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## Dietary practices in isovaleric acidemia: A European survey



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## ABSTRACT

**Background:** In Europe, dietary management of isovaleric acidemia (IVA) may vary widely. There is limited collective information about dietetic management.

**Aim:** To describe European practice regarding the dietary management of IVA, prior to the availability of the E-IMD IVA guidelines (E-IMD 2014).

**Methods:** A cross-sectional questionnaire was sent to all European dietitians who were either members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG) or whom had responded to previous questionnaires on dietetic practice (n = 53). The questionnaire comprised 27 questions about the dietary management of IVA.

**Results:** Information on 140 patients with IVA from 39 centres was reported. 133 patients (38 centres) were given a protein restricted diet. Leucine-free amino acid supplements (LFAA) were routinely used to supplement protein intake in 58% of centres. The median total protein intake prescribed achieved the WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Centres that prescribed LFAA had lower natural protein intakes in most age groups except 1 to 10 y. In contrast, when centres were not using LFAA, the median natural protein intake met WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Enteral tube feeding was rarely prescribed.

**Conclusions:** This survey demonstrates wide differences in dietary practice in the management of IVA across European centres. It provides unique dietary data collectively representing European practices in IVA which can be used as a foundation to compare dietary management changes as a consequence of the first E-IMD IVA guidelines availability.

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## 1. Introduction

Isovaleric acidemia (IVA) (McKusick 243500) is a rare inherited condition, caused by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (EC 1.3.99.10), leading to accumulation of isovaleryl-CoA and its metabolites including free isovaleric acid, 3-hydroxyisovalerate and N-isovalerylglycine [1]. The major goal of IVA management is to reduce the production and increase excretion of isovaleryl-CoA. This is achieved by: 1) limiting leucine intake via protein restriction [2–4]; 2) enhancement of alternative metabolic pathways using carnitine [5,6] and glycine [7,8] which conjugate with isovaleryl-CoA to produce the non-toxic compounds isovalerylglycine and isovalerylcarnitine; and 3) application of an emergency management protocol at times of metabolic stress (e.g. illness and fasting). However, partly due to IVA's heterogeneity, its rarity, shortage of large, multi-centre longitudinal studies and long-term outcome data, there is disagreement regarding optimal dietary management. Almost all reports are from case studies or small case series only.

The first case studies of IVA reported signs of dietary protein intolerance typically with episodes of vomiting, lethargy and acidosis with ketonuria after increased intake of protein-rich foods [9,10]. Many patients maintain long term metabolic stability on dietary protein restriction only [1,11–18]. In fact, the majority of IVA case studies advise some protein restriction [1–7,9,11,14–16,19–30] but with wide differences in the amount of natural protein given. Some centres prescribe less than the WHO/FAO/UNU 2007 safe levels of protein intake [31] and may specifically calculate and control leucine intake supplemented with leucine-free L-amino acid supplements (LFAA) [3,5,22,23,26–29,32–35].

In September 2014, the web based E-IMD IVA guidelines [36] advocated that natural protein intake be restricted to reduce the isovaleric acid burden but should supply at least the WHO/FAO/UNU 2007 safe levels of protein intake [31]. The use of LFAA was not discussed [36] and some considered they may provide little clinical benefit and thus provide extra burden to patients and families and unnecessary expense to health services.

This paper aims to describe European practice regarding the dietary management of IVA prior to the introduction of the E-IMD IVA guidelines in 2014.

## 2. Material and methods

A cross-sectional questionnaire was sent to all European dietitians who were either members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG) or whom had responded to previous questionnaires on dietetic practice (n = 53) [37]. We requested dietitians cascade the questionnaire to other dietitians and/or physicians within their own country between July and August 2014. The questionnaire consisted of 27 multiple choice and short answer questions. The questions were aimed at patients on dietary treatment. The following data were collected by age group: total protein intake prescribed, amount of natural protein and use of LFAA. Specific questions were asked about: special low protein foods, energy, vitamin and mineral supplements, use of enteral feeding, monitoring, treatment criteria and treatment drugs. The results were divided into geographical regions to examine trends in protein prescription. The groupings were: Western Europe Group A (Netherlands, Belgium, France), Western Europe Group

B (Germany, Switzerland, Austria), Eastern Europe (Poland), Southern Europe (Italy, Spain and Portugal), and Northern Europe (Denmark, Norway, Sweden and UK).

Clinical outcome data or patient specific data were not included in this questionnaire. Therefore, ethical approval was not required.

### 2.1. Statistical analysis

Data were analysed using descriptive statistics (percentage of total responses, means or medians). Prior to analysis, responses to some open answer questions were grouped or categorised according to answers received.

## 3. Results

Dietitians from 53 centres, representing 14 countries returned questionnaires. Fourteen of 53 centres reported they had no patients with IVA. For each country a median of 3 centres responded (range 1–14).

### 3.1. Patient description

In total, 140 patients with IVA were reported. Seven of 140 patients were excluded from analysis as they were not prescribed a protein restriction. Therefore 133 patients from 38 centres were on protein restriction with a median of 2 patients (range 1–17) per centre.

The numbers of centres and patients in each geographical grouping were: Western Europe Group A,  $n = 14$  centres, 44 patients; Western Europe Group B,  $n = 6$  centres, 24 patients; Eastern Europe,  $n = 1$  centre, 8 patients; Southern Europe,  $n = 4$  centres, 9 patients; and Northern Europe,  $n = 13$  centres, 48 patients. In the 133 IVA patients presentation age was: neonatal,  $n = 81$  (61%); late,  $n = 48$  (36%), and unknown,  $n = 4$  (3%). Patients were distributed in the following age ranges at the time of questionnaire completion:  $<1$  y ( $n = 7$ ), 1–10 y ( $n = 71$ ), 11–16 y ( $n = 31$ ) and  $>16$  y ( $n = 24$ ).

### 3.2. Total protein prescription

All centres distributed by region and age range are presented in Fig. 1. Total protein intake (g/kg/day) in almost all centres (32 of 38, 84%) met WHO/FAO/UNU safe levels of protein intake [31].

Twenty centres (53%) prescribed total protein prescription according to the WHO/FAO/UNU safe levels of protein intake [31], and 15 centres (39%) used the countries national reference protein intake as a guide for protein prescription. The median total protein prescription (g/kg/day) with and without LFAA is given in Table 1.

The following criteria were used by all centres for adjusting protein prescription: quantitative plasma amino acid profiles, growth and

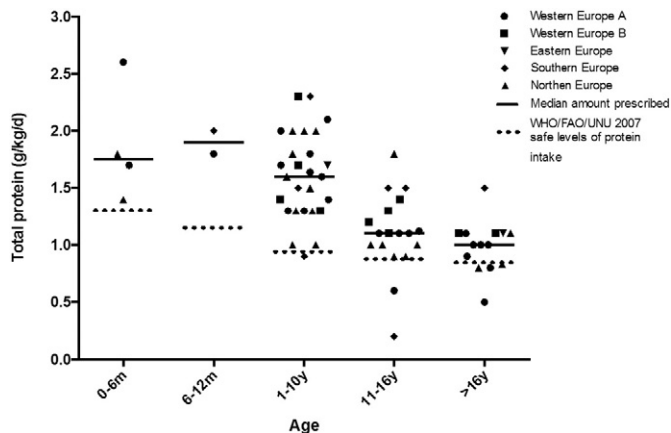


Fig. 1. Mean total protein prescription to IVA patients by centre in each age range ( $n = 38$  centres).

severity of IVA. Protein prescription was a combined decision between medical doctors and dietitians in 24 centres (63%), medical doctors only in 11 centres (29%) and a dietitian's decision only in 2 centres (5%). One centre did not answer this question.

### 3.3. Natural protein prescription

The median natural protein prescription (g/kg/day) compared with WHO/FAO/UNU safe levels of protein, with and without LFAA is given in Table 2. In Fig. 2, natural protein prescription is presented by region and age. Almost half of the centres ( $n = 18$ ; 47%) prescribed natural protein intakes below WHO/FAO/UNU 2007 safe levels of protein intake [27] in at least one age range. However, the use of LFAA in 12 (66%) centres improved protein intake allowing safe levels to be achieved. Five of 38 centres (13%) prescribed a low protein diet (without LFAA) that did not provide safe levels of protein intake [27] in patients above 11 y (centres from France  $n = 2$ ; UK,  $n = 2$ ; and Italy,  $n = 1$ ).

Ten centres (26%) reported avoiding animal protein as part of the natural protein allowance. Seven of these centres used LFAA to supplement natural protein intake.

### 3.4. Prescription of LFAA

LFAA were used routinely to supplement protein intake by 23 of 38 (61%) centres (Fig. 3). The amount of LFAA prescribed per kg is given in Table 1. The median percentage of total protein provided by LFAA was over 40% (range 17–82%) in all age groups. The numbers of centres prescribing LFAA declined from 10 years of age [aged 0 to 12 months, 67% ( $n = 4$  centres)]; 1 to 10 y, 67% ( $n = 18$  centres), 11 to 16 y, 50% ( $n = 9$  centres) and  $>16$  y of age, 43% of centres ( $n = 6$  centres)]. None of the UK centres prescribed LFAA for IVA. Centres within countries that varied in their approach to using LFAA were Austria, Belgium, France, Germany, Italy and Netherlands.

LFAA were given in divided doses throughout the day mixed with water/fruit juice or as a puree. The preferred LFAA were for: infants, a leucine-free infant formula supplemented with carbohydrate, fats, vitamins and minerals, and patients over 1 y, a leucine-free L-amino acid supplement (powder/liquid) containing carbohydrate, vitamins and minerals. LFAA without added vitamins and minerals were rarely used.

### 3.5. Nutritional support

Only 8 of 133 patients (6%) were given tube feeds (for neurological dysfunction and feeding difficulties). Of this group all had gastrostomy tubes and 3 of 8 were on nocturnal enteral feeds only.

The majority of centres (34 of 38; 89%) used special low protein foods such as low protein pasta but the amount varied according to individual patient needs and the dietary practices of local centres. Seventy-four percent (28 of 38 centres) prescribed a low protein milk replacement instead of cow's milk. Only 11% (15 of 133) of patients were given additional energy supplements.

### 3.6. Monitoring

All centres monitored weight, height, quantitative plasma amino acids and nutritional blood markers. The frequency was age dependent (3–12 monthly) with infants and young children (pre-school age) assessed more frequently. Nutritional markers included: quantitative amino acids, zinc, selenium, haemoglobin, ferritin and vitamins B12 (and plasma MMA), D, A and E. Some centres reported monitoring essential fatty acids (23 centres; 60%), but at infrequent intervals.

### 3.7. Drugs treatment

Most centres reported using carnitine (37 centres, 97%) and glycine (29 centres, 76%) as a standard treatment approach. Nitrogen scavenger

**Table 1**

Descriptive statistics comparing centres (using/not using LFAA) for dietary prescription of: total protein (g/kg), natural protein (g/kg), LFAA (g/kg) and % of protein provided by LFAA compared with total protein prescription.

	Centres using LFAA					Centres not using LFAA				
	Age 0–6 m (n = 2)	Age 7–12 m (n = 2)	Age 1–10 y (n = 40)	Age 11–16 y (n = 16)	Age >16 y (n = 5)	Age 0–6 m (n = 3)	Age 7–12 m (n = 0)	Age 1–10 y (n = 31)	Age 11–16 y (n = 15)	Age >16 y (n = 19)
Total protein (g/kg)										
Median	2.2	1.9	1.7	1.1	1.1	1.6	None reported	1.3	1.0	0.9
Min	1.7	1.8	0.9	1.0	1.0	1.4		1.0	0.2	0.5
Max	2.6	2.0	2.3	1.5	1.5	1.8		2.0	1.8	1.1
Natural protein (g/kg)										
Median	1.1	0.4	1.0	0.7	0.7	1.6	None reported	1.3	1.0	0.9
Min	1.0	0.4	0.4	0.4	0.4	1.4		1.0	0.2	0.5
Max	1.1	0.5	1.9	1.0	0.8	1.8		2.0	1.8	1.1
LFAA (g/kg)										
Median	1.1	1.5	0.7	0.5	0.6	0	None reported	0	0	0
Min	0.7	1.3	0.2	0.4	0.3	0		0	0	0
Max	1.5	1.7	1.2	0.6	0.8	0		0	0	0
% amount of total protein from LFAA										
Median	50	77	44	42	48	0	None reported	0	0	0
Min	41	72	17	29	27	0		0	0	0
Max	58	82	75	60	64	0		0	0	0

LFAA: leucine free L-amino acids.

n: number of patients.

drugs were used by 2 centres (5%) but only to treat hyperammonemia at initial presentation. Laxatives for constipation were used by 7 centres (18%).

#### 4. Discussion

This multicentre pan European survey describes the dietary management of 133 patients with IVA on protein restriction prior to the introduction of the E-IMD IVA guidelines. This provides a foundation to compare any changes in dietary approach as a consequence of the availability of the first European guidelines. Most centres managed only small numbers of IVA patients, constraining the development of dietetic expertise with this condition. There was little consensus in dietary approach. Centres that prescribed a natural protein restriction only, generally achieved the WHO/FAO/UNU [2007] safe levels of protein intake [31] but in 5 of these centres, particularly in patients  $\geq 11$  years of age, natural protein intakes were well below safe levels.

LFAA were used by almost two thirds of European metabolic centres to compensate for the low natural protein prescription in order to meet safe levels of protein intake. The need for LFAA has been challenged [1,11–18] and the use of LFAA is not advocated by the IVA-EIMD guidelines [36]. There is some suggestion that LFAA may correct amino acid imbalance or deficiency [27,30,38,39] but the effectiveness of this is

unknown and remains unstudied with severe natural protein restriction appearing unnecessary. There is limited published IVA patient outcome data that describes dietary management in depth. In a recent study, data from a patient registry outlined 45 patients with IVA who had baseline height and weight z scores that were close to zero but dietary intake was unreported [40]. In 4 adults with IVA, managed with low protein diets only, had normal growth and no progressive disease [17]. In a group of 21 IVA patients, catabolic episodes mainly occurred in early childhood and protein intake did not appear to be a major precipitating factor [41]. Generally, long term treatment with carnitine, glycine and a low protein diet (with or without LFAA) appears to lead to relative metabolic stability, particularly after the early childhood years.

Geographical location appeared to have a large influence on the prescription of LFAA with more centres prescribing in Western Europe A (79% of centres), Southern Europe (75% of centres), Western Europe B (67% of centres), and Eastern Europe (the only centre participating used LFAA). Less LFAA was prescribed in Northern Europe (only 31% of centres), and no centres in the UK used LFAA (Fig. 3). In addition, companies that produce LFAA for IVA only supply a limited range. These are mainly unflavoured with narrow presentation choice (mainly powders). It is possible adherence may be sub-optimal but this question was not asked and remains unreported in IVA.

**Table 2**

Comparison of natural protein and total protein with WHO/FAO/UNU [2007] safe levels of protein intake for all centres.

Age	Centres using LFAA					Centres not using LFAA				
	0–6 m (n = 2)	7–12 m (n = 2)	1–10 y (n = 40)	11–16 y (n = 16)	>16 y (n = 5)	0–6 m (n = 3)	7–12 m (n = 0)	1–10 y (n = 31)	11–16 y (n = 15)	>16 y (n = 19)
Natural protein (g/kg)										
Median	1.1	0.4	1.0	0.7	0.7	1.6	None reported	1.3	1.0	0.9
WHO/FAO/UNU 2007	1.31	1.14	0.94 <sup>a</sup>	0.89 <sup>a</sup>	0.84	1.31	1.14	0.94 <sup>a</sup>	0.89 <sup>a</sup>	0.84
% intake compared to WHO reference value 2007	84	35	106	79	83	122	–	138	112	107
Total protein (g/kg)										
Median	2.2	1.9	1.7	1.1	1.1	1.6	None reported	1.3	1.0	0.9
WHO/FAO/UNU 2007	1.31	1.14	0.94 <sup>a</sup>	0.89 <sup>a</sup>	0.84	1.31	1.14	0.94 <sup>a</sup>	0.89 <sup>a</sup>	0.84
% intake compared to WHO reference value 2007	168	167	181	124	131	122	–	138	112	107

LFAA: leucine free L-amino acids.

n: number of patients.

<sup>a</sup> Mean protein values for ages 1–10 y, 11–16 y taken for WHO/FAO/UNU [2007] recommendations.

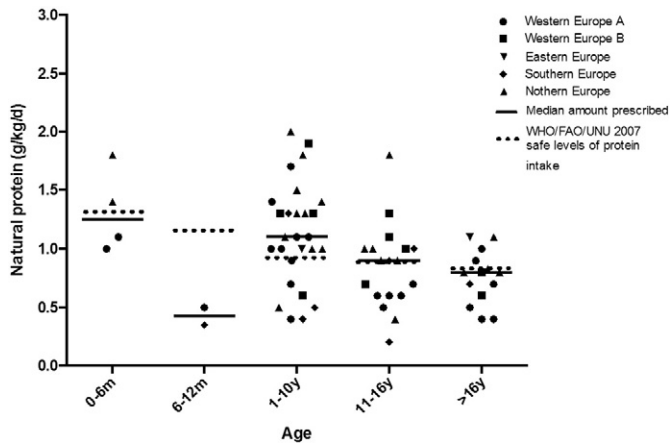


Fig. 2. Mean natural protein prescription to IVA patients by centre in each age range (n = 38 centres).

The IVA E-IMD guidelines [36] recommend that natural protein intake should be restricted to reduce the isovaleric acid burden but ought to supply at least the safe levels of protein intake advocated by WHO/FAO/UNU 2007 [31]. They emphasise that over-restriction of natural protein could lead to catabolism and metabolic instability [42]. From case reports, patients are able to maintain metabolic stability when consuming at least the WHO/FAO/UNU safe levels of protein/leucine intake although some younger patients have tolerated double this amount [1,14,15,24]. In IVA, there are no reported differences in leucine/protein prescription for age, growth rate and severity of disorder. There are also no case reports describing protein intake in adolescents and adults or for patients with the milder 932C-T mutations. Although in our cohort some of the older patients, in particular, were prescribed less than safe levels of protein intake, it is possible that their actual natural protein intake was higher but we did not collect this data.

Leucine is an essential amino acid; it plays an important role in the regulation of metabolism, promotes global protein synthesis by signalling an increase in translation [43,44], promotes insulin release [45] and inhibits autophagic protein degradation [46]. Over restriction will lead to anorexia, triglyceride lipolysis [47], weight loss [48], and amino acid imbalance. Leucine provides 10% of the amino acid content of animal protein but only 6% of vegetable protein [49]. In this study, almost one third of centres used only low biological food sources to provide natural protein intake. This may potentially lead to leucine deficiency, which has been reported in IVA children [50].

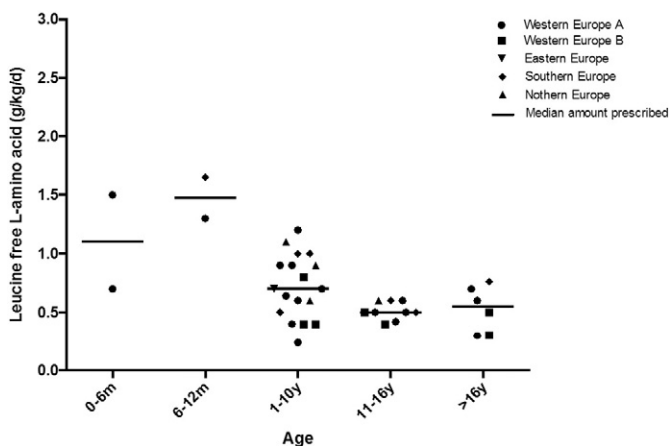


Fig. 3. Mean leucine free L-amino acid prescription to IVA patients by centre in each age range (n = 23 centres).

Generally, in IVA, emphasis has been placed on protein intake but maintenance of energy intake may be as important as protein restriction. In an early study, Millington et al. [51] demonstrated that the turnover of endogenous protein, rather than dietary protein intake, is the main cause for the production of toxic metabolites in IVA. He suggested that suppression of endogenous catabolism is more effective than exogenous dietary protein restriction. Therefore, although there was low use of tube feeding (8 of 133 patients) in this survey, overall evidence would suggest that attention should be paid to adequate energy intake when patients are both stable and during metabolic stress.

There are some limitations in this survey. Initially participant interpretation of some questions was inconsistent, but all answers were quality checked with individual participants until we were certain data was interpreted correctly. No data was collected about patient clinical outcome, disease severity or detailed information about drug treatments which may have impacted on centres practices with protein prescription. Also data was collected about dietary prescriptions rather than actual dietary intake.

There remains much to be done to define the optimum dietary management of IVA considering all age groups and disorder severity. The prescription of median natural protein intake was below safe levels of protein intake when centres were giving LFAA. Overall, there may be 'over restriction' of natural protein and unnecessary use of LFAA creating a diet that is burdensome and expensive [51,52], particularly in older patients who have fewer episodes of metabolic instability. It is also important that further guidelines should differentiate dietary management for the "classic" IVA and the "mild" phenotype [52]. This study provides baseline data from a large cohort of IVA patients and will help enable the development of controlled trials to further investigate dietary management and help standardise treatment.

#### Author's roles

All authors were involved in data collection, interpretation of data, critical revision of the paper for important intellectual content and final approval of the version to be published. Alex Pinto was involved in quality check of data, data analysis and writing of the manuscript. Anne Daly was involved in data analysis and manuscript development. Sharon Evans was involved in questionnaire design, collection of data and manuscript development and Anita MacDonald was involved in questionnaire development, interpretation of data and writing of the manuscript.

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#### Conflict of interest

Alex Pinto has received an educational grant from Cambrooke Therapeutics and grants from Vitaflor, Merck Serono and Biomarin to attend scientific meetings.

Anita MacDonald has received research funding and honoraria from Nutricia, Vitaflor International and Merck Serono. She is a member of the European Nutrition Expert Panel (Biomarin), member of Sapropterin Advisory Board (Biomarin), member of the Advisory Board entitled ELEMINT (Danone-Nutricia), and member of an Advisory Board for Arla and Applied Pharma Research.

Anne Daly has undertaken evaluation work for the nutritional companies – Vitaflor Ltd, Nutricia Ltd and Metax.

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