, respectively). Considering grams of saturated fats in 100 g of food, the difference was -2.5 g, -0.5 g and -8.6 g, respectively.

About 75.7% of SLPFs (134/177) contained an added source of fats; the main source of added fats was palm oil or palm fat, added in 69/177 SLPFs (39%); 42/177 (23.7%) SLPFs contained sunflower oil; only 13/177 SLPFs contained extra virgin olive oil (7.3%). Added fats were found in 7 of 177 products (3.95%) without specifying the origin in the ingredient list (Figure 3).

Fats with a prevalent content of unsaturated fatty acids (extra virgin olive oil, sunflower oil, colza oil, soybean oil and canola oil) were found in 44/177 (24.8%) SLPFs. Of these 44 foods, 28 were included in the bread group (77% of bread food group), four were meat replacers (44% of meat substitute foods), two salty snacks (13% of salty snack food group), two desserts (33%), five sweet snacks (11%), one egg replacer (20%). They were distributed by seven companies, of which three distributed 30 products.

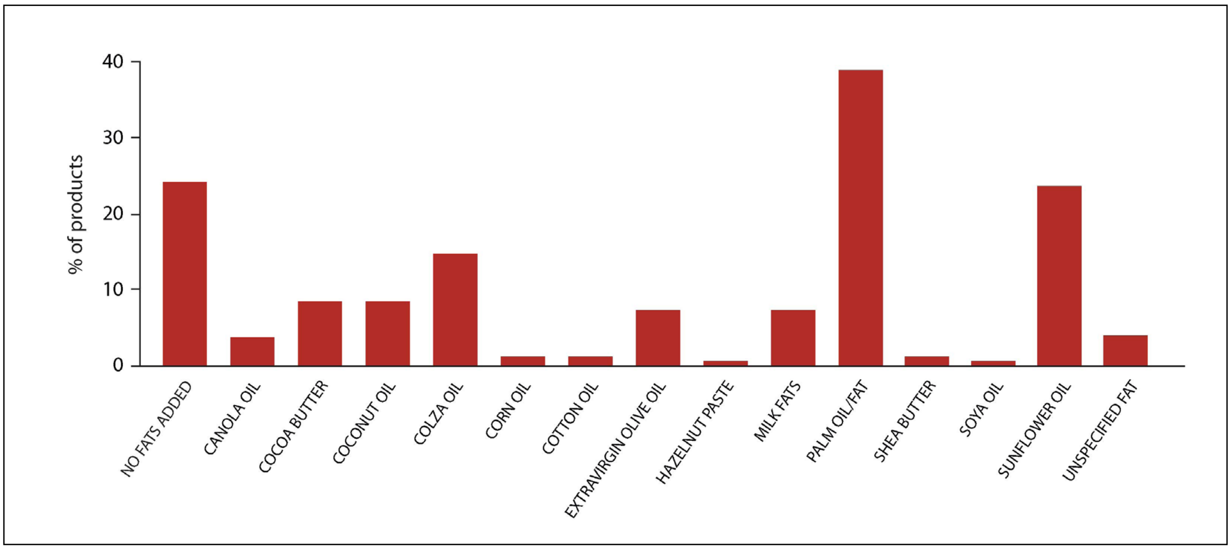


**Figure 3.** Sources of added fats in SLPFs identified from the ingredient list.

Added fats high in saturated fatty acids were present in 85/177 SLPFs; 54 contained only this type of fats, while the other 31 contained both unsaturated and saturated fats. Of these 85 foods, 37 were included in the sweet snack group (82% of sweet snack food group), 12 were salty snacks (80%), 10 milk replacers (90%), 8 bread products (22%), 4 pasta (21%) and baked products for breakfast (44%), 3 desserts (50%), 4 mixes (18%) and cheese replacers (75%) and 1 meat replacer (11%).

## Fiber

From the nutritional analysis, 85% (*n*=151/177) of SLPFs quantified a fiber amount (>0) and 76% (*n*=135/177) contained added fiber. The most frequent fiber sources added to SLPFs were guar gum (37%), hydroxypropyl-methylcellulose (31%) and psyllium (24%). Following, methylcellulose, carob seed flour, wheat fiber, cellulose and inulin/chicory inulin were often represented (10–17%) (Figure 4).

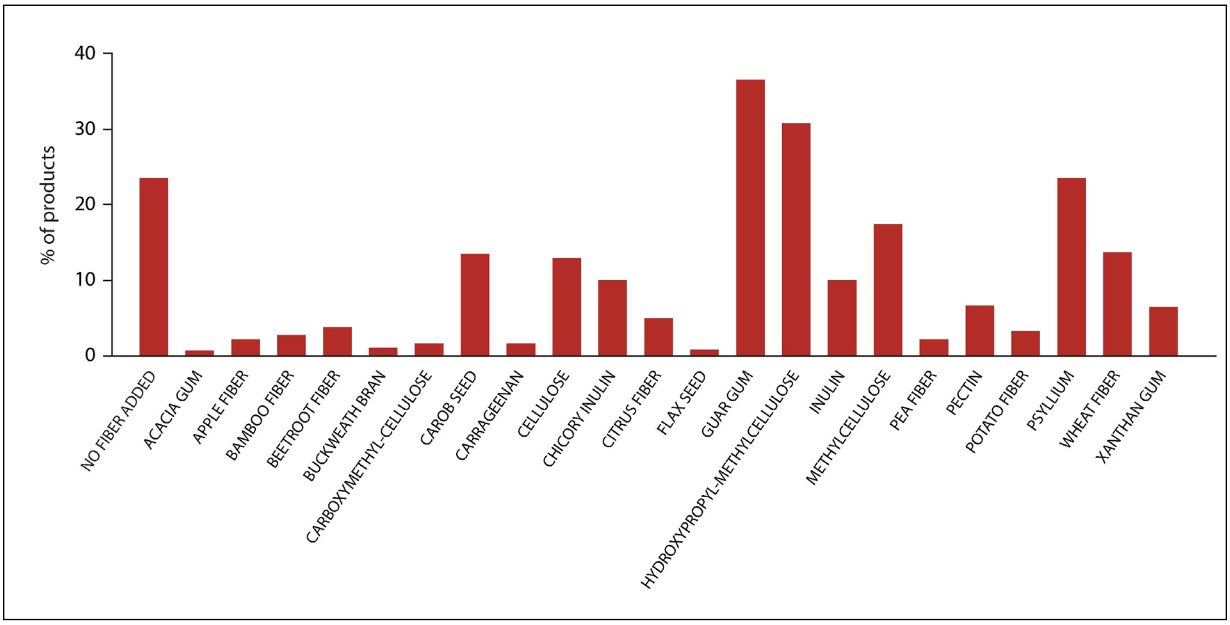


**Figure 4.** Percentage of SLPF products containing different types of fiber (total n=177).

When analyzing RFs, we observed that an average amount of fiber was available for 92% of the products (*n*=93/100), but only 13% of the RF list were wholegrain products or products with added fiber. Our RF sample does not represent the actual consumption frequency of whole grains but reflects the categorization of the BDA (about one wholegrain product per cereal-based food group). This limitation should be considered when interpreting the following results: fiber content in the nutritional analysis showed that all SLPFs contained an average of 60.7% more fiber than regular protein-containing products (average total fiber of SLPFs=4.5 g/100 g; average total fiber of RFs=2.8 g/100 g). Low-protein bread, pizza, piadina, frozen ready-to-eat pasta, rusks, crispbread, pancake/waffle/muffin mixes and dessert mixes contained significantly more fiber than the corresponding RF products (71–451%, see **Supplementary Table 1**). The largest difference was between low-protein yogurt mixes and real yogurt (2400%). Only flour, breakfast cereals and some snacks like salted crackers, biscuits, cakes, or chocolate replacers were found to contain less fiber (16–63%, see **Supplementary Table 1**). The fiber content of meat, eggs and cheese replacers was higher than that of RF equivalents, which contained only trace amounts.

### Salt and Micronutrients

The mean salt content (per 100 g) for all SLPFs (*n*=177) was 0.54 g (range: 0.0–3.7 g) and for all RFs (*n*=103) was 0.78 g (range: 0.0–2.5 g). For SLPFs, the mean salt values were 17-93% lower than in regular varieties, except for low-protein pasta/rice, flour, crispbread, hazelnut spread, crisps and instant cereal blend, which contained 14–2800% more salt than regular versions. For the milk subgroup, the salt content was comparable. For 19% of SLPFs (*n*=34/177), the salt content was ≥1 g (400 mg of sodium) on 100 g of product. The content of vitamins and minerals (except sodium, potassium and phosphorus, as required by the Ministry of Health guidelines 2023) is minimally specified in the labels of SLPFs; therefore, it was not possible to compare them with RFs.

Considering all the 177 SLPFs analyzed, only 24 (14%) stated the vitamin and mineral content in the ingredient list.

## DISCUSSION

To our knowledge, this is the first paper to analyze in detail the macro- and micronutrient composition of SLPFs available in Italy and their comparison with the corresponding RFs; the ingredient list of SLPFs was also analyzed.

Previously, only the numerical availability of SLPFs in Italy was quantified by Pena et al[18] about 10 years ago; they showed an availability of 256 SLPFs in Italy (more than twice as many products as in other European countries). In our count, we found only 177; this difference may be due to different ways of counting pasta substitutes because we unified the various pasta shapes produced by the same company when they had the same composition. Furthermore, in recent years, some companies have reduced the range of SLPFs distributed. However, the Italian availability of SLPFs is higher than that in the UK (146 SLPFs)[16], Turkey (148 SLPFs)[19] and Portugal (73 SLPFs)[18] and lower than that in Spain (250 SLPFs)[10]. To achieve good metabolic control, adequate caloric intake is essential; therefore, high SLPF availability is a fundamental part of dietary therapy because it contributes to increasing variety[18].

Our comparison between the nutritional characteristics of SLPFs and RFs in Italy showed several differences, as found in studies from other European countries[10,16,18,19].

Energy content was similar to 67% of the product subgroups, with only 26% of SLPF subgroups containing more (>10%) than RFs and 15% of SLPF subgroups containing less (<10%) than RFs. For 54% of SLPFs, the Phe content was ≤25 mg/100 g of the product. The remaining 46% of SLPFs contained Phe >25 mg/100 g, whereas, in the UK study, only 9% of SLPFs contained Phe >25 mg/100 g (Wood et al[16]). Therefore, in Italy, more types of foods should be restricted and given in controlled amounts in a low-Phe diet. SLPFs containing Phe ≥100 mg/100 g (7%) and SLPFs in which Phe is not declared on the label (19%) make it more difficult to follow a low-Phe diet because patients and healthcare professionals may be unsure of their suitability.

The sugar content was higher in 33.3% of SLPF subgroups than in RFs. Added sugars were also added in some types of SLPFs where it would not be expected to find them; for example, two out of 16 types of pasta contained added sugar; 7/7 types of flour (excluding cake mixes and pancake/waffle/muffin mixes) contained added sugars and had 111% more sugars than the corresponding RFs; sugars were contained in 13/14 crackers/breadsticks/taralli/toasts and the difference with RFs was +31%. Since these types of foods are widely consumed in Italy, it will be easier to eat an excessive amount of sugars. Carbohydrates were also contained in meat replacers (42 g/100 g), cheese sauce (88 g/100 g) and egg replacers (83.9 g/100 g). As for meat replacers, 3/9 contained added sugars.

For overall health, it is important to limit daily consumption of simple sugars, and consequently it is essential that SLPFs contain no sugars where corresponding RFs do not include any (flour and salty snacks).

Higher than the recommended sugar intake in children and adolescents is known to be associated with increased dental caries and adiposity[20]. In addition, salt and free sugars are important risk factors for hypertension and obesity, which are positively associated with the early development of vascular alterations leading to cardiovascular diseases in adulthood[21].

Moretti et al[9] analyzed the glycemic index and glycemic load of the diet in 21 children with PKU. It showed that they consumed more carbohydrates than healthy controls and their diets had a higher glycemic index and a higher glycemic load; they had higher plasma triglyceride levels than healthy controls, while blood glucose and insulin concentrations were not different.

Couce et al[22] evaluated biochemical markers of basal and postprandial carbohydrate metabolism in patients with PKU and healthy controls. They observed increased rates of insulin resistance with higher levels of basal insulin, particularly evident in adults and overweight and obese patients; caloric intake in the form of carbohydrates was higher and positively correlated with fasting insulin, BMI and waist circumference[22].

Brambilla et al[15] evaluated anthropometric parameters, body composition, metabolic syndrome risk and REE in patients with UCD; they found that patients with argininosuccinic aciduria had reduced indirect calorimetry-REE associated with increased blood pressure, increased waist-to-height ratio and dyslipidemia, with the risk of excessive energy intake and consequently the possibility of increased cardiovascular risk.

Therefore, it is very important that SLPFs, which represent an important part of energy intake and a lifelong treatment, contain a controlled amount of simple sugars to support the best long-term healthy eating pattern.

About 10.7% of SLPFs (19/177) contained artificial sweeteners, 47% (9/19) of SLPFs without natural sugars and 53% (10/19) together with natural sugars. One of the purposes of adding NNS was to reduce energy content, but in our sample, the reduction was -10% of Kcal in cakes and -5% in biscuits; this may have short-term effects, but the efficacy and safety of NNS as a long-term weight management strategy remain to be evaluated. Furthermore, research on the effects of NNS in children is lacking[20]. Therefore, SLPFs containing NNS should have a clear label claim.

Regarding fat content, 14/27 SLPF subgroups had higher total fat content than RFs. Among these, liquid milk substitutes contained 84% more total fats and 76% more saturated fats; crackers/breadsticks/taralli/toast 13% more total fats and 129% more saturated fats; biscuits or cookies had a fairly similar total fat content, but 67% more saturated fat. Knowing that these products are generally consumed frequently by the Italian population implies a higher consumption of mainly saturated fats. Low-protein bread contained 100% more total fats and 63% more saturated fats than RFs, but the difference in saturated fats was only 0.4 g/100 g, so the increase in fat content was mainly due to unsaturated fats.

In a review of the literature on cardiovascular risk in PKU, Verduci et al[23] concluded that children with PKU adhering to the diet did not exhibit a different cardiovascular risk than the healthy population. Children with PKU had lower blood total cholesterol, LDL cholesterol, plasma asymmetric dimethylarginine levels and diastolic pressure than healthy controls; there was no difference in obesity prevalence and HDL cholesterol levels[23]. In contrast, Azabdaftari et al[14] showed an increase in traditional cardiovascular risk factors in a group of 23 adult patients with PKU (high blood pressure, increased total and LDL cholesterol, reduced HDL cholesterol) and high levels of inflammatory markers and oxidative stress, highlighting the need for early control of risk factors.

Gündüz et al[13] analyzed atherogenic risk factors in non-compliant and well-compliant adolescents with PKU and detected a reduction in high-density lipoprotein cholesterol and an increase in homocysteine in patients with PKU; this was more prominent in compliant patients, concluding that PKU might be at risk for atherosclerosis.

Garcia-Arenas et al[10] evaluated the effect of SLPF consumption on lipid and plasma glucose profiles; children who consumed more than 5% of calories from dairy SLPFs had higher intakes of calories from SLPFs and higher intakes of saturated fats and sugars with increased levels of LDL cholesterol than children with lower consumption of these products.

Regarding label clarity, only 7/177 SLPFs did not have clear indications of the origin of the added fats. Based on a similar assessment by the authors in 2003, the number of SLPFs that did not specify the origin of the fats was 14/23 (Unpublished personal data); the two figures are not comparable because the 2003 analysis did not include all the products available but only bread, salty snacks and sweet snacks. However, there seems to be a trend toward greater label clarity. Product labels must be as clear as possible for informed consumer choice and proper nutritional assessment by healthcare professionals.

Reading the labels, only four SLPFs declared the presence of partially or fully hydrogenated fats on the label and 19 contained non-hydrogenated fats. In the other SLPFs, it was not specified whether added fats were hydrogenated; this did not allow the consumer to know which SLPFs might contain trans fatty acids. Trans fatty acids are unsaturated fats that contain at least one double bond in the trans configuration; they are formed during the widely used industrial process of partial hydrogenation of vegetable oils to obtain solid fats. Research has shown that they are harmful to health, with a particular connection to cardiovascular disorders[24]. Avoiding the consumption of trans fats is an important dietary habit to prevent cardiovascular disorders[25]. Te Morenga et al[26] suggested reducing saturated fatty acids to below 10% of total energy intake and replacing them in the diet with polyunsaturated fatty acids or with a mixture of polyunsaturated fatty acids/monounsaturated fatty acids to achieve the greatest effect on cholesterol. This agrees with the World Health Organization (WHO) recommendations to reduce saturated fat intake in adults and children to less than 10% of the total energy intake and to reduce trans fatty acids to less than 1% of the total energy intake[27].

The European and Italian regulations governing SLPFs do not provide specific indications on the content of saturated, hydrogenated and trans fatty acids. However, given their detrimental health effects, more clarity from companies and stricter rules by institutions are needed. Nowadays, most SLPFs are enriched in fiber and Italian SLPF labeling regulations are becoming more precise than in the past. The fiber content per 100 g of product is reported much more frequently, even compared with other countries[10,16].

Given the abundant use of SLPFs by patients with inborn errors of protein metabolism, knowing the quantity and quality of fiber intake of these products is essential (as is the intake of sugars, saturated fats and salt). In patients with PKU, about 59–67% of their total energy intake may come from SLPFs[8] and studies have shown that children with PKU have higher carbohydrate and fiber intake[11,28,29]. Several articles have reported improved or similar biomarkers of cardiovascular disease in patients with PKU compared with healthy controls[23,30-32].

According to other scientific evidence[16,19], we observed an increased amount of fiber in SLPFs *vs.* RFs. In our study, SLPF products had 60.7% more dietary fiber overall than products with regular protein content. As already specified, the reliability of this result may be somewhat limited by the assembly of an RF sample that is not fully representative of the real consumption frequency of wholegrain products and their availability on the Italian market. If we compare the average fiber content of low-protein bread (7.7 g/100 g; 30/30 of the products contained added fiber) with the same datum for regular wholegrain bread (4.2 g/100 g; 3/12 of the items were whole grains), the percentage difference is about +15% and not +86%, as shown in **Supplementary Table 1**. Further investigations are needed to better compare fiber intake from regular SLPFs or wholegrain RF consumption. Regarding sweet and salty snacks, our results are in contrast to those of Turkish researchers[19], who reported significantly higher fiber values in the low-protein varieties.

The predominant source of fiber added to SLPFs is hydrocolloids. Our results are consistent with recent scientific evidence from the analysis of SLPFs in other countries that adding hydrocolloids is predominant in improving the quality, formulation and consistency of low-protein products[16,19]. These types of fibers are increasingly used by the food industry as they help generate a solid, gelatinous mass, improving consistency, appearance and palatability[16,19]. The most frequent fibers in our sample of SLPFs were guar gum, hydroxypropyl-methylcellulose and psyllium. Although hydrocolloids have a fiber content of 60–90%, their evaluation status as a dietary source of fiber has not been fully investigated[19,33].

On the other hand, fibers, such as carrageenan (E407) and carboxymethylcellulose (E466), have been found to be poorly represented. They are used as thickening and emulsifying additives and their regular consumption has been associated with the condition of dysbiosis that characterizes inflammatory bowel diseases in the context of a typical Western diet[34,35].

In any case, regular consumption of SLPFs may impact gastrointestinal function and influence the gut microbiota. Verduci et al[11] highlighted that microbial diversity in children with PKU is indeed associated with gut dysbiosis compared with children with mild hyperphenylalaninemia. Subjects with hyperphenylalaninemia revealed an enriched microbial ecosystem compared with children with PKU, who showed a decrease in total short-chain fatty acids and butyrate production and depletion of butyrate-producing bacteria (such as *Faecalibacterium prausnitzii* and *Roseburia*) and *Lactobacillus* spp[11]. An increase in the *Prevotella* strain was observed in children with PKU with increased vegetable and fiber intake[29]; the supplementation of SLPFs with inulin was correlated to a beneficial change in the microbial composition[11].

Another common feature of SLPFs is the lack of micronutrient information on the label compared with regular-matched foods. Micronutrients are mainly consumed through L-amino acid supplements in conditions where the diet requires their use (e.g., PKU, MSUD, glutaric aciduria type 1). In other conditions (e.g., UCD) where the use of these supplements is not mandatory, taking adequate levels of minerals and vitamins may be difficult depending on the degree of protein restriction of the diet. For this reason, the nutritional profile must be fully identified on the label. For 19% of SLPFs (*n*=34/177), salt content was elevated ≥1 g (400 mg of sodium) per 100 g of product. Excessive sodium intake (defined by WHO as more than 2 g of sodium or more than 5 g of sodium chloride per day) is directly linked to high blood pressure; it has been found that the higher the daily salt intake, the higher the systolic blood pressure[36]. Therefore, educating patients to read the label and not exceed the daily amount of salt is important. In general, low sodium content is defined as <140 mg of sodium per serving, while high sodium content is defined as >400 mg per serving[37].

Providing only energy and macronutrient contents on the labels of special medical diet products may prevent patients with PKU from tracking their micronutrient status. For example, vitamin B12 deficiency may occur in patients with PKU who stop consuming protein sources, vitamins and mineral supplements but maintain a low-protein intake[38].

Additionally, SLPFs should contain a warning indicating that their nutritional profile does not replicate RFs because patients, caregivers and healthcare professionals may assume they provide other nutrients besides energy. Currently, no detailed studies outline their full nutritional contribution to a low-Phe diet[18]. In nutritional education, the dietitian must explain to patients the nutritional differences of SLPFs from RFs, in particular for meat, cheese, eggs and milk substitutes, as the minerals classically present in RFs are absent in SLPFs (e.g. calcium, iron, vitamin B12).

Our study has some limitations, such as the lack of information regarding the ingredients and the source of sugars/fats/fiber of RF products, when nutritional data were collected from the BDA and the need to assemble a better sample of RFs, taking into account frequency of consumption and market availability of wholegrain products, for a most reliable analysis of fiber intake. At the same time, our analysis represents the first attempt to report the macro- and micronutrient composition of all SLPFs available in Italy and to compare these features with the corresponding RFs, representing the basis for future, more in-depth analyses.

## CONCLUSIONS

SLPFs provide an important part of the energy requirements in the diet of patients with hereditary metabolic diseases. Therefore, improving the quality of the entire diet is necessarily linked to their characteristics. It is essential to have access to their detailed composition and, since patients with hereditary metabolic diseases have to follow the diet for life, to improve the nutritional quality of these products as much as possible, consistent with what may be the requirements related to production processes. The guidelines issued by the institutions should contain more precise indications on the type of ingredients used, maximum limits of certain nutrients (such as simple sugars and saturated fats) and limitations of ingredients that may have negative health implications, contributing to the development of cardiovascular complications.

In this way, the best possible dietary quality could be proposed to these patients, with attention not only to metabolic compensation but also to dietary characteristics that help to promote the maintenance of good health in adulthood, such as limiting the intake of saturated fats and simple sugars, not exceeding in energy intake and providing adequate fiber intake of good nutritional quality.

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SS, MG and SC collected data on SLPFs; AC and VP collected data on RFs. All the authors contributed to the first draft of the manuscript and were involved in interpreting the data, critically revising the paper and finalizing the version before publication.

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The authors declare no conflict of interest.

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