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OPTIMIZING PROTEIN INTAKE IN UREA CYCLE DISORDERS: AN EXPERT OPINION

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ABSTRACT **–** Urea cycle disorders (UCDs) are rare inherited metabolic diseases caused by defects in urea cycle enzymes or transporters. The main objective of dietary management in patients with UCDs is to ensure stable metabolic control and prevent long-term complications, while supporting normal growth and development. Dietary protein restriction remains the cornerstone of long-term management, in combination with nitrogen-scavenging drugs, supplementation of arginine/citrulline, vitamins, minerals and essential amino acids if needed. However, lifelong low-protein diets raise concerns regarding growth, bone health, body composition, immune function and quality of life in patients with UCDs. Evidence on optimal protein intake in UCDs is scarce and heterogeneous, largely based on retrospective data and inconsistent nutritional methodologies. In this expert opinion, a multidisciplinary panel comprising eight inherited metabolic disease specialists from five Italian reference centers reviewed current challenges. It proposed recommendations for optimizing protein intake in UCD patients. The panel highlighted that dietary management involves not only metabolic aspects but also psycho-relational factors, both of which must be addressed to achieve optimal health outcomes in patients with UCDs. Clinical, biochemical, nutritional, instrumental, and psychological tools should be integrated to monitor outcomes, and optimization strategies should be tailored individually across all ages. The panel emphasized that all patients are potentially eligible for protein optimization, provided that individual tolerance, nutritional status, metabolic control, and psychosocial context are carefully assessed. Nitrogen-scavenging therapy may support higher protein intake, with close clinical and biochemical monitoring required during titration. This consensus represents the first expert opinion specifically addressing protein optimization in UCDs, providing a practical framework for dietary management.

Keywords: Urea cycle disorders, Low protein diet, Nutritional status, Inherited metabolic disease, Nitrogen-scavenging therapy.

Abbreviations: BCAA: branched-chain amino acid; E-IMD: European Registry and Network for Intoxication-type Metabolic Diseases, HrQoL: health-related quality of life, UCD: Urea cycle disorder.

INTRODUCTION

Urea cycle disorders (UCDs) are rare inborn errors of nitrogen detoxification/arginine synthesis due to defects in urea cycle enzymes or transporters (carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase, arginase, N-acetyl glutamate synthetase, ornithine translocase)[1]. UCDs can present at any age with acute, chronic, or intermittent symptoms. Their signature feature is the life-threatening hyperammonemic crisis, often triggered by catabolic stress, protein load, or certain drugs, leading to neurological damage[2].

The primary goal of dietary management for patients with UCDs is to maintain good metabolic control and prevent chronic complications, while enabling normal growth and development. This involves restriction of natural dietary protein in combination with nitrogen-scavenging drugs, supplementation of arginine/citrulline, vitamins, minerals, and essential amino acids if needed[3,4]. Protein intake recommendations for patients with UCDs are based on the 2007 WHO/FAO/UNU "safe levels of protein intake"[2,5]. A combination of low and some high-biological-value proteins divided between three to five meals should be provided daily. Despite the goal of the WHO/FAO/UNU safe level, considering that the population's normal protein intake on a free diet easily overcomes this level, UCD diets need to be restricted, limiting food groups like meat, fish, eggs, dairy products, and often substituting cereal-based products with special low-protein foods that have lower palatability. Essential amino acid supplementation, especially branched-chain amino acid (BCAA), is essential when protein tolerance is too low, up to 30% of the total protein intake[2]. However, optimal protein intake must be carefully individualised in every patient, according to age, severity of the disorder, protein tolerance, gender, and physical activity. Moreover, regular clinical, biochemical, and nutritional monitoring by a multidisciplinary metabolic team following an individualized schedule is recommended[2,3].

Protein aversion is a common feature of UCDs that can serve as a diagnostic clue for earlier diagnosis when investigating symptoms, such as food refusal, recurrent vomiting, and episodic altered consciousness, and it also highlights that metabolic decompensation is more frequently related to low rather than high protein intake. Protein aversion can persist or develop even after diagnosis and the initiation of a diet, making it difficult for patients to meet their prescribed protein requirements and, consequently, leading to metabolic decompensation[6].

Adherence to a protein-restricted diet can be challenging for patients with UCDs and is commonly associated with a reduced health-related quality of life (HrQoL)[7-12]. For example, a cross-sectional study[10] that included six children with UCDs reported lower general well-being than children with leukemia and lower relations with friends than healthy peers, identifying dietary constraints as a major contributing factor. Likewise, focus group interviews with nine UCD pediatric patients and parents revealed that dietary restrictions and stigmatization/social exclusion were the factors considered most relevant for HrQoL[11]. In addition, self-reports and proxy reports of HrQoL in 42 children and adolescents with UCDs showed significantly lower HrQoL total scores compared to healthy controls, as a consequence of both the burden of disease and dietary treatment[12]. A disease-specific assessment tool for HrQoL in UCDs and other intoxication-type metabolic diseases was developed (MetabQoL 1.0). It may be a promising option to study aspects specifically relevant to patients with UCDs and their caregivers, including the dietary burden[13]. Poor adherence to diet is a commonly reported problem for UCDs in all age groups, but it is known to deteriorate with age, especially from the age of 10 years onwards. The factors that could positively or negatively affect adherence across inherited metabolic disorders treated by low-natural-protein diets have been highlighted in a comprehensive review and include the burden of diet and amino acid supplement administration, patient responsibility, family characteristics, cultural and religious influences, social aspects, and information sources[14].

Nutritional complications, such as impaired growth, have been documented in children and adolescents with UCDs on low-protein diets[15-18]. However, less information is currently available in the literature regarding bone health and body composition in adult patients[18-21]. Moreover, data remain inconsistent regarding the relative importance of total protein intake, essential amino acid supplementation, and the protein-to-energy ratio in determining growth and metabolic outcomes[19,22-24]. For instance, a retrospective longitudinal study of 77 patients with UCDs found that the final height was significantly below the target height, tended to be lower in males, worsened during puberty, and was negatively associated with total protein intake. The mean total protein intake was reported to be below the recommended safe levels during the pubertal period (0.6 g/kg/day) and after reaching final height (1.2 g/kg/day). Bone demineralization and body-composition abnormalities with low lean mass were also observed[18]. On the contrary, retrospective longitudinal data from 44 patients with UCDs showed that growth patterns were within normal ranges, but median protein intake was found to meet or exceed the FAO/WHO/UNU safe

levels. A protein-to-energy ratio range of 1.5-2.9 g protein/100 kcal/day was indeed associated with optimal growth, and a significant negative correlation was observed between total protein intake and fat mass[19]. Similarly, total and natural protein intake were inversely related to fat mass percentage in a retrospective study[20] that included 12 adults affected by UCDs. The average protein intake was lower than the recommended safe levels (0.61 g/kg/day), and more than one-third of the patients were classified as overweight. On the other hand, in 307 UCDs individuals longitudinally followed by the Urea Cycle Disorders Consortium and the European Registry and Network for Intoxication-type Metabolic Diseases (E-IMD) [22], growth impairment was determined by disease severity (as reflected by early onset individuals) and associated with reduced plasma BCAA concentrations, but was not predicted by the amount of natural protein intake alone. In addition, a longitudinal study[23] of 311 UCD patients from the E-IMD found that height was positively associated with the natural protein-to-energy ratio and BCAA levels, but did not significantly differ between asymptomatic and symptomatic patients and those with and without a protein restriction.

Toxic metabolites, such as ammonia and insufficient supplies of essential nutrients and micronutrients, as in low-protein diets, may compromise the immune system function[25-29]. However, very little data has been reported on patients with UCDs in the literature to date[30-32]. For example, in a recent study[30] that enrolled 24 UCD patients, the proliferation of T cells in response to mitogens was found to be impaired, with amino acid analysis revealing distinct metabolic disruptions, emphasizing the complex interplay between metabolism and immune function. Similarly, in a case report[31] of a child with hyperornithinemia–hyperammonemia–homocitrullinuria syndrome, decreased lymphoproliferation rates in response to most mitogens were reported, and significantly decreased levels of inflammatory cytokines were detected.

This article reports the authors' advice from their best practice on the optimization of protein intake in patients diagnosed with UCDs, including the metabolic and psycho-relational issues involved in the low-protein diet, the tools used to identify these issues, the characteristics of the potential candidate for optimization, and how this could be proposed and implemented in clinical practice.

METHODS

A multidisciplinary panel of experts from five Italian inherited metabolic diseases reference centers met to identify current challenges and provide recommendations for the optimization of protein intake in UCD patients. The expert panel comprised eight inherited metabolic disease specialists, including four pediatricians (F.M., M.S., R.T., A.T.), two dietitians (A.D., S.S.), an adult endocrinologist (E.S.), and a psychologist (B.G.).

A preliminary free-response survey that included eight main questions regarding existing challenges and available tools for optimizing protein intake in UCDs was sent to all the participants two weeks before the virtual meeting. Answers to the survey were collected and summarized, and later shared with all the expert panel members during the virtual meeting.

Consensus and recommendations evolved during the virtual meeting, which was held on 25 June 2025. Experts shared their current clinical practices, highlighting the process of care and services for the dietary management of UCD patients in their centers. Following the virtual meeting, the discussion was summarized in this paper.

RESULTS

In the described process, the panel provided eight shared consensus answers to the eight initial questions proposed in the survey.

Which Metabolic and/or Psycho-Relational Domains are Involved in a Low-Protein Diet?

The panel agreed that a low-protein diet for the management of UCD patients engages both metabolic and psycho-relational domains.

Metabolic domains include maintenance of good metabolic control to prevent decompensation and hospitalization, support of normal growth and development, and achievement of optimal nutritional status in terms of protein, energy and vitamin intake.

Psycho-relational domains encompass difficulties in sustaining long-term adherence to dietary therapy, challenges in establishing and maintaining social relationships, cognitive and neuropsychological functioning, as well as family dynamics, parenting styles, and cultural or religious influences. Both individual and family-related issues should be addressed during initial and follow-up evaluations. Key areas include: emotional well-being, acknowledging that restrictive dietary therapy may constitute a vulnerability factor for dysfunctional eating patterns; social and relational dynamics, promoting coping strategies to prevent isolation; autonomy, focusing on developing patient awareness and competence in dietary self-management; and cognitive and neuropsychological functioning, considering both the risk of neurocognitive impairment and the impact of specific neuropsychological deficits on diet management. Of fundamental importance are the processes of elaboration and adaptation, including acceptance of the diagnosis, awareness of its long-term implications, and the family's adjustment to the chronic condition, all of which are crucial for adherence to restrictive dietary therapy.

The panel agreed that metabolic and psycho-related domains are interrelated and that both need to be addressed to ensure the best health outcome for the patients diagnosed with UCDs. However, it is recognized that without overcoming the psycho-relational issues through education and engagement of both the patient and the family, the metabolic goals are inevitably at risk (Figure 1).

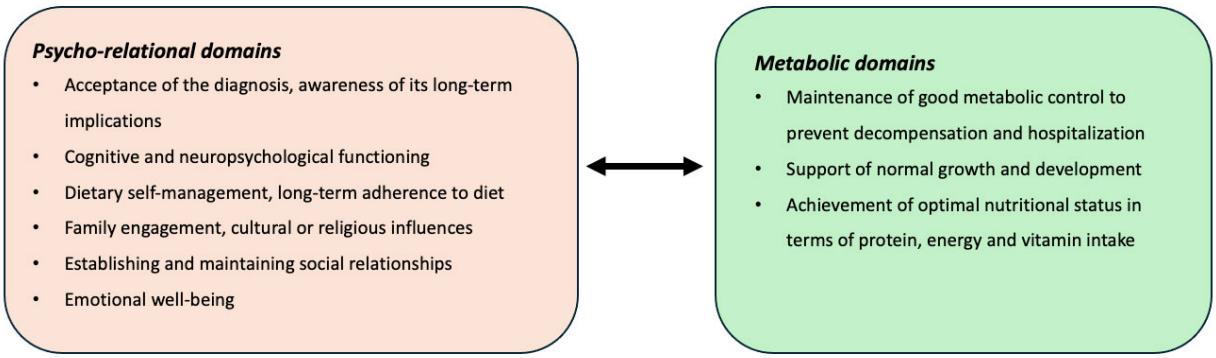

Figure 1. Issues and challenges of low-protein diet management in UCDs.

Which Tools Could Be Used in Clinical Practice to Identify Possible Issues Related to a Low-Protein Diet?

The panel agreed that clinical, biochemical, instrumental, and psychological tools should be used in clinical practice to identify possible issues related to a low-protein diet in UCD patients.

Among clinical tools, auxological measures plotted on growth charts, including the child's height/length, weight, weight-for-height, and body mass index (BMI) for age, body circumferences, and skinfold thickness measurement, together with physical examination, are mandatory to identify possible developmental issues and/or nutritional deficiencies. A careful examination of skin, hair, and nails should also be part of the diagnostic workup.

A comprehensive nutritional assessment conducted by an expert dietitian should be performed at each visit, allowing for a detailed examination of a patient's macronutrient and micronutrient intake, helping to identify potential deficiencies or excesses that may correlate with biochemical and clinical tests, or be predictive if they are not immediately apparent from standard biochemical tests. Standard dietary assessment tools, such as 3 to 7-day food diaries or 24-hour recalls, are typically self-reported by the patient, and then interpreted by the dietitian, combining diet history, and analyzed with food composition tables and software to estimate nutrient intake. Since there are no specific nutritional requirements defined for patients with UCDs, it is both necessary and appropriate to use standard nutritional guidelines to interpret dietary intakes, such as those from the WHO and the dietary reference values of nutrients and energy for the Italian population (LARN, National Recommended Energy and Nutrient Intake Levels). These values serve as a starting point for calculating individual nutritional requirements, which must then be adapted during follow-up, based on the patient's specific protein tolerance and clinical status. Ultimately, a complete dietary assessment complements other tools by providing a di-

rect, practical view of the patient's eating habits, preferences, and motivation, which is essential for the long-term management of their nutritional therapy.

Biochemical examinations should include complete blood count (including differential leukocyte count), renal and hepatic function, ammonia, plasma amino acids (comprising BCAA), protein, iron, calcium, phosphorus, vitamin status, urine test with sediment and urinary biochemistry.

Among instrumental tests, dual-energy x-ray absorptiometry and bioelectric impedance analysis are useful to investigate bone status and body composition, respectively.

A patient's developmental delay may be detected during a routine clinical exam, but periodic neuropsychological evaluations with developmental and cognitive testing are often necessary. Screening and monitoring of psychopathological aspects, such as irritability, aggression, somnolence, apathy, anxiety, mood changes and social withdrawal, should also be conducted. Health-related quality of life questionnaires can be used alongside clinical evaluations to provide a comprehensive assessment that captures the patient's and caregiver's perspective, offering insight into the real-life impact of the disease and chronic dietary therapy on daily functioning as experienced by patients and families (Figure 2).

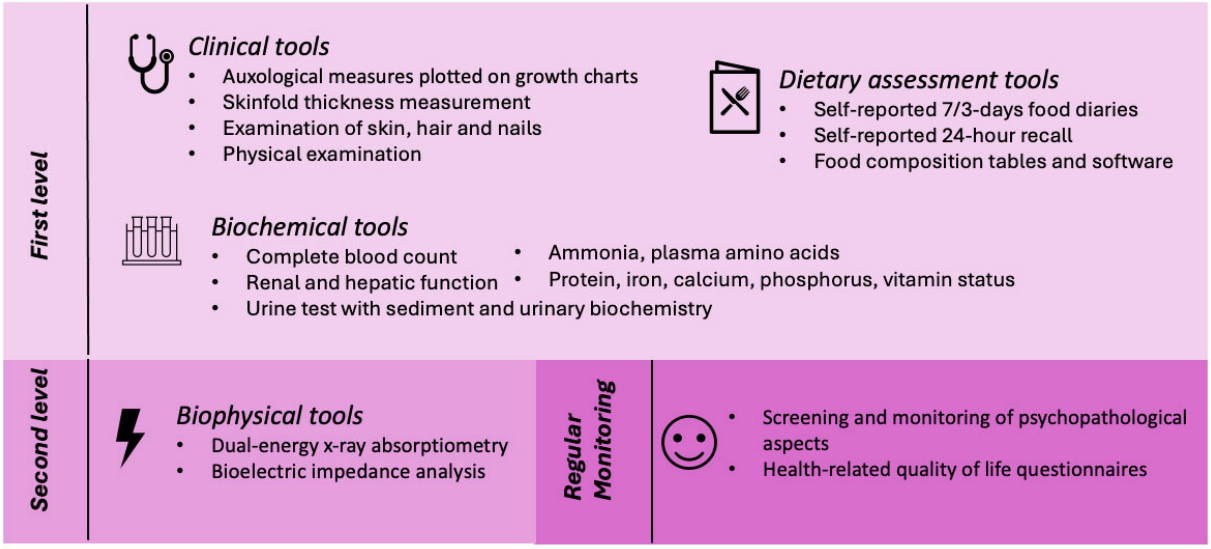

Figure 2. Identification of possible issues in metabolic and psycho-relational domains.

Which of These Tools are Used Routinely in Your Clinical Practice?

The panel concurred to divide the above-mentioned tools into first and second tiers, according to the severity of the disease, the extent of protein restriction, and the resources available in each metabolic center.

Clinical and biochemical tools should ideally be performed at every visit. However, the extent and frequency of clinical and biochemical monitoring depend on the age, severity of the disease, and metabolic stability of the patient and should be individualised by the healthcare team.

On the other hand, instrumental assessment can be performed on a less frequent basis, according to the general recommendation for the age group and the presence of established complications.

Ideally, all previously described psycho-relational variables should be regularly monitored as part of routine patient follow-up. In practice, the extent and frequency of these assessments depend on the resources available at each center, including the presence of a psychologist in the multidisciplinary metabolic team. In particular, a comprehensive evaluation of the child's developmental and emotional profile performed during the early years of childhood can promptly identify any delays in achieving developmental milestones, communicative-relational difficulties, or emotional-behavioral alterations, allowing for the early initiation of a tailored intervention (Figure 2).

At Which Stages of Life Do The Metabolic and/or Psycho-Relational Domains Have the Greatest Impact?

The panel agreed that all stages of life (childhood, preadolescence, adolescence, adulthood, pregnancy) can be profoundly impacted by the metabolic and psycho-relational domains for different reasons.

During childhood, the main metabolic issues regard the correct growth of the child during different nutritional phases, which also include breastfeeding and weaning. On the contrary, psycho-relational concerns predominantly involve caregivers and encompass acceptance of the disease, guidance on the dietary regimen, promotion of healthy eating behaviours, and development of coping skills to manage emotional stress.

During preadolescence, optimal growth remains a crucial concern, with the timely onset of puberty representing a key developmental milestone. Additionally, children start to form more complex social relationships with their peers and gradually become aware of the challenges and impact associated with their dietary treatment, which can influence both adherence and emotional well-being.

During adolescence, achievements of normal final height, weight, and peak bone mass are the main metabolic goals. At the same time, psycho-relational factors strongly influence adherence to dietary treatments during this phase. Social integration and peer acceptance are crucial for the adolescent's overall well-being. This period also marks the beginning of a gradual transition of responsibility from caregivers to the patients themselves. Therefore, it is essential to actively involve adolescents in learning more about their condition and managing their care. At the same time, typical adolescent behaviors, such as rebellion against rules, risk-seeking, impulsivity, difficulty planning for future consequences, social pressure and the drive to conform with peers, can challenge adherence and require tailored support and guidance.

During adulthood, bone and reproductive health are metabolic priorities. Periodical reinforcement of adherence to the dietary regimen is essential, as professional responsibilities and social interactions may pose potential challenges to maintaining consistent compliance.

Finally, pregnancy represents a unique physiological condition during which patient motivation is typically high, often leading to improved adherence to dietary treatment. Nevertheless, careful nutritional assessments are mandatory throughout pregnancy and the post-partum period, since protein and other nutrient requirements change significantly (Figure 3).

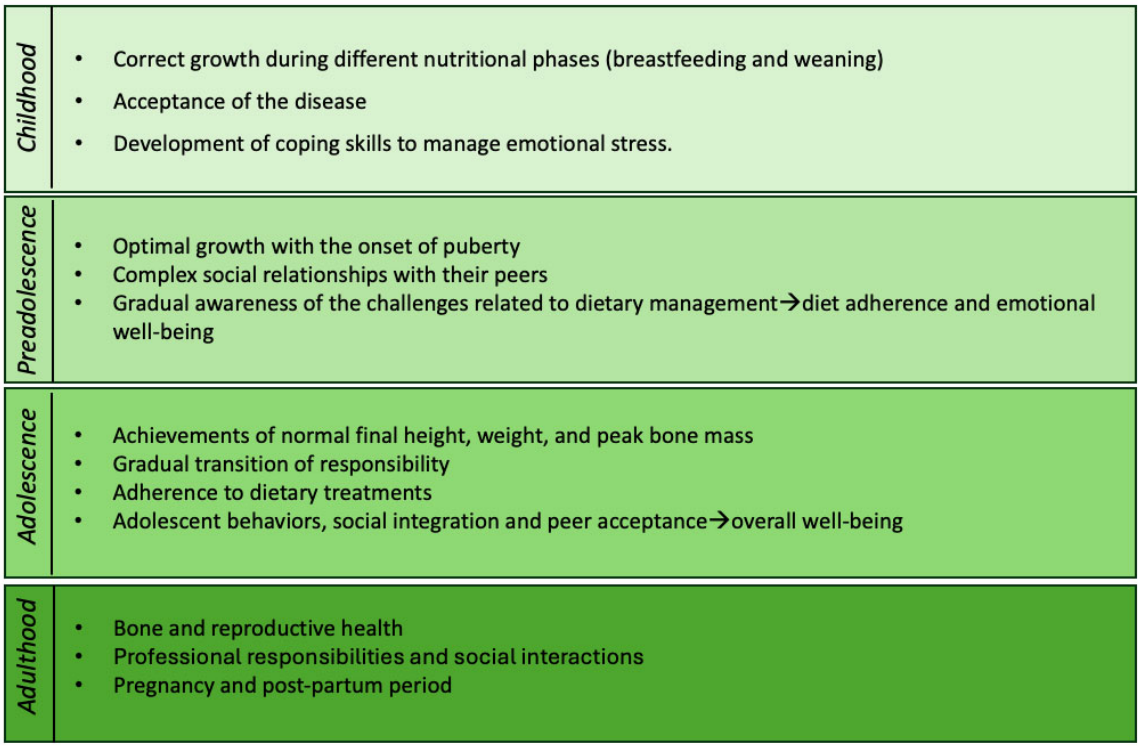

Figure 3. The impact of psycho-relational and metabolic domains at different life stages.

Which Patients Would You Consider Eligible for optimization of Protein Intake?

The panel agreed that every patient is potentially eligible for optimization of protein intake. The main motivation is that improving metabolic and psycho-relational outcomes is beneficial at every age.

Most metabolic outcomes (such as growth and development) are primarily influenced during childhood and adolescence. Metabolic stability and maintenance of a healthy body composition and bone mass are warranted throughout adulthood. Regardless of age, patients could benefit from improvements in psycho-relational aspects.

It was emphasized, however, that optimal protein intake must be carefully determined by individual titration for each individual, based on protein tolerance, nutritional status, and metabolic control.

Which Patients Would You Exclude from Protein Optimization?

For the same reason, the panel concurred that none of the patients should be excluded from protein optimization.

Nevertheless, it recognized that certain hindering factors may exist, but these do not preclude patients from being eligible for protein optimization. These factors are multiple and encompass, for example, loss of motivation, poor knowledge of the condition and its treatment, lack of trust in the healthcare team, reluctance to undergo additional monitoring, emotional stress, eating and feeding disorders, or other psychiatric conditions (e.g., anxiety and/or depression). Also, disease-related symptoms, such as protein aversion, loss of appetite, persistent nausea, and/or vomiting, can complicate the ability of patients to achieve their prescribed daily protein and energy requirements with food (Figure 4).

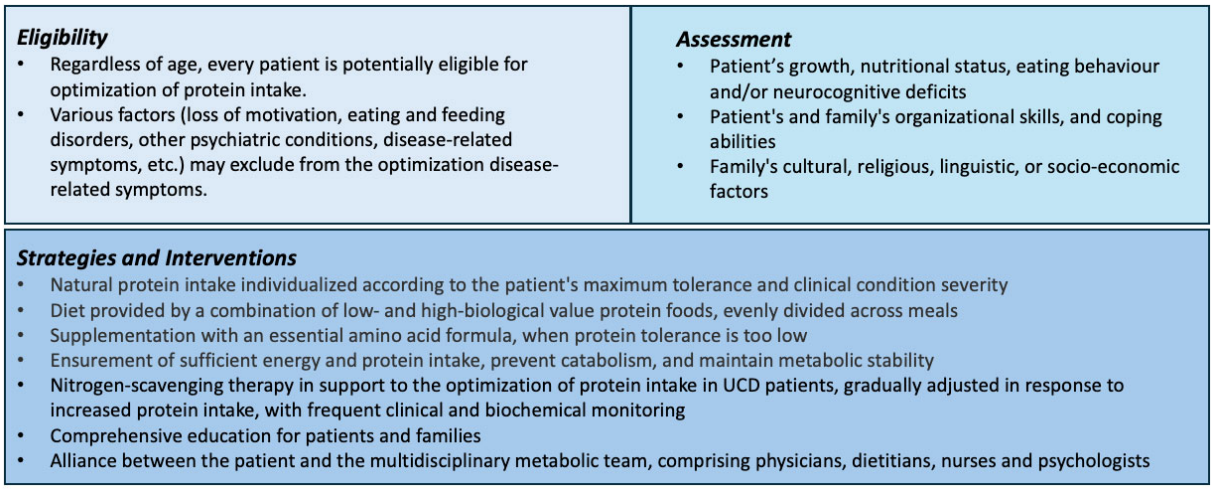

Figure 4. Framework for protein intake optimization.

How Would you Propose the Optimization of Protein Intake to the Patient and/or the Caregiver?

The panel agreed to aim for achieving, and potentially exceeding, the safe levels of protein intake recommended for each age group. On the other hand, natural protein intake should be individualized according to the patient's maximum tolerance and clinical condition severity. Ideally, diet should be provided by a combination of low- and high-biological value protein foods, evenly divided across meals. Supplementation with an essential amino acid formula is necessary when protein tolerance is too low to meet the safe intake levels through diet alone. Regular nutritional assessment and monitoring are essential, as protein requirements and tolerance may vary depending on age, growth rate, nature and severity of the disorder, and the frequency of intercurrent illnesses.

Optimizing protein intake in patients with UCD also requires a critical balance with energy intake to avoid catabolism, and must address protein aversion through individualized diets. In case of poor appetite and/or food refusal, using tube feeding (nasogastric tube or gastrostomy) can help ensure sufficient energy and protein intake, prevent catabolism, and maintain metabolic stability.

The panel also acknowledged the importance of assessing, through a multidisciplinary approach, the patient's and the family's ability to implement protein optimization in practice. Potential challenges – such as the patient's eating behaviour and/or neurocognitive deficits, and the family's cultural, religious, linguistic, or socio-economic factors – must be identified, and where present, the approach should be tailored to the specific situation of patients and caregivers. Family engagement, social support, financial and time resources, organizational skills, and coping abilities all play a key role in the success of protein optimization (Figure 4).

How Would you Set up the Optimization of Protein Intake in Clinical Practice, Also Including a Rational Use of Nitrogen-Scavenging Therapy?

The panel concurred that nitrogen-scavenging therapy may support the optimization of protein intake in UCD patients. The scavenger dose should be gradually adjusted in response to increased protein intake, with frequent clinical and biochemical monitoring recommended during this phase.

Moreover, in patients with mild urea cycle disorders identified through newborn screening, a restriction of protein foods could be avoided or mitigated by the prioritized initiation of a nitrogen-removing scanger, particularly in families with low compliance to diet and specific social issues.

Based on their clinical experience, the panel supported the preferential use of a scavenger with proven pharmacological efficacy and favorable patient response, like glycerol phenylbutyrate (Figure 4).

DISCUSSION

As reported in the most recent guidelines, a low-protein diet remains the cornerstone of long-term management for UCDs[2]. Although not supported by randomized controlled studies, mainly for ethical reasons, this assumption is strongly grounded in physiological rationale, the patient's natural aversion to protein-rich food, and extensive clinical experience[6]. However, the improved life expectancy of patients with UCDs due to early diagnosis and treatment has resulted in lifelong protein restriction, raising concerns not only about growth but also about nutritional status, body composition, bone health, immune system function, and overall well-being in both pediatric and adult patients[10-12,18-20,22,23,30,31].

In general, evidence from the literature on the optimal nutritional requirements and management in patients with UCDs, as well as their association with possible complications, is scarce and often conflicting. One possible explanation is that many available studies are retrospective, with long follow-up periods during which therapeutic options were limited and dietary management practice differed from current standards. Moreover, more recent studies have included cohorts of patients with milder forms of UCDs, such as those identified through newborn screening, who may have different nutritional outcomes. Finally, most studies lack consistency in dietary methodologies and assessment tools, and this aspect may further limit comparability and interpretation. For example, food diary-based data on protein intake are not usually available, and patients' adherence to dietary treatment is not routinely assessed, making it impossible to evaluate real nutritional intakes. Furthermore, a recent systematic review highlighted significant variability and critical deficiencies in dietary management and monitoring across nutrition-related clinical trials, comprising those for inherited metabolic disorders of protein metabolism. These included inconsistent dietary methodologies and inadequate assessment of patient adherence, which impedes accurate evaluation of actual nutrient intake and limits the reliability and comparability of study outcomes[33]. In addition, different methods to assess body composition (bioelectric impedance analysis or dual-energy x-ray absorptiometry) are generally employed, and a control group of healthy subjects is often missing.

On these bases, it is not surprising that current dietary practices among patients with UCDs differ widely. For example, cross-sectional questionnaire data collected from 464 patients with UCDs on protein-restricted diets at 41 European inherited metabolic disorder centres showed that median prescribed protein intake decreased with age across all disorders. The UK tended to prescribe higher total protein intakes than other European countries, particularly during infancy, while Italy generally prescribed lower protein intakes to children over 10 years old, although only one center was included, so this may not reflect overall Italian practices. Overall, essential amino acid supplements were prescribed to 38% of patients, especially in cases of plasma amino acid deficiencies, inadequate total protein intake,

and poor metabolic control[34]. In addition, an evaluation of dietary treatment and amino acid supplementation in 361 UCD patients from the E-IMD registry revealed that 80% received a protein-restricted diet. In general, natural protein prescriptions were often close to the recommended daily allowance, while total protein prescriptions were even above it. Protein prescriptions varied between countries, with low natural and total protein prescriptions reported in two Italian centers. Notably, plasma BCAA levels were below reference ranges in approximately 20-30% of patients. Despite lower natural protein prescriptions in patients receiving amino acid supplementation, their BCAA levels were comparable to those of patients not receiving supplementation[35] Finally, as summarized in a recent review, protein intake in patients with UCDs ranges broadly, both in children and in adults, due to differences in individual tolerance and prescribing practices between centers. Many patients do not reach safe levels of protein intake and are therefore at risk of malnutrition, with some also exhibiting micronutrient intakes below recommended values. Lean body mass was generally lower than the normal range, while fat body mass was often found to be normal or higher than reference values. Protein intake correlated inversely with fat mass in both adult and pediatric UCD patients[36].

Regarding nitrogen-scavenging therapy, a recent retrospective study involving 40 pediatric individuals with UCDs in the UK showed that almost one-third of patients had plasma BCCA levels below the lower limit of the normal range, which were inversely associated with protein intake, ammonia levels, and scavenger dose in those receiving sodium benzoate. The authors suggested that, to increase the proportion of plasma BCAA levels within the normal range, it may be necessary to adjust the biological value of protein intake, prescribe higher doses of scavengers to support safe protein intake, and provide essential amino acid supplements when indicated[24]. Glycerol phenylbutyrate is a tasteless and odourless scavenger that is administered in a small volume, and has been shown to be non-inferior to sodium phenylbutyrate[37]. Experiences in transitioning patients from either sodium benzoate or sodium phenylbutyrate to glycerol phenylbutyrate have been reported to maintain metabolic control, preserve BCAA levels, increase treatment adherence, and improve the quality of life of both patients and caregivers[38-42]. Furthermore, as suggested in a recent consensus, in mild urea cycle disorders identified through newborn screening, it is advised to base the choice of an active therapeutic approach with diet and nitrogen-scavenging therapy on the biochemical and/or genotypic profile, since beginning a low-protein diet alone after an initial period of unrestricted intake may lead to inadequate long-term adherence[43].

This expert opinion paper aims to serve as a guide for metabolic physicians on optimizing protein intake in patients with UCDs, drawing from clinical experience. The discussion focused on identifying key challenges – both metabolic and psycho-relational – associated with low-protein diets, evaluating current and ideal tools for addressing these issues, defining the profile of patients who may benefit from protein optimization, and outlining strategies for introducing and implementing such optimization in clinical practice. To the best of our knowledge, this is the first expert opinion paper specifically focused on protein optimization in UCDs. We believe that this consensus can offer a valuable framework for dietary management of UCDs and serve as a foundation for the design of specific clinical studies aimed at generating further evidence.

CONCLUSIONS

To conclude, a personalized treatment plan that includes careful dietary modification to optimize protein intake, nutrient and essential amino acid supplementation, administration of nitrogen-scavenging drugs, and comprehensive education for patients and families represents the cornerstone of UCD's management. Furthermore, initial assessment and regular monitoring of growth, nutritional status, dietary intake, neurocognitive functioning, and disease-specific quality of life are mandatory in these patients. This multifaceted approach relies on a strong therapeutic alliance between the patient and the multidisciplinary metabolic team, comprising physicians, dietitians, nurses, and psychologists.

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No artificial intelligence-assisted technologies were used in the production of this article.

Authors' Contributions:

Study conception and design, B.G., A.D., F.M., M.S., S.S., E.S., R.T., A.T.; manuscript drafting, E.S.; approval to submit, B.G., A.D., F.M., M.S., S.S., E.S., R.T., A.T. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Material:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest:

The authors have been involved in consultancy activities for Immedica Pharma.

Ethics Approval and Informed Consent:

This work is based on an expert consensus developed through a multidisciplinary discussion and a preliminary, non-interventional survey among healthcare professionals. No patients were involved and no sensitive or identifiable personal data were collected. Written informed consent was not required, as participation was entirely voluntary, implying consent. Ethics Committee approval was therefore not required.

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