Dietary practices in pyridoxine non-responsive homocystinuria: A European survey

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ABSTRACT

Background: Within Europe, the management of pyridoxine (B6) non-responsive homocystinuria (HCU) may vary but there is limited knowledge about treatment practice.

Aim: A comparison of dietetic management practices of patients with B6 non-responsive HCU in European centres.

Methods: A cross-sectional audit by questionnaire was completed by 29 inherited metabolic disorder (IMD) centres: (14 UK, 5 Germany, 3 Netherlands, 2 Switzerland, 2 Portugal, 1 France, 1 Norway, 1 Belgium).

Results: 181 patients (73% > 16 years of age) with HCU were identified. The majority (66%; n = 119) were on dietary treatment (1-10 years, 90%; 11-16 years, 82%; and >16 years, 58%) with or without betaine and 34% (n = 62) were on betaine alone. The median natural protein intake (g/day) on diet only was, by age: 1-10 years, 12 g; 11-16 years, 11 g; and >16 years, 45 g. With diet and betaine, median natural protein intake (g/day) was: 1-10 years, 13 g; 11-16 years, 20 g; and >16 years, 38 g. Fifty-two percent (n = 15) of centres allocated natural protein by calculating...
methionine rather than a protein exchange system. A methionine-free \( \text{L-} \)-amino acid supplement was prescribed for 86\% of diet treated patients. Fifty-two percent of centres recommended cystine supplements for low plasma concentrations. Target treatment concentrations for homocysteine/homocysteine (free/total) and frequency of biochemical monitoring varied.

Conclusion: In B\(_6\) non-responsive HCU the prescription of dietary restriction by IMD centres declined with age, potentially associated with poor adherence in older patients. Inconsistencies in biochemical monitoring and treatment indicate the need for international consensus guidelines.

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1. Introduction

Pyridoxine (B\(_6\)) non-responsive homocystinuria (HCU) is a multisystem disorder due to cystathionine-\( \beta \)-synthase (CBS; EC 4.2.1.22) deficiency. HCU causes increased plasma concentrations of homocysteine leading to accumulation of the amino acid methionine (MET) [1]. CBS deficiency also causes elevated concentration of S-adenosylmethionine and S-adenosylhomocysteine and prevents synthesis of cystathionine [2]. It is characterized in childhood by low IQ [3], osteoporosis [4], skeletal disproportion, dislocation of the optic lens [5], cardiovascular risk and thromboembolic events [6]. Psychiatric disturbances [7,8] are present in up to 50\% of patients [9,10]. HCU is rare, with a worldwide incidence of 1:65,000 to 1:900,000 [11], although it is predicted it could be as high as 1:6400 [12] and 1:15,500 [13] in some European countries.

In the absence of newborn screening programmes, diagnosis is commonly delayed. As a consequence, if patients are not detected early, the condition is associated with significant long-term morbidity and mortality [14–16]. A high proportion of individuals with c.833T \( \rightarrow \) c.837T (p.1278 T) (pyridoxine-responsive HCU) remain undiagnosed [13], and may have a thromboembolic episode in the third decade of life [1].

The aim of treatment is to reduce the concentration of homocyst(e)ine (Hcy) in the plasma and tissues. Two treatment interventions are used either singly or in combination: 1) low methionine or low natural (Hcy) in the plasma and tissues. Two treatment interventions are used either singly or in combination: 1) low methionine or low natural protein diet with a methionine-free \( \text{L-} \)-amino acid supplement [17] (with or without the addition of vitamins, minerals, carbohydrates and lipids) and/or 2) betaine, a medicine which promotes the recycling of homocysteine to methionine thereby decreasing plasma Hcy concentrations [18]. Both interventions are effective in lowering blood Hcy concentrations but both are associated with substantial patient adherence issues [8,16,19,20]. Medical and dietary treatment of HCU varies between inherited metabolic disorder (IMD) centres and there is limited knowledge about dietary practices. Although many agree that the aim of any treatment is to lower total Hcy (tHcy) close to normal reference range, there is no international consensus which defines optimal biochemical control and monitoring in this disorder.

The aim of this paper is to compare current dietary management practices of European metabolic centres and examine dietary treatment of patients with B\(_6\) non-responsive HCU. Treatment outcome measures are not reported.

2. Materials and methods

2.1. Study design

A questionnaire (26 multiple choice and short answer questions) was sent to all European members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG) in 2011. This was to collect retrospective life-time dietary management data of B\(_6\) non-responsive HCU patients in existing care from each IMD centre.

In this cross-sectional audit, data was collected on: treatment (use of diet only, betaine only, or combination of diet and betaine) for each patient categorized into age groups, description of diet therapy, including prescribed natural protein or methionine intake (for diet only or diet and betaine), mean protein equivalent intake (from dietary protein/methionine and methionine-free \( \text{L-} \)-amino acid supplement), use of cystine supplementation including dose and method of administration, treatment aims and frequency of monitoring of biochemical parameters (tHcy, free homocysteine [fHcy], methionine and cyst(e)ine [Cys]), and use of other nutritional supplements. Clinical outcome data was not included in this audit.

Ethical approval was not required for this study as no specific identifiable patient data was obtained or used.

3. Results

Questionnaires were returned from 29 IMD centres providing data on 181 patients with HCU: UK (14 centres, 108 patients), Germany (5 centres, 39 patients), Netherlands (3 centres, 19 patients), Switzerland (2 centres, 5 patients), Portugal (2 centres, 4 patients) and Belgium, France and Norway (1 centre per country, each with 2 patients). Newborn screening (NBS) was uncommon (28\% [n = 8] of centres).

3.1. Patient description

The ethnic origin of patients was: white European 86\% (n = 155); Black African/Caribbean 3\% (n = 6); Pakistani 3\% (n = 6); Indian 3\% (n = 6); Arabic 3\% (n = 5) and Turkish 2\% (n = 3).

3.2. Treatment

The most common choice of treatment was a combination of measured/unmeasured diet and betaine (61\%, n = 110 of all patients); followed by betaine alone (34\%, n = 62) and then diet alone (5\%, n = 9; all from the UK) (Table 1, Fig. 1). There was a declining preference for prescribing diet with increasing patient age, whilst the preference for using betaine only, increased with age particularly >16 years (Fig. 1). Treatment choice was influenced by previous experience: problems with diet alone (38\% of centres), good experience with diet alone (31\%) and efficacious therapy with betaine alone without the need for diet (21\%).

3.3. Treatment versus age of diagnosis (Table 2)

Only 19\% (n = 25/131) of those with a known age of diagnosis were identified by NBS. All patients on ‘diet only’ treatment had been diagnosed by the age of 10 years (50\%; n = 4/8 on NBS). Those on ‘betaine only’ were mainly (42\%, n = 11/26) diagnosed after 10 years of age, 8\% (n = 2/26) by NBS and in 36 patients the diagnostic age was unknown. Patients on ‘diet and betaine’ were mostly (84\%; n = 81/97) diagnosed by the age of 10 years and 19\% (n = 19/97) by NBS.

The age of diagnosis was unknown for just over one quarter of patients (28\%; n = 50/181); all aged >16 years at the time of data collection and the majority (72\%; n = 36) on a treatment of ‘betaine only’.

3.4. Allocation of natural protein using methionine analysis

Approximately one half (52\%, n = 15) of IMD centres prescribed a diet primarily using methionine analysis of foods. However, in practice...
significant protein equivalent in g/kg/day prescribed from a combination natural protein/methionine restriction under the age of 16 years. The age (products are listed below Fig. 2), in particular all patients on (approximately 30 to 50 mg/1 g protein equivalent).

16 years (Table 3). All of these supplements contained cystine and natural protein analysis (1 g protein exchanges or calculated the protein content of all foods eaten). Ten of the 15 centres used a methionine exchange system (UK, n = 7; Portugal, n = 2; Switzerland, n = 1). All 7 UK centres used 20 mg exchanges, Portugal 10 mg exchanges and Switzerland 10 mg for fruit, 20 mg for vegetables and 80 mg for starches. The other five centres used lists of methionine content of foods.

Total daily dietary methionine intake increased with age whilst intake per kg body weight/day decreased (Table 3).

3.5. Natural protein intake for patients on dietary restriction

A low protein diet was used by 48% (n = 14) of IMD centres to limit methionine intake, using either 1 g protein exchanges or calculating the protein content of all foods eaten. Total median natural protein intake (g/day) generally increased with age particularly after the age of 16 years (Table 3).

3.6. Methionine free l-amino acids

Eighty-six percent (n = 97/113) of all patients on dietary restriction were prescribed methionine-free l-amino acid supplements based on age (products are listed below Fig. 2), in particular all patients on a natural protein/methionine restriction under the age of 16 years. The median protein equivalent in g/kg/day prescribed from a combination of natural protein methionine and l-amino acids decreased with age with much greater variation across IMD centres for patients aged <10 years (Fig. 2). All of these supplements contained cystine (approximately 30 to 50 mg/1 g protein equivalent).

3.7. Cystine supplementation

Fifty-two percent (n = 15), (UK, n = 10; Germany, n = 3; Portugal, n = 1; Switzerland, n = 1) of IMD centres advocated additional cystine supplements but only if plasma concentrations were below the lower limit of the reference range and one Swiss centre prescribed them routinely. Only 18 subjects from 10 centres at the time of data collection were prescribed cystine supplements. The median dose was ≤2.3 g/day in children ≤16 years of age (1–10 years, 2.3 g/day [range: 0.5–4 g; n = 4]; 11–16 years, 2 g/day [range: 1–4 g; n = 8]; and >16 years, 4 g/day [range: 1–10 g; n = 6]). Supplements were given either as pre-measured sachets (n = 4 centres), tablets (n = 2), powder measured with scoops (n = 3) or weighed on scales (n = 2). Powdered supplements were mixed with either methionine-free l-amino acid supplements (n = 7 centres) or water/juice (n = 3).

3.8. Other prescribed energy and micronutrient supplements

Low protein milks and low protein foods were prescribed routinely by most IMD centres to improve energy intake; general vitamin and mineral supplements by at least two thirds of centres; long chain polyunsaturated fatty acids (LCPUFAs) and essential fatty acids (EFAs) by less than a quarter of centres (Table 4).

Pharmacological doses of vitamin B6 and folinic acid were prescribed routinely by most IMD centres and vitamin B12 by nearly two thirds of centres.

3.9. Biochemical monitoring and treatment aims

There was little consensus about target ranges for blood tHcy (median < 55 μmol/l; range < 20–100) (Fig. 3) and fHcy (median <5 μmol/l; range < 1–11). Normal tHcy concentrations are <15 μmol/l [21,22] and fHcy concentrations <5 μmol/l. Ninety-six percent (n = 28) of IMD centres routinely measured tHcy, and 28% (n = 8) (UK, n = 6; Germany, n = 1; Switzerland, n = 1) also measured fHcy. Sixty-nine percent (n = 20) of centres measured cystine. Whilst the median frequency of blood monitoring generally decreased with age there was a wide variation in the range of frequency particularly for patients over the age of 10 years (Fig. 4).

4. Discussion

This is the first multi-centre European paper to describe management practices in B6 non-responsive HCU. Most centres preferred a combined approach of diet and betaine, whilst many adult patients, particularly if late diagnosed, were on betaine only without dietary restriction. Most patients were late diagnosed (during childhood or older) as only 8 centres performed newborn screening. There were wide variations in treatment aims for biochemical control, dietary practices and use of adjunct supplements.

Betaine was a common treatment choice, particularly in late diagnosed patients, adolescents and adults. It is a methyl donor that stimulates the remethylation of homocysteine to methionine via the enzyme betaine–homocysteine S-methyltransferase, and decreases high plasma concentrations of tHcy [21,23,24] by 20 to
Table 2
Age of diagnosis of patients according to treatment (diet only, diet and betaine, and betaine alone) and age at time of data collection.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age at time of study</th>
<th>n = 181</th>
<th>Newborn/sibling screen</th>
<th>&lt;1 year</th>
<th>1–4 years</th>
<th>5–10 years</th>
<th>11–16 years</th>
<th>&gt;16 years</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet only</td>
<td>&lt;1 year</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–10 years</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11–16 years</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;16 years</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and Betaine</td>
<td>1–10 years</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11–16 years</td>
<td>21</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;16 years</td>
<td>74</td>
<td>13</td>
<td>2</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>110</td>
<td>19</td>
<td>4</td>
<td>26</td>
<td>32</td>
<td>6</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Betaine only</td>
<td>1–10 years</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11–16 years</td>
<td>55</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;16 years</td>
<td>62</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>36</td>
</tr>
</tbody>
</table>

Note: some centres used a combination of MET and natural protein to allocate dietary methionine/protein allowance.

Table 3
Median natural protein (diet alone/diet and betaine) and methionine (diet alone/diet and betaine) intake by patient age (n = number of IMD centres).

<table>
<thead>
<tr>
<th></th>
<th>1–12 monthsa</th>
<th>1–10 years</th>
<th>11–16 years</th>
<th>&gt;16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diet only</td>
<td>8 (6–10)</td>
<td>12 (10–15)</td>
<td>11 (10–15)</td>
<td>45 (45)</td>
</tr>
<tr>
<td>g/day (range)</td>
<td>1.0 (0.8–2.0)</td>
<td>1.0 (0.5–1.0)</td>
<td>0.6 (0.2–1.0)</td>
<td>0.9 (0.7–1.0)</td>
</tr>
<tr>
<td>(5 patients; 4 centres) n = 4</td>
<td>n = 4</td>
<td>n = 4</td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>Natural protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diet &amp; BET</td>
<td>No data</td>
<td>13 (10–16)</td>
<td>20 (10–40)</td>
<td>38 (10–84)</td>
</tr>
<tr>
<td>g/day (range)</td>
<td>1.7 (1.1–2.0)</td>
<td>0.8 (0.3–1.5)</td>
<td>0.3 (0.2–1.0)</td>
<td>0.8 (0.2–1.0)</td>
</tr>
<tr>
<td>(64 patients; 21 centres) n = 2</td>
<td>n = 9</td>
<td>n = 13</td>
<td>n = 14</td>
<td></td>
</tr>
<tr>
<td>MET diet only</td>
<td>143 (120–180)</td>
<td>180 (140–220)</td>
<td>213 (200–250)</td>
<td>300 (200–400)</td>
</tr>
<tr>
<td>mg/day (range)</td>
<td>13 (13–13)</td>
<td>10 (8–14)</td>
<td>No data</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>(5 patients; 3 centres) n = 3</td>
<td>n = 3</td>
<td>n = 2</td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>MET diet &amp; BET</td>
<td>200 (200)</td>
<td>250 (140–382)</td>
<td>275 (160–430)</td>
<td>365 (180–900)</td>
</tr>
<tr>
<td>mg/day (range)</td>
<td>No data</td>
<td>9 (4–15)</td>
<td>7 (3–10)</td>
<td>5 (2–15)</td>
</tr>
<tr>
<td>(53 patients; 10 centres) n = 4</td>
<td>n = 5</td>
<td>n = 7</td>
<td>n = 9</td>
<td></td>
</tr>
</tbody>
</table>

Note: some centres used a combination of MET and natural protein to allocate dietary methionine/protein allowance.
a Includes retrospective data on reported patients when they were in that age bracket.

30% of pre-treatment levels [25]. Betaine is mainly considered as an adjunct therapy so it was surprising that it was used as the primary therapy in 34% of patients. There are no controlled studies examining its long term effectiveness when given without diet; we did not collect data on blood HCY control. Doses of betaine are large (up to 6 g/day in teenagers) [26], and compliance is commonly poor [16,19]. In addition, the “human only” (HO) HCU mouse model demonstrated betaine’s ability to lower tHcy which significantly decreased over time [2].

Although betaine is considered safe, it commonly raises plasma MET and the long term effectiveness when given without diet; we did not collect data on blood HCY control. Doses of betaine are large (up to 6 g/day in teenagers) [26], and compliance is commonly poor [16,19]. In addition, the “human only” (HO) HCU mouse model demonstrated betaine’s ability to lower tHcy which significantly decreased over time [2].

With dietary management, IMD centres differed in the way that methionine allowance was calculated. Equal numbers of centres either calculated natural protein intake only or gave more accurate advice using the methionine content of foods. There is no evidence to suggest that either method has clinical advantage. Theoretically, methionine analysis is more precise as some foods are lower in methionine relative to their protein content (e.g. methionine content per 1 g protein: peas 10 mg; lentils 7 mg; egg 31 mg; and milk 28 mg) enabling larger and more varied food portions to be consumed but unfortunately validated methionine analysis is only available for a limited range of foods in some countries.

Using natural protein analysis as an alternative may be appropriate particularly for late diagnosed patients who have followed a normal diet for several years or for those with learning difficulties [8].

The optimal amount of MET-free l-amino acids to supplement natural protein intake is not determined and there are no disorder specific recommendations. Methionine-free l-amino acid supplements are an important source of cystine (providing 1.8 g to 3 g/day per 60 g protein equivalent), and as for other amino acid disorders, they may help improve metabolic control [29]. The median amount of total protein prescribed (from methionine-free l-amino acids and natural protein/methionine from diet) decreased with age, but practices were highly variable, with some patients taking no l-amino acids. Although it was unclear why some patients were not prescribed l-amino acids, it is likely in adults/teenagers that previous adherence may have been poor. Unfortunately, due to the relative infrequency of B6 non-responsive HCU, the choice of suitable l-amino acids has lagged behind the more common disorders such as PKU.

Surprisingly, few patients on diet were taking separate cystine supplements. It is known that tHcy concentrations increase significantly when total Cys (tCys) concentrations are <170 μmol/L [30], and so cystine supplementation should be considered when concentrations are low. However, the optimal cystine dose is undefined, adherence may be poor due to its taste, it has a poor solubility and it is difficult to ensure that patients receive the full dose when administered as a separate supplement. Some IMD centres did not measure Cys concentrations routinely. Data on the type of Cys (free or total) analysed was not collected.

There is a need for consensus guidelines to define the optimal biochemical tHcy treatment reference range in HCU, which is being addressed by the European registry and network for HCU and methylthionyl defects (E-HOD), which was established in 2013. From our survey, there was no agreement, even within the same country, about desirable target concentrations for tHcy, with target ranges...
Fig. 2. Median protein equivalent prescribed by centres for the different age bands from both dietary protein (methionine) and l-amino acid supplements*. Footnote: *Includes retrospective data on reported patients when they were in that age bracket. HCU Anamix infant, HCU Anamix Junior LQ, XMet Maxamaid, XMet Maxamum, HCU LV, XMet Homidex, HCU Lophlex LQ, M-AM 2, M-AM 3 [Nutricia/SHS], HOM 1 Mix, HOM 1, HOM 2, HOM 2 prima, HOM 2 secunda, HOM 3 advanta [Miliupa/Nutricia]; HCU Gel, HCU Express, HCU Cooler [Vita International]; ZeroMet Infant Mix, ZeroMet Kid, ZeroMet Junior, ZeroMet Advance [MetaX].

varying from <20 to <100 μmol/L, leading to inconsistencies in management and confusion for patients. It is known in B6 non-responsive HCU, a lifetime plasma fHcy median <11 μmol/L seems to be protective against complications [3], although published data is still limited. In a HO mouse model of HCU study, there is a relatively sharp effect whereby elevated tHcy above a certain concentration increases thrombocytic risk and is accompanied by an increased pro-inflammatory cytokine expression [2]. Moat et al. [31] demonstrated that tHcy must exceed 60 μmol/L before plasma fHcy is detectable by conventional ion-exchange chromatography.

There was also no consensus about the frequency of tHcy monitoring. In patients aged over one year, mean plasma tHcy/fHcy monitoring was only at 3 monthly intervals; less than other amino acid disorders such as PKU. Unfortunately, home monitoring is currently not feasible and regular hospital visits for blood monitoring may be an unacceptable burden to many patients. However, it is established that infrequent blood monitoring is associated with poor treatment adherence in other conditions [32], particularly when there may be no obvious early symptoms associated with non-adherence.

In summary, it is clear that in the European IMD centres participating in this study there are wide differences in the treatment policy of B6 non-responsive HCU. There was no consistent approach to diet and drug treatment by centres but it appeared to be influenced by increasing patient age and their possible rejection of dietary treatment. Further studies are required looking at outcome data, particularly with betaine therapy only. In B6 non-responsive HCU, it is important to develop dietary and pharmacological management guidelines to assist health professionals in the provision of safe, effective treatment for this challenging condition.

Authors’ roles

All authors were involved in the data collection, interpretation of data, critical revision of the paper for important intellectual content and final approval of the version to be published. AMcD and SE were additionally involved in the initial conception and design, collation of data and drafting of the initial article.

Source of funding

There has been no direct funding for this study; it has been completed as part of normal dietetic research.

Conflict of interest

Sarah Adam — funding from SHS and Vitafluo to attend study days and conferences.
Marjorie Dixon — research funding, honoraria and sponsorship from Nutricia and Vitafluo International.
Katharina Dokoupil — Member of the European Nutrition Expert Panel (Merck Serono International).
Sharon Evans — a research dietitian funded by Nutricia; financial support from Nutricia and Vitafluo to attend study days and conferences.
Linn Helene Stolen — travel/accommodation/meeting expenses from Nutricia and Vitafluo.
Sharan Lowry — financial support from SHS and Vitafluo to attend study days and conferences; honoraria for speaking at sponsored meetings by SHS and Vitafluo.

Table 4
Other energy and micronutrient supplements prescribed by centres.

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Number of centres</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential fatty acids</td>
<td>4*</td>
<td>14</td>
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<tr>
<td>LCPUFA</td>
<td>6**</td>
<td>21</td>
</tr>
<tr>
<td>Low protein foods</td>
<td>27</td>
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</tr>
<tr>
<td>Low protein milks</td>
<td>24</td>
<td>83</td>
</tr>
<tr>
<td>Vitamin &amp; mineral supplement</td>
<td>22*</td>
<td>76</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>25</td>
<td>86</td>
</tr>
<tr>
<td>Folic Acid</td>
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<td>93</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>18</td>
<td>62</td>
</tr>
</tbody>
</table>

Supplements added to l-amino acid supplement in *1 of 4 centres, **6 of 6 centres, and *7 of 22 centres.

Fig. 3. Biochemical total homocysteine (tHcy) treatment aims by centres (n = 28).

Fig. 4. Median frequency of blood monitoring to estimate biochemical control.
References


