Foods for Special Medical Purposes (FSMP) in the Dietary Management of Inborn Errors of Metabolism (IEM)

The role of the clinical and industry dietitians


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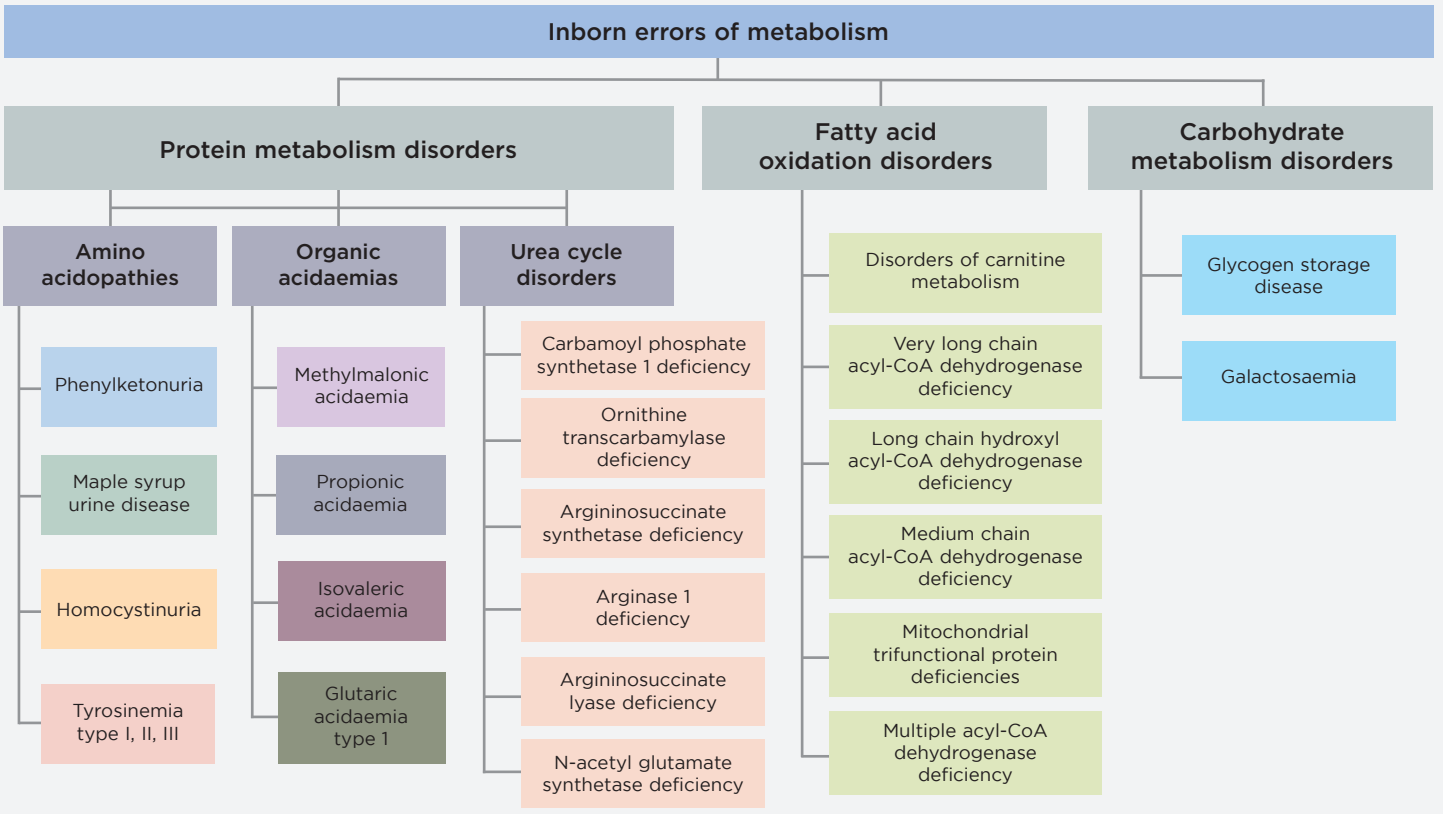
Medical foods (also known as food for special medical purposes – FSMP) are essential in the dietary management of many inborn errors of metabolism (IEM). This article focuses on inborn errors of protein metabolism, mainly the aminoacidopathies, and the challenges of developing protein substitutes for these disorders. We also describe the essential combined role of dietitians working in clinical practice and industry in developing medical foods for IEM.

Inborn errors of metabolism (IEM)

Inborn errors of metabolism are a group of conditions caused by a deficiency of an enzyme in a specific metabolic pathway.[1] This specific enzyme defect interferes with the normal metabolism of protein, fat, or carbohydrate. **Figure 1** shows a list of IEMs in the categories of disorders of protein, fat and carbohydrate metabolism, typically where medical foods can be used. As a result of reduced or absent enzyme activity in IEM, toxic metabolites accumulate in the body and nutrients the body normally produces may become deficient. Without medical and dietary management these metabolic disturbances can lead to a host of irreversible, adverse and often life threatening consequences.[2] Newborn screening (NBS) for different ranges of IEMs is performed in many countries and has been vital in the successful prevention of detrimental consequences associated with many of these conditions.[3] Through NBS with early identification and initiation of specific dietary modification, many of the adverse outcomes of IEM can be prevented. For many IEM, dietary management is heavily reliant on the provision of specialised medical foods.[2]

Figure 1: Overview of inborn errors of metabolism



Dietary Management of aminoacidopathies

(refer to list in Figure 1)

The management of these conditions is multifaceted, challenging, and lifelong. To achieve effective management, a multidisciplinary team approach is required. In the UK these teams exist in specialised metabolic centres to ensure holistic care, and the dietitian is an integral part of this team. The goals of dietary management in these conditions are:

- Prevent the accumulation of excess 'offending' amino acids by strict control of natural protein intake.
- Replacement of natural protein removed from the diet with an amino acid-based supplement. This medical food is typically termed 'protein substitute'. All protein substitutes are free or very low in the offending amino acids.
- Attainment of normal growth and nutritional status. Ensuring the diet contains a balanced intake of all nutrients and energy. Vitamins and mineral supplements are either added to the protein substitute or given separately.

The level of protein restriction will vary depending on the degree of enzyme deficiency. Individuals with IEM2 – e.g. those with PKU or MSUD – may tolerate natural protein intakes as low as 4-5 g per day.[4] Natural protein restriction in the diet is titrated according to the individual's tolerance, ensuring target biochemical levels for optimal disease management are met. In PKU, blood phenylalanine levels are monitored and protein intake is adjusted accordingly. Optimum blood phenylalanine levels are based on national and international agreed guidelines.[5] A maximum blood level is set to avoid toxicity and a minimum level to prevent excessive restriction of essential amino acids, required for protein synthesis to support normal growth and development.[6] In practice, this results in a diet which excludes or severely restricts the intake of high protein foods, such as meat, fish, dairy (including milk, yoghurt, cheese), pulses, nuts and soy-based foods. Other foods that contain moderate amounts of protein must also be severely restricted – for example, breakfast cereals, rice, pasta, bread and baked goods such as cakes and biscuits. Specially manufactured low protein alternatives to these foods are available on prescription and are essential to provide bulk and satiety in the diet, allowing energy requirements to be met, and to minimise protein catabolism leading to poor metabolic control.[7] Practice within the UK allows a number of fruits and vegetables to be used freely in the diet due to their very low protein content, although a number still contain significant amounts of protein and are are limited in the diet. The dietary approach is illustrated in **Figure 2**.[7]

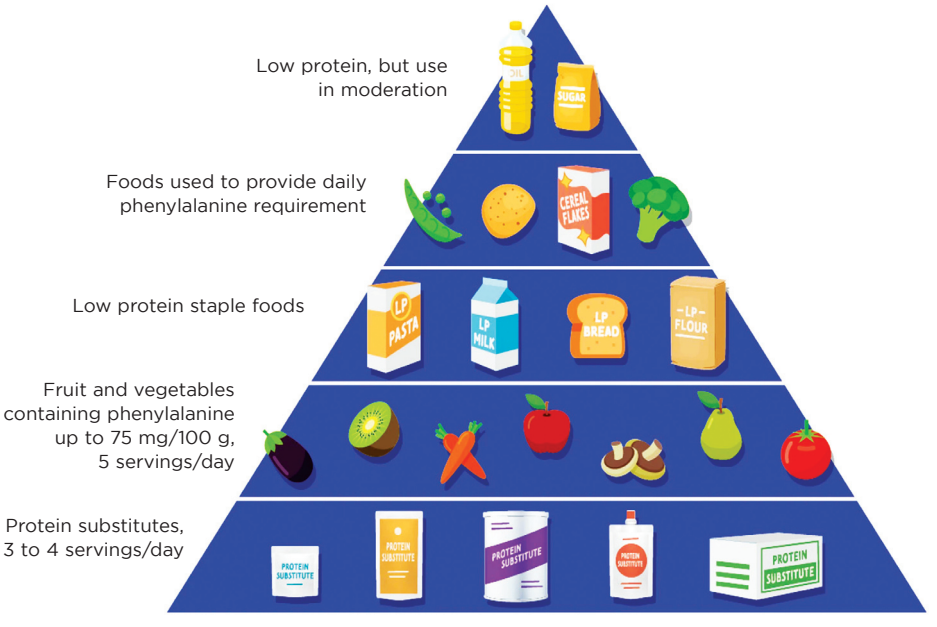
Due to the restrictive nature of the low protein diet, individuals are at a greater risk of multiple micronutrient deficiencies.[5] Protein substitutes play an essential role in providing nutrients that may otherwise not be consumed in sufficient quantities on a low protein diet.[8-10] Micronutrient deficiencies have been reported in individuals with PKU who were not adherent with taking their protein substitute.[11]

Dietetic challenges in managing IEM's: Partnership between clinical and industry dietitians

Food and eating are an integral part of life, an experience many describe as enjoyable whether this relates to feeding yourself or your child. It's also an aspect of daily living which ordinarily one has general control over. Part of this control and enjoyment is removed when adhering to severe dietary restrictions, sometimes being replaced with a lack of confidence and anxiety in choosing or providing the wrong foods. To achieve good metabolic control, a high degree of meal planning and preparation is involved, and much of the spontaneity of life is removed due to these stringent dietary restrictions. As clinical and industry dietitians working in IEM, we aim to teach, counsel, and help these families and individuals across their lifespan to grow, gain confidence, enjoy food and of course to manage and follow the diet, meeting nutritional needs.

Many dietary challenges must be tackled by the clinical dietitian. Children experience many changes to their individual nutritional needs as they advance from infancy to adulthood. During this time they will experience periods of rapid growth with heightened requirements for specific nutrients, along with developing behavioural and social skills associated with food and eating.[12] Fussy eating and food neophobia can affect all children, but research in IEM shows there is a high prevalence amongst this group.[13-15] Unfortunately, adherence remains a commonly reported problem in inborn errors of protein metabolism, as has been demonstrated in PKU, and is known to deteriorate with advancing age.[16, 17] In 2018, a paper reported more than 70% of patients with PKU and caregivers of children reported finding dietary management to be 'difficult'.[18] Dietitians within industry work with colleagues in clinical practice to continually keep abreast of the challenges of management and how these evolve over time. Industry dietitians use their insight into the difficulties faced within practice and are best placed to understand problems and translate them into potential product solutions.

Figure 2: Food pyramid for PKU from the PKU dietary handbook



Source: MacDonald A, et al. (2020). PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis.; 15(1): 1-21. Permission to include diagram provided from lead author

"As clinical and industry dietitians working in IEM, we aim to teach, counsel, and help these families and individuals across their lifespan to grow, gain confidence, enjoy food and of course to manage and follow the diet, meeting nutritional needs."

As industry dietitians, we aim to continually conduct reviews, initiate research, follow current trends and developments in dietary management or innovations in novel, non-dietary therapies. Protein substitutes continue to play a key role in the maintenance and improvement of metabolic control, along with optimising nutritional status. The continued improvement of protein substitutes, in terms of nutrient provision and sensory attributes, is essential to promote adherence with these lifelong therapies.

Development of protein substitutes for aminoacidopathies

Protein substitutes (PS) have dramatically improved over the decades, and they remain of fundamental importance in the dietary management of these conditions. Historically, the technology and raw materials available to manufacture protein substitutes were crude and limited, but now precision manufacturing and availability of a wider range of suitable ingredients has improved their quality.[19] Dietitians in the medical food industry play a critical role in product formulation with most medical nutrition companies ensuring dietitians work as an integral part of the research and development team and other support functions.

When developing new PS, the specific IEM, nutritional requirements, age indication and current challenges relating to the management of specific groups must be considered to optimise the acceptability and suitability of the product. Technological challenges in developing these complex products include the limited range of available ingredients that are protein free, poor solubility of some raw materials and specific nutrient interactions affecting product processing. Flavouring PS requires expertise to mask the poor taste of amino acids. Dietitians in industry may work alongside development technologists to identify critical product features and propose potential technical solutions.

Convenience and non-medicalised packaging can help children and adults with an IEM feel less different to their peers and may promote adherence. Having different types of PS in powdered, liquid and flavour variants are essential in the management of IEM, to provide choice and meet varying individual preferences and lifestyles. Not only is it important that PS are designed to benefit the different stages of childhood and beyond,[7, 20] it is critical that the composition shows efficacy in maintaining good metabolic control. In PKU, for example, the development of glycomacropeptide (GMP) based PS has enabled a more palatable alternative to amino acid-based PS to be developed, which may also offer additional potential health benefits.[21, 22] GMP contains small amounts of phenylalanine and therefore it has been vital to work together with clinical dietitians to evaluate the effect of using this type of protein substitute in maintaining metabolic control.

The gold standard for clinical studies is a double-blind randomised controlled trial. However, due to the complexity of the management and small numbers of individuals with rare conditions, this is not possible in IEM. The overall incidence of PKU is estimated to be 1 in 10,000,[23] with the incidence of other IEMs being much smaller. This has an impact on the potential study design that can be adopted. As industry dietitians, the relationship with our colleagues in clinical practice is key in collaborating on clinical trial protocol design, analysis and report preparation. However, the hard work of recruitment and gathering data is ultimately the role of our colleagues in practice and we recognise that with increasing demands on clinical time this becomes more and more difficult.

Global and regulatory considerations

Aminoacidopathies are very rare, often with a very small patient population in each country. PS are typically developed to be made available in many countries across the globe, thereby creating a viable manufacturing volume, allowing a wide range of patients to benefit from innovative solutions. Creating globally suitable products, however, poses some challenges. Firstly, UK dietary reference values are over 30 years old. The US have more recent nutritional guidelines; however, these are now approaching 20 years old for some nutrients. In the last decade, The European Food Standard Agency (EFSA) have produced more up to date guidance reviewing recommendations across European countries for selected nutrients, resulting in a recent updated summary report in 2019.[24]

Global micronutrient recommendations vary despite the use of the same scientific reports as a basis. Scientific bodies often interpret data differently, for example using different uncertainty factors. The role of the industry dietitian is to scientifically evaluate country recommendations and ensure that products are designed to the most up to date evidence and are nutritionally optimal.

IEM products are classed as nutritionally incomplete Foods for Special Medical Purposes (FSMP) in the UK and EU and are regulated under Article 2 (1)(c) of EU Regulation 2016/128 on FSMPs.[25] Clinical practice globally is to prescribe products for inborn errors of protein metabolism based on protein content. The micronutrient levels in protein substitutes are designed based on protein equivalent content. This approach ensures the product provides sufficient micronutrients when prescribed according to its intended use as an alternative protein source. The regulatory compositional standards are based on energy content; therefore, the micronutrient content of PS for IEM necessarily needs to deviate from the regulated compositional standards per 100 kcal. This poses a challenge and requires input from industry dietitians to explain the intended use of the product and justify the nutritional adequacy and safety of the product.

Conclusion

IEM encompasses a wide range of conditions, often complex and multifaceted, requiring expert dietetic management. Medical foods (FSMP) are an essential part of dietetic care, and innovations in formats and new flavours can offer much needed variety and play a crucial role in dietary management. Collaborative working between industry and metabolic dietitians in clinical practice ensures that optimal products are developed, with the needs of affected individuals and their families in mind thereby encouraging effective and sustained long term metabolic control.

About the British Specialist Nutrition Association

BSNA is the trade association representing the manufacturers of products designed to meet the particular nutritional needs of individuals; these include specialist products for infants and young children (including infant formula, follow-on formula, young child formula and complementary weaning foods), medical nutrition products for diseases, disorders and medical conditions, including oral nutritional supplements, enteral tube feeding and parenteral nutrition, as well as companies who aseptically compound chemotherapy, parenteral nutrition and CIVAS.

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