Effect of folate supplementation on folate status and health outcomes in infants, children and adolescents: A systematic review

SZIMONETTA LOHNER¹, KATALIN FEKETE², CRISTIANA BERTI³, MARIA HERMOSO⁴, IRENE CETIN³, BERTHOLD KOLETZKO⁴, & TAMÁS DECSI¹

¹Department of Pediatrics, University of Pécs, Pécs, Hungary, ²Department of Biochemistry and Medical Chemistry, University of Pécs, Pécs, Hungary, ³Unit of Obstetrics and Gynecology, Center for Fetal Research Giorgio Pardi, University of Milan, Milano, Italy, and ⁴Division of Metabolic and Nutritional Medicine, Dr von Hauner Children’s Hospital, Ludwig-Maximilians-University of Munich Medical Centre, Munich, Germany

Abstract

The aim of this systematic review was to collect all available randomized controlled trials on the effect of folate supplementation on folate status and health outcomes within the paediatric age group. The method included a structured search strategy on MEDLINE, Embase and Cochrane databases, with formal inclusion/exclusion criteria and data extraction procedure. We included 26 studies. We conclude that both serum and erythrocyte folate values reflect folate intake; however, serum folate reacts more rapidly to folate intake than erythrocyte folate. As to health outcomes, we found no evidence indicating that additional intake of folate can influence haematological parameters in non-anaemic paediatric patients. We were unable to find evidence of a favourable effect of folate supplementation on the growth of infants. However, the limited data available suggest that supplementing the diet of low-birth-weight infants with folic acid may moderate the rapid fall of serum and red cell folate in the first months of life.

Keywords: folic acid, biomarker, EURRECA

Introduction

Folate, which is the naturally occurring form of folic acid, is an essential nutrient. It is required for replication of the DNA and is involved as a substrate for a number of enzymatic reactions in amino acid synthesis and vitamin metabolism. Certain foods are very high in folate content: leafy green vegetables such as spinach, legumes such as dried or fresh beans, sunflower seeds, citrus fruits, egg yolk and animal liver. Folic acid is a synthetic dietary supplement, which is more bioavailable than natural folates (Bailey 2004). However, neither folate nor folic acid is metabolically active; they have to be reduced to L-5-methyltetrahydrofolate, or to other derivatives, to be able to participate in cellular metabolism.

The recommended daily intake defined by the US National Institute of Health (NIH) is as follows: 0–6 months: 65 µg, 7–12 months: 80 µg, 1–3 years: 150 µg, 4–8 years: 200 µg, 9–13 years: 300 µg, 14–18 years: 400 µg, 19 years and older: 400 µg of dietary folate equivalents (DFE). The DFE system was established because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food; one DFE is defined as 1 µg of dietary folate or 0.6 µg of folic acid supplement. The upper tolerable limit (UTL) for folic acid intake, which was developed in order to avoid masking vitamin B₁₂ deficiency, is set at 1 mg/day in adults. In children, UTL is extrapolated from the folate UTL for adults on the basis of body weight; according to Zlotkin (2006), the extrapolated value may be too low in such age groups, where there is no vitamin B₁₂ deficiency among the individuals.

It should also be taken into consideration that due to their relatively high energy and nutrient requirements, children and adolescents represent a vulnerable group from the nutritional point of view. Indeed,
a possible deficiency of folate was reported recently in a study on healthy European adolescents (Al-Tahan et al. 2006).

Several studies dealing with the question of the negative consequences of folate deficiency and the beneficial health effects of appropriate folate intake were published in recent years (Muskiet 2005; Malouf and Grimley Evans 2008; Olsen and Knudsen 2008; Fekete et al. 2010). However, most of these studies investigated the health effects of folate either in adults and elderly people, or in pregnant or lactating women, while there are only few data available regarding the effect of folate supplementation on folate status and health outcomes in children. The aim of this review was to assess the effect of folate on folate status and on health outcomes in infants, children and adolescents.

Methods

This systematic review is a part of the European Micronutrient Recommendations Aligned (EURRECA) network that aims to identify micronutrient requirements for optimal health in European populations (www.eurreca.org). The data reported in this review originate from the data collection process to identify studies assessing the effect of folate intake on different status markers and health outcomes.

To be included into the present review, a study is needed to be carried out in infants, children or adolescents and should investigate the effects of folate supplementation. To identify publications, the following databases were searched: Ovid MEDLINE (www.ovid.com), Embase (www.embase.com) and the Cochrane Library CENTRAL database (www.thecochranelibrary.org). The search was in the form of (randomized controlled trial terms), (folate or folic acid terms), (intake or status terms) and (human studies).

The original search was carried out by March 2009; however, it was repeated in a reduced form (restricted to publications dating after the original closure) in October 2011. The reference lists of all the included studies and review articles were also screened to identify possible studies of interest. The literature search was not limited by language.

Results

Biomarkers of folate intake

Our literature search identified 21 publications addressing the effect of folate supplementation in children on the folate status. The principal data of these studies and the main intervention outcomes are shown in Tables I and II. Seventeen studies investigated the effect on serum folate content and 11 studies the effect on erythrocyte folate content.

The effect of folate supplementation on folate status in healthy children was investigated in six studies.
Table II. Basic characteristics of included studies in non-healthy children or in children receiving drug therapy.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Subjects</th>
<th>No. of participants</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Age range (years)</th>
<th>Supplementation (daily dose, duration)</th>
<th>Effect on folate status (biomarker)</th>
<th>Health outcomes</th>
<th>Blood parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arya et al. (2011)</td>
<td>Epilepsy</td>
<td>62/58</td>
<td>6–15</td>
<td>0.5 mg FA; 6 months</td>
<td>–</td>
<td>Phenytoin-induced gingival overgrowth§</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Beca and Saieh (1975)</td>
<td>Premature</td>
<td>8/5</td>
<td>†I: 35, 2; C: 35, 2</td>
<td>0.1 mg FA; 120 days</td>
<td>–</td>
<td>Weight†</td>
<td>Vascular function (FMD§, GTN§), total antioxidant activity‡</td>
<td>Hgb§, TC§, TG§, HDL§, LDL§</td>
<td>–</td>
</tr>
<tr>
<td>Bennett-Richards et al. (2002)</td>
<td>Chronic renal failure</td>
<td>25/25</td>
<td>7–17</td>
<td>5 mg/m2 FA; 8 weeks</td>
<td>Serum, RBC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Blehaut et al. (2010)</td>
<td>Down syndrome</td>
<td>43/41</td>
<td>0.25–3</td>
<td>1 mg/kg FA; 12 months</td>
<td>–</td>
<td>Cognitive functions§</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Bowe et al. (1971)</td>
<td>Epilepsy (on phenytoin therapy)</td>
<td>20/18</td>
<td>13</td>
<td>15 mg FA, 12 months</td>
<td>Serum, whole blood</td>
<td>Number of fits§, gum hyperplasia‡</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Burland et al. (1971)</td>
<td>Premature</td>
<td>10/20</td>
<td>†I: 33 (30–36); C: 33 (26–40)</td>
<td>0.1 mg FA every second day; 4 weeks</td>
<td>Serum, RBC</td>
<td>Growth rate (weight‡, length§)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ek et al. (1984)</td>
<td>Premature infants</td>
<td>10/12</td>
<td>†I: 30.6 (29–34); C: 30.7 (28–33)</td>
<td>0.05 mg FA; 12 months</td>
<td>Serum, RBC</td>
<td>Growth rate (weight‡, length§)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premature infants</td>
<td>10/9</td>
<td>†I: 32.1 (31–33); C: 32.9 (32–35)</td>
<td>0.05 mg FA; 12 months</td>
<td>Serum, RBC</td>
<td>Growth rate (weight‡, length§)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ellis et al. (2008)</td>
<td>Down syndrome</td>
<td>36/39</td>
<td>&lt; 7 months</td>
<td>0.1 mg FA; 18 months</td>
<td>–</td>
<td>Cognitive functions§</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ek et al. (1989)</td>
<td>Small-for-gestational-age infants</td>
<td>10/11</td>
<td>†I: 37–41; C: 37–41</td>
<td>0.25 mg FA; 3 months</td>
<td>RBC</td>
<td>Growth rate (weight‡, length§)</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>Fuller (1988)</td>
<td>Healthy children receiving malaria chemotherapy</td>
<td>ND/ND</td>
<td>0.25–5</td>
<td>5 mg FA; 2 weeks</td>
<td>RBC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Gandy and Jacobson (1977)</td>
<td>Erythrosplastic infants</td>
<td>17/34</td>
<td>†I: 37; C: 38</td>
<td>2.5 or 5 mg FA; 3 months</td>
<td>Serum</td>
<td>Weight†</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>Hadler et al. (2008)</td>
<td>Anemic</td>
<td>43/43</td>
<td>0.5–2</td>
<td>0.05 mg FA; 3 months</td>
<td>Serum</td>
<td>Weight†</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>Hogeveen et al. (2010)</td>
<td>Premature newborns</td>
<td>19/18</td>
<td>†I: 29.7 (28–31); C: 29.7 (28–34)</td>
<td>0.07 mg/kg/day; 2 weeks</td>
<td>Serum</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Huemer et al. (2005)</td>
<td>Epileptic (hyperHcy)</td>
<td>10/9</td>
<td>2–18</td>
<td>1 mg FA; 3 months</td>
<td>Serum</td>
<td>–</td>
<td>–</td>
<td>Cobalamin</td>
<td></td>
</tr>
<tr>
<td>Kendall et al. (1974)†</td>
<td>Small-for-gestational-age infants</td>
<td>29/33</td>
<td>†I: 37.2, 0.33; C: 36.8, 0.34</td>
<td>0.05 mg FA; 6 months</td>
<td>Serum, RBC</td>
<td>Growth rate§</td>
<td>–</td>
<td>Hgb§, MCV§</td>
<td></td>
</tr>
<tr>
<td>MacKenzie et al. (2006)</td>
<td>Type 1 diabetes mellitus</td>
<td>31/30</td>
<td>11–17</td>
<td>5 mg folic acid; 8 weeks</td>
<td>Serum, RBC</td>
<td>Vascular function (FMD§, GTN§)</td>
<td>–</td>
<td>–</td>
<td></td>
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</tbody>
</table>
Matoth et al. (1979) observed a fourfold increase in red cell folate after supplementing healthy newborns with a fairly large dose of daily 1 mg folic acid for 4 months. Asfour et al. (1977) reported a significant increase in both serum and erythrocyte folate levels in children younger than 2 years of age by applying a folate supplementation of only 0.005 or 0.01 mg for 8 months. In the same age group, Hadler et al. (2008) observed no significant effect by applying a five times larger dose than that used in the study of Asfour et al. (1977), but for only 3 months.

Areekul et al. (1980) observed 15-fold increase in serum folate and 4-fold increase in erythrocyte folate levels in a small group of children aged 8–12 years by using a very large daily dose (15 mg) of folic acid for 5 weeks. In the same age group, 5 mg folic acid for 8 weeks increased the serum folate levels significantly also in obese, but otherwise healthy children (Pen˜a et al. 2007). Applying the 5 mg supplementation dose only twice a week for 2 months also proved to be effective in significantly increasing serum folate levels (Papandreou et al. 2010).

The effect of folate supplementation on folate status in non-healthy children was investigated in 14 studies (Table II). In premature infants, Hogeveen et al. (2010) conducted a short intervention (2 weeks) with approximately 0.1 mg folic acid per day. Plasma concentrations of folate at 2 weeks were significantly higher in the intervention group than the control group. Worthington-White et al. (1994) applied the same dose of supplementation to premature infants for 4 months and found significant increase in serum folate and a concomitant, though slower, increase in erythrocyte values compared with the values measured at birth. In another RCT, Samuel et al. (1973) supplemented premature infants with 50 µg folic acid per day, for only 2 weeks. By the 14th day of supplementation, serum folate concentrations fell significantly both in the intervention and in the control group; however, the extent of fall was more pronounced in the untreated group. By applying the same cumulative dose of supplementation in the form of 100 µg folic acid every second day for 4 weeks, Burland et al. (1971) observed significant difference in both serum and red cell folate levels at the 28th day of the study.

In small-for-gestation-age infants, Foged et al. (1989) observed significantly higher erythrocyte folate concentrations in supplemented than in non-supplemented infants after giving 250 µg folic acid per day. Kendall et al. (1974) investigated in a RCT small-for-gestation-age infants, the supplementation for 4 or 6 months with 50 µg folic acid per day resulted in significant rise of serum folate level; however, serum folate levels were within the normal range also in the untreated group.

In the investigation from Hadler et al. (2008), anaemic children younger than 2 years of age were assigned to treatment with either ferrous sulphate combined with
50 μg folic acid per day, or ferrous sulphate with placebo and showed significantly higher folic acid levels in the intervention than in the placebo group.

Gandy and Jacobson (1977) supplemented infants with erythroblastosis for 4 months. At the end of treatment, serum folate in the treated group was significantly higher than in the control group; however, after discontinuing the supplementation, serum folate showed no change by the end of the year. In children with chronic renal failure, 5 mg/m² folic acid resulted in a significant increase in both serum and erythrocyte folate (Bennett-Richards et al. 2002).

Antiepileptic treatment, especially the treatment with phenytoin may decrease serum levels of folate, and so additional folate supplementation may be given to the diet of epileptic patients. There were only two studies investigating the effect of folate on serum folate values of epileptic children. In the longer investigation lasting for 12 months, daily supplementation with 15 mg folic acid produced more than 13-fold increase in the mean concentrations of folate, both in whole blood and in serum (Bowen et al. 1971). However, also a shorter intervention lasting only for 3 months proved to be effective: the intervention with 1 mg folic acid per day resulted in significantly higher serum folate at weeks 6 and 12 than patients receiving placebo (Huemer et al. 2005).

The drug pyrimethamine, used for malaria prophylaxis, is also known to cause folate deficiency when taken in large amounts. Hence, Fuller et al. (1988) measured red cell folate levels in children receiving chemoprophylaxis and in controls, and studied the effects in both groups of fortnightly supplementation with folate. Mean levels of red cell folate in children receiving antimalarial therapy were similar to the levels of healthy children not on chemotherapy; mean erythrocyte folate levels increased in both groups after a 2-week-long supplementation with 5 mg folic acid.

**Health outcomes related to folate intake in children**

The most often investigated health outcome was growth (gain in weight and length). In term newborns, Matoth et al. (1979) found in the group of infants supplemented with 1 mg of folic acid from the age of 2 months that the weights and lengths attained by 4 and 6 months were significantly higher in the supplemented than in the unsupplemented group; however, this difference was no longer seen in the second half of the year, when supplementation was discontinued. In the study of Asfour et al. (1977), folic acid intakes of 4.3–5.0 μg/kg body weight supported the rate of growth. Peña et al. (2007) addressed the question of effects of folic acid intake on body composition by analysing body mass index (BMI) and waist-to-hip ratio in obese children supplemented with 5 mg folic acid daily for 5 weeks. BMI, weight Z-scores and waist-to-hip ratio improved significantly in both groups, but this change did not significantly differ between the intervention and placebo groups.

In premature infants, Burland et al. (1971) observed significant difference in gain neither in body weight, nor in longitudinal growth between the treated (daily supplementation dose of 0.05 mg for 4 weeks) and untreated groups. The same dose of 0.05 mg was used by Ek et al. (1984) for 12 months, but even this longer intervention did not result in significant differences in growth between the two groups. Similarly, Beca and Saieh (1975) observed no significant difference in weight gain between the two groups of premature infants receiving a daily supplement of 0.1 mg folic acid or placebo.

In small-for-gestational-age infants, 0.05 mg folic acid was given by Kendall et al. (1974) for 6 months, but failed to cause significant differences in growth between the two groups. Using a fivefold larger dose, Foged et al. (1989) did not find significant differences in weight and length between folic acid supplemented (0.25 mg/day) and non-supplemented small-for-gestational-age infants either.

There was only one study investigating the effect of folic acid supplementation on blood pressure in healthy children: Papandreou et al. (2010) found that a daily dose of 5 mg folic acid twice a week significantly decreased the systolic as well as the diastolic blood pressure in hyperhomocysteinaemic, but otherwise healthy children.

There was only one study investigating growth in each anaemic (Rosado et al. 2010), in erythroblastotic (Gandy and Jacobson 1977) or in malnourished (Ratanachu-Ek 2003) children. In anaemic and malnourished children, folic acid supplementation had no effect on weight gain. In erythroblastotic infants, folic acid supplementation proved to be effective in influencing growth: by the end of the supplementation period the average centile of weight was significantly higher in the treated group. In epileptic patients, gingival overgrowth is an important adverse effect of phenytoin therapy. Arya et al. (2011) observed that significantly fewer epileptic children developed gingival hyperplasia when they received daily 0.5 mg folic acid. However, by applying a multiple dose, Bowen et al. (1971) found no association between gingival condition and folic acid intake.

Two studies investigated the connection between increased folic acid intake and cognitive function in children with Down syndrome. In one study using 0.1 mg folic acid daily, no significant differences in Griffith developmental quotient or in the mean number of words said were observed (Ellis et al. 2008). However, another study, using the larger dose of daily 1 mg/kg folic acid, revealed significant positive effect on developmental age (Blehaut et al. 2010). One study addressed the question whether high dose (5 mg daily) folic acid can improve endothelial function in children with type 1 diabetes (MacKenzie et al. 2006). After 4 weeks supplementation, significant increase in
flow-mediated dilatation (FMD) was seen; however, glyceryl trinitrate-induced vasodilatation (GTN), which is considered as endothelium-independent vasodilatation, was not altered by folate supplementation. Vascular function in connection with folic acid supplementation was also investigated with 5 mg/m² folate, in children with chronic renal failure (Bennett-Richards et al. 2002). After an 8-week-long supplementation, there was significant improvement in FMD, but no change in GTN.

Surrogate parameters of health status

The changes in some blood parameters considered to reflect health status in paediatric subjects following folic acid supplementation are shown in Tables I and II. With the exception of one study (Worthington-White et al. 1994) reporting significantly lower haemoglobin concentrations in the supplemented than in the control group, folic acid supplementation did not result in the change of haemoglobin concentrations. Mean corpuscular volume (MCV) was investigated in three studies. Burland et al. (1971) saw no difference in MCV between treated and untreated groups after supplementing the diet of premature infants with 0.1 mg folic acid for 1 month. In the investigation of Kendall et al. (1974), the administration of 0.05 mg folic acid daily for small-for-gestational-age infants resulted in no difference in the MCV between intervention and control groups after 2 weeks or 4 months supplementation, but at 6 months the MCV value in the group receiving folic acid was significantly lower (p < 0.05). Moreover, there was significant negative correlation between MCV and red cell folate.

Discussion

In pregnancy, beneficial effects of folate supplementation are well established: additional 0.4 mg folic acid per day taken periconceptionally reduces the risk not only for neural tube defects, but also for orofacial clefts (Hartridge et al. 1999; Johnson and Little 2008) or congenital heart defects (Bailey and Berry 2005) as well. However, in paediatric populations only few RCTs addressing the question of the effect of folate supplementation on folate status and health outcomes met our inclusion criteria. There were three studies investigating low-birth-weight infants. We classified these studies either to the group of small-for-gestational-age infants or to the group of premature infants according to the mean gestational age, so it cannot be excluded that some premature infants were also between the term, small-for-gestational-age infants and conversely.

There is an active transport of folate from mother to the foetus, with increasing concentrations of folate in foetal serum, red blood cells and liver tissues with increasing gestation ages. However, stores of folate in preterm infants are limited and are sufficient for only a few weeks; after birth serum folate levels decrease and reach the lowest values at 1–2 months post-partum. Because of limited stores and rapid growth, preterm infants are especially vulnerable to folate deficiency, and may have higher folate requirements. In the studies included in this review, researchers (also observed a rapid fall of serum folate (and a concomitant slower fall of red cell folate) in the first 3 months of life. Data also indicate that the fall of folate levels can be moderated by folate supplementation. These findings support the concept of supplementing folic acid in a multiple dose to the diet of premature infants, as suggested in recommendations (Klein 2002).

In most studies, enhanced folic acid intake resulted in the increase in serum and erythrocyte folate levels. In studies investigating the effect of folate on both serum and RBC folate (Matoth et al. 1979; Areekul et al. 1980; Peña et al. 2007), RBC folate values were less influenced by additional folate than were the serum values. Overall, both plasma and erythrocyte folate levels appear to be a good biomarker of folate status in the paediatric population. Plasma folate reacts rapidly to supplementation, while erythrocyte folate only slower. A literature review of folate status biomarkers has been produced in the frame of EURRECA (34), as well as a quality-rated table of biomarkers of status (www.eurreca.org), both of which support the selection of plasma/serum folate and erythrocyte folate as folate status indicators. Red cell folate is considered to be the best index of longer term status (i.e. over the previous months), while serum folate reflects more recent dietary intake (McNulty and Scott 2008), as indicated by the studies included in our review.

In non-anaemic subjects, folic acid supplementation did not have significant haematological effects. Further studies are required to reveal whether MCV is a good biomarker of folate deficiency in healthy children.

Conclusions

1. Both serum and erythrocyte folate values are good biomarkers of folate intake; however, serum folate reacts more rapidly to folate intake than does erythrocyte folate.
2. There is no evidence that an additional intake of folate can influence haemoglobin levels in non-anaemic paediatric patients.
3. The limited data available suggest that supplementing the diet of low-birth-weight infants with folic acid may moderate the rapid fall of serum folate and red cell folate in the first months of life.
4. More research is required on the effects of an enhanced supply of folic acid in the paediatric age, especially regarding health outcomes. The effects of folic acid alone and in combination with
multivitamin or multimicronutrient supplements should be better documented.

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