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Dietary protein in urea cycle defects: How much? Which? How?☆

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ABSTRACT

Dietary recommendations for patients with urea cycle disorders (UCDs) are designed to prevent metabolic decompensation (primarily hyperammonaemia), and to enable normal growth. They are based on the 'recommended daily intake' guidelines, on theoretical considerations and on local experience.
A retrospective dietary review of 28 patients with UCDs in good metabolic control, at different ages, indicates that most patients can tolerate a natural protein intake that is compatible with metabolic stability and good growth. However, protein aversion presents a problem in many patients, leading to poor compliance with the prescribed daily protein intake. These patients are at risk of chronic protein deficiency. Failing to recognise this risk, and further restricting protein intake because of persistent hyperammonaemia may aggravate the deficiency and potentially lead to episodes of metabolic decompensation for which no clear cause is found. These patients may need on-going supplementation with essential amino acids (EAA) to prevent protein malnutrition.
Current recommendations for the management of acute metabolic decompensation include cessation of protein intake whilst increasing energy (calorie) intake in the first 24 h. We have found that plasma concentrations of all EAA are low at the time of admission to hospital for metabolic decompensation, with correlation between low EAA concentrations, particularly branched-chain amino acids, and hyperammonaemia. Thus, supplementation with EAA should be considered at times of metabolic decompensation.
Finally, it would be advantageous to treat patients in metabolic decompensation through enteral supplementation, whenever possible, because of the contribution of the splanchnic (portal-drained viscera) system to protein retention and metabolism.

1. Introduction

The primary goal of the dietary therapy of patients with urea cycle disorders (UCDs) is to maintain good metabolic control whilst enabling normal growth and development. Since CNS toxicity in UCDs is directly related to tissue concentrations of ammonia [1,2], and thus to nitrogen load, these goals have been translated in various guidelines into: "*Avoid too much protein*", and "*Provide sufficient protein for growth*" [3–6]. It is recognised that during times of illness there is (a risk of) catabolism and therefore, it has long been recommended that treatment should consist of: "*Avoid/reverse catabolism: provide sufficient calories*" and "*Assume catabolism: stop protein intake*" [3–6]. However, treatment recommendations in IEM in general and, more specifically, in UCDs are based on theoretical considerations and on a considerable number of assumptions, on personal experience, on small or large cohort retrospective studies and very rarely on double-blind, comparative-controlled studies. Moreover, local practices may change based on availability of foods, cultural habits and diets etc.

Within the scope of the UCD treatment guidelines, there remain several questions regarding the total daily protein and energy requirements of patients with UCDs for good metabolic control and adequate growth, the amount of natural protein that these patients tolerate, protein intake and reversal of catabolism at times of hyperammonaemia and the optimal mode of providing protein to these patients at times of metabolic decompensation. The purpose of this review is to address some of these questions.

2. What do we need to know when designing a diet for patients with UCDs?

The current inherent assumption in designing an age appropriate diet is that energy (calorie) requirement is the drive for food intake, whereas protein requirement does not drive food intake [7]. In order to prescribe an age-appropriate diet for a patient with UCD we need to know the patient's energy requirements (which are dependent on the patient's age, gender and physical activity), their protein requirements for metabolic stability and for growth, and, ideally, measurements of the capacity of protein metabolism and tolerance when the

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patient is 'well' and acutely when 'unwell'. It is assumed (but not proven) that children with UCDs do not differ from their healthy peers in their essential dietary requirements. Thus, the basis of the age-appropriate dietary recommendations in the treatment of patients with UCDs has been the Recommended Daily Intake (RDI) for energy and protein, which is a population-based mean intake (of energy, or protein, or nutrient intake) +2 SD of the mean (i.e. 95% percentile for nutrient intake). It follows that about 45–50% of patients can do with less daily protein intake and would still consume the mean protein intake of the respective population. Alternatively, a fractional calculation of dietary requirements can be made, which takes into account the basal metabolic rate + growth + activity + other factors. However, there are disturbing differences between different studies (and authors). For example, the WHO technical report on protein intake, published in 2007, differs from the same report published in 1985 [7]. Regardless of the method used for assessing energy needs, in prescribing a diet for patients with UCDs it is often recommended that energy intake be increased by a 'factor' to prevent catabolism and improve metabolic control during illness and during activity, usually through increased fat and carbohydrate intake.

The basis for the dietary recommendations of protein intake in patients with UCDs is: "Protein and amino acid requirements in human nutrition: Report of a joint FAO/WHO/UNU expert consultation (WHO technical report series; no. 935), 2007" [7] (cited in the recent suggested guidelines for the treatment of UCDs) [6]. The recommended daily protein intake in this report is considerably low. However, the authors of the report acknowledge that nitrogen balance does not necessarily reflect optimal protein intake and that "*the safe population intake will approximate to a value which is somewhat greater than the requirement + 1.96 SD of intake*" (Section 14.1.1; page 241). Thus, a correction for protein digestibility and amino acid score value needs to be made (Section 14.1.5; page 242). In practice, natural protein intake is usually individualised and, in some metabolic centres, may be 'pushed to maximum tolerance'. In other centres the prescribed intake of natural protein is limited and amino acid formulae are used to substitute for natural protein intake. This has been translated in some guidelines into: "*provide 0.8 g natural protein/kg/day + essential amino acid formula*" [8].

3. What is the natural protein tolerance of patients with UCDs?

We recently analysed the daily amount of protein (in g/kg body weight) consumed by 28 paediatric patients with UCDs (up to 18 years of age) at different ages, all in good metabolic control, as recalled and recorded in the outpatient clinics over time (Fig. 1) (Kuypers et al., unpublished observations). Although these data may not be compatible with stringent scientific criteria, they are practical, given that on-going treatment decisions are based on information obtained in follow-up clinic reviews. There were 16 female- and 12 male-patients with various UCDs: 17 had ornithine transcarbamylase (OTC) deficiency; three had citrullinaemia type I (Cit I); five had carbamyl-phosphate synthetase I (CPS I) deficiency; and three had argininosuccinic-aciduria (ASA). All patients were treated with sodium benzoate (but not with phenylbutyrate, phenylacetate or Ammunol) and citrulline or arginine. Most patients consume between 1 and 1.8 g natural protein/kg body weight per day and some (mainly male patients with late onset OTC deficiency) tolerate larger amounts of natural protein/kg/day. Thus, at most times, patients with UCDs may tolerate natural protein intake well within the age-appropriate recommendation, whilst maintaining good metabolic control. However, some patients, or patients at particular times, consume less than the optimal daily protein intake. These patients warrant special attention.

4. Specific dietary issues of patients with UCDs

Food refusal and protein aversion have long been recognised in patients with UCDs. Food refusal in these patients could be the result of protein aversion, alterations in serotonin and other neurotransmitters affecting satiety and nausea post high protein ingestion due to high ammonia levels [9].

In a 'real time observational study' we collected dietary data of patients with UCDs treated at our centre during 2007 (Fig. 2) (Watkins et al., unpublished observations). There were 17 patients (10 male patients, 7 female patients) aged 11 months–56 years. Nine patients had OTC deficiency, four had CPS I deficiency, three had ASA and one had Cit I (these patients were also included in the study mentioned

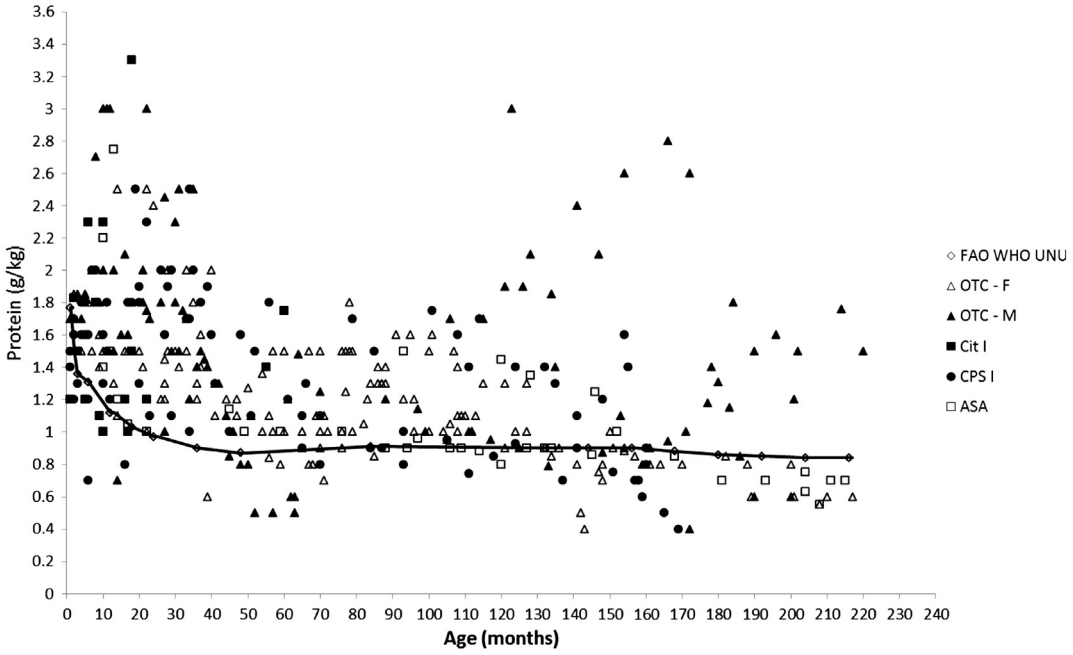

Fig. 1. Natural protein intake of patients with UCDs. Data were collected during clinic reviews (by and large), through phone communication and through 3-day food diaries. OTC: ornithine transcarbamylase (F—female; M—male); Cit I: citrullinaemia type I; CPS I: carbamyl-phosphate synthetase I deficiency; ASA: arginine-succinic aciduria. The symbols represent different urea cycle diseases (legend). The solid line represents the age-related recommended daily protein intake. Note: Protein intake >2.5 g/kg/day was noted consistently in 2 male patients with 'attenuated' OTC deficiency, and sporadically in one patient with ASA and one with Cit I.

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