Chapter 4. Nutritional Assessment and Interventions

Prepared by James Sargent, MD

Table 4.1. Summary of Recommendations for Nutritional Assessment and Interventions

Nutritional measures have not yet been proven to have a clinically important impact on elevated blood lead levels (EBLLs) in children. However, children with EBLLs are often at risk for poor nutrition, and their caregivers should receive nutritional counseling to help these children obtain a well-balanced and age-appropriate diet.

Assessment

- Test children at risk for anemia (e.g., those from low income, migrant, or recently arrived refugee families, or those qualifying for the Special Supplemental Nutrition Program for Women, Infants, and Children [WIC]).
  - Between ages 9 and 12 months
  - 6 months later
  - Annually from ages 2 to 5 years
- Evaluate the diet of children at risk for anemia, paying particular attention to dietary iron, vitamin C, and calcium.

Interventions

- Evaluate the WIC eligibility of children with EBLLs and ensure their access to this program if eligible.
- Advise caregivers to provide children with an adequate intake of iron-containing foods. Recommend that they:
  - Introduce pureed meats as soon as the child is developmentally ready.
  - Provide one serving of lean red meat per day to older children.
  - Provide supplements only under the supervision of a physician or nutritionist and only when anemia or iron deficiency is documented.
- Encourage caregivers to provide children with adequate intake of vitamin C-containing foods. Recommend that they:
  - Provide two servings of fruit juices or fruits per day.
  - Provide supplements only under the supervision of a physician or nutritionist.
- Encourage caregivers to provide children with adequate intake of calcium (500 mg/day @ 1-3 years; 800 mg/day @ 4-8 years). Recommend that they:
  - Provide two servings per day of dairy products or other calcium-rich foods.
  - Provide supplements only under the supervision of a physician or nutritionist.

Always keep recommended interventions within the ability of the caregiver to implement them.

Chapter 4. Nutritional Assessment and Interventions

Introduction

While the assessment and remediation of lead sources should be the top priority for the management of children with EBLLs, nutritional interventions may also be beneficial (*1-4*). This chapter evaluates the evidence supporting commonly used nutritional interventions, makes recommendations, and suggests an agenda for future clinical research. In evaluation studies on the effects of various nutritional interventions on EBLLs, we considered both the design of the studies and the effectiveness of the interventions. Because of a lack of randomized, controlled clinical trials of nutritional interventions among children with EBLLs, most recommendations are based on generally accepted nutritional principles, as well as on the results of adult human, animal, or cross-sectional studies, with greater weight being given to those studies with designs that are less subject to bias and inferential error.

Nutritional Interventions: Summary of the Evidence

Iron

Are children at higher risk for EBLLs also at higher risk for iron deficiency?

Despite declines in the prevalence of iron deficiency over the past 30 years with the routine supplementation of infant foods with iron, iron deficiency remains the most common nutritional deficiency in infants and young children (*5*). Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that in 1988-94, 9% of toddlers aged 1 to 2 years were iron deficient (*6*). As with EBLLs, young age, poor nutrition, and low socioeconomic status are associated with iron deficiency. In addition, some reports suggest that iron deficiency in young children is associated with pica, a risk factor for lead ingestion (*7-10*). In short, many nutritional and behavioral factors associated with iron deficiency may also be found in children with EBLLs.

Is iron deficiency associated with EBLLs?

Because animal studies and other evidence suggest that iron deficiency and EBLLs are associated, the Centers for Disease Control and Prevention (CDC) in the past has recommended providing an iron-rich diet for all children with EBLLs, evaluating children with blood lead levels (BLLs) $\geq$ 20 Fg/dL for iron deficiency, and treating iron deficiency if present (*11*). However, the association between EBLLs and iron deficiency in children is not well defined. It is unknown whether this relationship is causal and operating through a nutritional or physiological mechanism or whether it is merely the result of shared risk factors. Prospective studies of children with and without iron deficiency living in lead-contaminated environments are difficult to conduct since treatment is indicated for both iron deficiency and EBLLs. Therefore, most studies that address this question are case series, case-control studies, or cross-sectional surveys. Though the results of most early studies suggested that iron deficiency is more common among

children with EBLLs, these studies can be criticized for one or more of the following reasons: 1) they lacked an appropriate comparison group; 2) they screened for EBLLs with erythrocyte protoporphyrin, an indicator of both lead and iron status; or 3) they failed to adjust results for factors associated with both EBLLs and iron deficiency, including age and socioeconomic status.

Of the four studies we found that avoided these methodological problems, two reported a positive association between iron deficiency and BLLs in children and two suggested no association. Each study used different definitions of iron status and EBLL. Of the studies finding a positive association, one suggested iron deficiency in children was associated with a 60% increased risk for a BLL $\geq$ 10 Fg/dL after adjustments for children's age, hemoglobin level, and insurance status (*12*). The second, a study on dietary iron, found that children in the highest quartile for iron intake were at a significantly lower risk of having a BLL $\geq$ 15 Fg/dL, after adjustments for maternal education, children's lead exposure, age, and total caloric intake (odds ratio 0.4, 95% confidence interval, 0.2-0.9) (*13*). Of the studies that indicated no association, one was conducted among black children 11 to 33 months of age who resided in urban areas, and the results may not be applicable to other groups (*14*). In that study, the prevalence of iron deficiency was 7% among children with BLLs 20 to 44 Fg/dL and 5% among children with BLLs $\leq$ 10 Fg/dL. The other study, using NHANES III data and published only in abstract form, reported no association between iron deficiency (with or without anemia) and BLLs $\geq$ 10 Fg/dL after adjusting for age of housing; education of household head; and children's age, race, and poverty status, and intake of fat, calcium, and vitamin C (*15*).

During the 1980s, some prospective studies of children's BLLs and development gathered data on the children's iron status as well; most of the data from these studies are unpublished. Bornshein (personal communication, University of Cincinnati Medical Center, November 1988) found that Cincinnati children who became more iron deficient (as evidenced by increased total iron-binding capacity) had greater increases in BLLs, but McMichael et al. (*16*) and Bellinger (personal communication, Harvard Medical School, March 1989) found no association between BLLs or changes in BLLs and initially low serum ferritin levels. Neither study, however, adjusted for children's use of iron supplements or for other factors. If children with initially low serum ferritin levels received iron supplements, this could have affected the association between initial low serum ferritin levels and changes in BLLs.

Does iron deficiency increase absorption of lead?

Some animal studies suggest mechanisms by which iron levels could affect lead retention. For example, one study of rats indicates that iron and lead absorption may be mediated by common carriers and that ingested iron decreases the absorption of lead in a dose-related manner, presumably by competitive inhibition of the carrier protein (*17*). Moreover, iron-deficient animals have significantly higher rates of lead absorption than iron-replete ones (*18*). However, the effect of iron levels and iron supplementation on radiolabeled lead retention in humans is controversial, with at least one study finding an effect (*19*) and at least one not (*20*). In their latest

study, Watson and colleagues (*19*) found a correlation between lead and iron absorption; however, the mean lead-absorption value for iron-deficient subjects was not significantly different from the value for those who were not iron deficient. No data are available for children.

Does iron deficiency enhance the adverse effect of lead on development?

Although iron deficiency may not modify children's risk for lead exposure or retention, iron deficiency and EBLLs have similar toxicity profiles. Both result in a lower production in heme; this is manifested clinically by higher erythrocyte protoporphyrin levels in children with EBLLs and iron deficiency than in those children with either condition alone (*21*). More importantly, both iron deficiency and EBLLs have a deleterious effect on cognitive development. This raises the possibility that the neurodevelopmental effects of lead may be more severe when iron deficiency is also present. However, there is no evidence to suggest that iron deficiency modifies the neurodevelopmental effect of EBLLs. Instead, in one study comparing the cognitive development of children living near a lead smelter with that of those in a nearby town in Yugoslavia, researchers found the neurodevelopmental effects of iron deficiency and EBLLs to be independent of one another (*22*).

Does iron supplementation have an effect on BLLs?

There is evidence to suggest that iron-sufficient children excrete more urinary lead when chelated with EDTA, although the increase is small and probably not clinically significant. In addition, after iron administration, chelation-induced lead excretion increased among patients with iron deficiency. The study in which this occurred, however, did not address the effect of iron deficiency on BLLs and lead excretion in the absence of chelation (*23*). In a study conducted by Ruff and colleagues (*24*), children with EBLLs and iron deficiency were given iron supplements, whereas children with EBLLs but no iron deficiency were not. The children who were iron deficient and received supplements had only half the reduction in BLLs of the children who were iron sufficient and did not. However, it is not clear whether this was due to the effect of iron supplementation on hemoglobin concentration or to another factor affecting lead biokinetics. The problem with using BLL as an indicator of body burden of lead in iron studies is that, because 99% of lead in blood is intraerythrocytic, any intervention that causes a significant increase in the hemoglobin concentration will similarly affect the BLL.

Summary

Although iron may help prevent lead absorption in animals, studies of the association between iron deficiency and BLLs in children have produced inconsistent results. There is little evidence that iron promotes a clinically important increase in lead excretion. However, the use of iron supplements among children with EBLLs and iron deficiency has been shown to improve their developmental scores, suggesting that the effects of iron deficiency on cognition can be partially reversed among children with EBLLs (*24*). This finding is consistent with a wealth of

data indicating that neurodevelopmental impairment among children with iron-deficiency anemia can be partially resolved by treatment with iron supplements (*25-28*). However, treatment with succimer (dimercaptosuccinic acid) to lower EBLLs (20 to 44 Fg/dL) in toddlers has not been shown to improve their cognition (*29*). Since the effects of iron deficiency on children's development appear to be independent of the effects of lead, there is no compelling reason to screen and treat children with lead exposure differently from children of similar age on the basis of their risk for iron deficiency, assessed independently of their lead exposure. Detailed recommendations for the prevention of iron deficiency can be found in a recent CDC report (*30*). Several of these recommendations are summarized later in this chapter.

Vitamin C

Could increasing children's vitamin C intake decrease their BLLs?

Decreased lead retention has been shown in rats fed vitamin C and exposed to lead (*31-33*). Clinical studies in humans actually predate these and other animal studies, as case reports of lead-poisoned workers' response to ascorbate began to appear in the literature as early as 1939 (*34*). Later, clinical trials were conducted among workers and other adults. An uncontrolled experiment involving 39 workers showed that their BLLs had declined 24 weeks after they began treatment with vitamin C (*35*). Results of a single-blind clinical trial of vitamin C (1 g daily) among lead smelter workers with BLLs of 28 to 76 Fg/dL did not show vitamin C to affect their urinary excretion of lead (*36*). In a double-blind randomized clinical trial, however, adult male smokers given a daily dose of vitamin C (1 g) experienced a statistically significant 80% decline in BLLs (from 36 to 20 Fg/dL) after 1 week of treatment that persisted through the 4-week period of the study (*37*).

Much less is known about the effect of vitamin C on BLLs in children. One correlative cross-sectional study using NHANES III data showed high levels of serum vitamin C to be associated with a low prevalence of EBLLs for both children and adults. Results of this study also showed an association between serum vitamin C levels and log BLLs among adults but not among children (*38*).This study, however, did not control for environmental lead risk or include children below the age of 4 years who are the usual subjects for case management (*39*). In summary, although there is fairly strong evidence to support giving vitamin C to adults with EBLLs, there is insufficient evidence to recommend for or against vitamin C supplementation for children with EBLLs. It is important to note that CDC recommends giving all children 6 months and older at least two servings of foods rich in vitamin C per day for the prevention of iron deficiency (*30*).

Calcium

Are children at higher risk for EBLLs also at higher risk for inadequate calcium intake?

Recommended daily allowance values for calcium intake have been replaced by "adequate intake"(AI) levels (*40*). AIs for young children are age-specific: 0-6 months, 210 mg/day; 7-12 months, 270 mg/day; 1-3 years, 500 mg/day; and 4-8 years, 800 mg/day. Actual mean calcium intake levels may be estimated from NHANES III data. Figure 4.1 depicts the median, 75th percentile, and 25th percentile levels for daily calcium intake among children aged 1 to 4 years by race. Calcium intake is below the AI level for more than 25% of Mexican American and non-Hispanic black 1- to 3-year-olds, and approaches 25% for non-Hispanic white 1- to 3-year-olds. Similarly, there is little variation in calcium intake across income groups (results not shown). Although these data do not specifically reflect the calcium intake of children with EBLLs, groups that typically have higher risk for EBLLs in this nationally representative sample of children have only a slightly higher risk for calcium intake below AI levels. One research group assessed the calcium intake of 314 mostly African-American children using a food frequency questionnaire (*41*). The results for children aged 1 to 3 years were similar to those of NHANES III, with about 30% of children having calcium intakes below the AI level of 500 mg per day. Because calcium intakes were not much higher for 4- to 8- year-old children in this sample, a substantially higher proportion of them (almost 60%) had calcium intakes below the AI level of 800 mg for their age group.

Does inadequate calcium intake confer a higher risk for EBLLs?

Animal studies have shown higher lead retention in animals fed low-calcium diets, raising the possibility that low-calcium diets could affect the BLLs of humans (*42-45*). Furthermore, studies of radiolabeled lead absorption in human adults show lower absorption of lead when lead is co-administered with calcium (*46, 47*). In 89 metabolic balance studies of 12 infants, dietary calcium intake was found to be inversely associated with lead retention (*48*). As the authors noted, however, dietary calcium intake closely paralleled the intake of phosphorus and other unmeasured components of milk and formula, so it is difficult to attribute this effect solely to calcium.

In NHANES II (1976 - 1980), calcium intake was inversely associated with BLLs in a nationally representative sample of children aged 3 to 11 years (*49*). The analysis included good controls for children's socioeconomic status, region of the country, and urban vs. rural residence. Results of this analysis showed that children's calcium intake had a small, inverse correlation with their BLL, with children's BLLs declining by only about 0.2% for each 100 mg increase in dietary calcium. The study was subject to the following limitations. First, it included no direct controls for environmental lead exposure. Second, because the backward selection procedure used for the regression analysis removed confounding nutritional variables from the final model, and the p-value for the calcium effect was close to 0.05, statistical significance would probably

be lost with the inclusion of only one nutritional confounder. Results of other smaller published cross-sectional studies generally support an inverse association between children's calcium intake and BLLs, but these studies also did not control for confounding (*50, 51*).

Calcium supplementation above the AI level

Meredith et al. showed that increases in dietary calcium of up to 5 mmol decreased lead retention in rats with no pre-existing calcium deficiency; however, they found no further decrease with oral doses of calcium above 5 mmol (100-fold molar excess of calcium) (*52*). This finding is consistent with those from the studies of radiolabeled lead absorption in human adults mentioned above (*46, 47*). In an unpublished balance study of the effect of calcium glubionate syrup supplementation (50 mg calcium/kg/day) on lead retention in six children, neither lead absorption nor lead retention was found to be affected by calcium supplementation (personal communication, Ekhard E. Ziegler, University of Iowa College of Medicine, May 14, 1990). Similarly, no effect of calcium supplementation was found in a randomized clinical trial of calcium glycerophosphate supplementation of infant formula involving 105 infants (*53*). In this study, infants in the treatment group received, on average, 1600 mg of calcium per day. Change in BLL over time was small for all of the infants in the prevention trial (only 1 Fg/dL), limiting the power of the study to examine a treatment effect.

Summary

There is little evidence that a child typically considered at high risk for lead exposure is at greater risk for low calcium intake than children without EBLLs. However, because of the frequency of inadequate calcium intake among all children, it is important to verify that a child with an EBLL is receiving enough calcium. The results of both animal studies and human laboratory studies provide good evidence that dietary calcium competitively inhibits lead absorption. The results of one cross-sectional study of older children with controls for socioeconomic status show an inverse association between dietary calcium intake and BLLs. There are few data on young children in the high-risk age range, and no clinical trials have evaluated the efficacy of supplementation among children with low calcium intakes who are at risk for lead exposure. The results of studies among older children and adults, animal studies, and cross-sectional studies all reinforce the importance of adequate calcium intake (i.e., two servings per day of dairy products or other calcium-rich foods). However, there is no clinical evidence that supplementation of calcium beyond the recommended AI level in children with EBLLs has a clinical effect on the BLLs; therefore, we do not recommend giving calcium supplements to children with EBLLs.

Total fat intake

The link between fat intake and BLLs comes primarily from animal experiments (*54*). In one cross-sectional experimental study, researchers found a direct association between dietary fat and BLLs (*55*); however, no such relationship between dietary fat and BLL was found in NHANES II (*47*). Thus, no strong case can be made for decreasing children's total fat intake. In addition, dietary fat is an important constituent in the diets of children under 2 years of age because calories from fat support high calorie requirements for growth during this period. Thus, we do not recommend low-fat diets for the treatment of younger children with EBLLs.

Zinc supplementation

Some evidence from animal studies suggests that high levels of dietary zinc inhibit the absorption and retention of lead in animals (*56*). However, in one small clinical study in which zinc was given with and without vitamin C to lead-exposed workers, the zinc had no demonstrable effect on their BLLs (*36*). As with calcium, we do not recommend adding zinc supplements to the diet of children with EBLLs.

Other factors

Many other factors have been evaluated as mediators of lead absorption and excretion in adults or animals. These factors include vitamins (thiamin, pyridoxine, vitamin D), minerals (phosphorus), dietary chelators (phytatic acid, alginates, oral EDTA), and frequency of meals. These were not included in this review because of a lack of evidence to determine their efficacy in children.

General Recommendations

WIC referral

- Because children with EBLLs are at risk for poor diet, refer children with EBLLs to supplemental food programs that provide nutritional counseling and access to healthy foods.
- Determine whether children with EBLLs are eligible for WIC and ensure their access to this program if they are eligible. An EBLL is a condition that should qualify age-eligible older children who might otherwise not be candidates for participation in the program.

Iron deficiency

- Low-income or minority children with EBLLs are usually at high risk for iron-deficiency anemia. Detailed recommendations for the prevention of iron deficiency can be found in a recent CDC report (*30*). Several of these recommendations are included below.

- Test those at risk for anemia (e.g., those from low-income, migrant, or recently arrived refugee families or those qualifying for WIC). These children should be tested at the following ages:
  - Initially between ages 9 and 12 months
  - Six months later
  - Annually from ages 2 to 5 years

Vitamin C intake

- Advise caregivers to provide children with an adequate intake of vitamin C. For children approximately age 6 months and older, encourage caregivers to provide two feedings per day of foods rich in vitamin C (e.g., fruits, vegetables, or juice), preferably with meals, as a way of improving their iron absorption.
- Do not recommend supplementation in children with EBLLs.

Iron intake

- Encourage caregivers to provide children with an adequate intake of iron by:
  - Introducing them to iron-fortified cereals and pureed meats at their appropriate developmental stages.
  - Providing one serving of lean red meat per day to older children.
- Do not recommend giving children iron supplements except under the supervision of a physician or nutritionist and only when iron deficiency or anemia is documented.

Calcium intake

- Encourage caregivers to see that children with EBLLs receive an adequate amount of calcium (500 mg/day @ 1 to 3 years; 800 mg/day @ 4 to 8 years), by:
  - Providing them with two servings of dairy products per day, unless they are lactase-deficient.
  - Providing lactase-deficient children with sufficient dietary calcium from other sources (e.g., broccoli, greens, kidney beans, and calcium-fortified juices).
  - Do not recommend giving children calcium supplements except under the supervision of a physician or nutritionist.
- Do not recommend supplementation in children with EBLLs beyond the recommended AI levels.

Fat intake

- Do not encourage a low-fat diet as a means of lowering children's EBLLs. Not only is there no clinical evidence to support the implementation of such a diet, but dietary fat is an important constituent in the diets of children, especially those under 2 years of age.

Zinc supplementation

- Do not recommend zinc supplementation.

Recommendations for Future Research

Evidence suggests that some population-based nutritional measures may reduce lead absorption in children. However, we do not yet know enough about the relationship between children's EBLLs and many specific nutrients to make recommendations. The literature is replete with animal studies that have not been adequately followed up in the human population. When they are, the epidemiologic work consists mostly of correlative cross-sectional studies without adequate controls for environmental lead exposure. Because of the sparse evidence for the efficacy of various nutritional interventions for children with EBLLs, it is premature to call for the implementation of population-based nutritional interventions. Instead, promising interventions should be evaluated in randomized clinical trials.

Such clinical trials are especially important for several reasons. First, correlative nutrition studies are hampered by our limited ability to measure dietary intake. In addition, many nutrient intakes correlate with each other, so only large observational studies can separate the effects of, for example, dietary fat from iron. An association between a nutritional factor and BLL, however, does not mean that manipulating the nutritional factor will have a clinically meaningful effect on an EBLL. Some of the randomized trials of dust control among children illustrate this (*57, 58*). Only clinical trials employing randomized designs can determine whether modifying children's intake of specific nutrients will actually influence their BLLs.

Furthermore, many patient-compliance and side-effects issues need to be resolved before nutritional interventions can be studied clinically. For example: Which vitamin C supplements will children reliably take? Which ones will caregivers reliably give? Does it matter when the dose is given? Should the supplement be given as a medication or through a frequently eaten food item? What is the level of supplementation that could result in side effects?

Finally, many nutritional interventions will involve behavioral change for families. Results of clinical studies of behavioral change (e.g., parental smoking cessation [*59, 60*] and environmental tobacco exposure reduction [*61*]), suggest that only modest behavioral changes can be expected from limited-contact counseling interventions. In addition, injury research shows that passive interventions (e.g., using childproof medicine caps) are much more effective in preventing injuries than are active interventions (e.g., asking parents to keep medicines out of reach). Therefore, controlled randomized studies should identify and evaluate actions and interventions that may result in improved compliance with recommendations.

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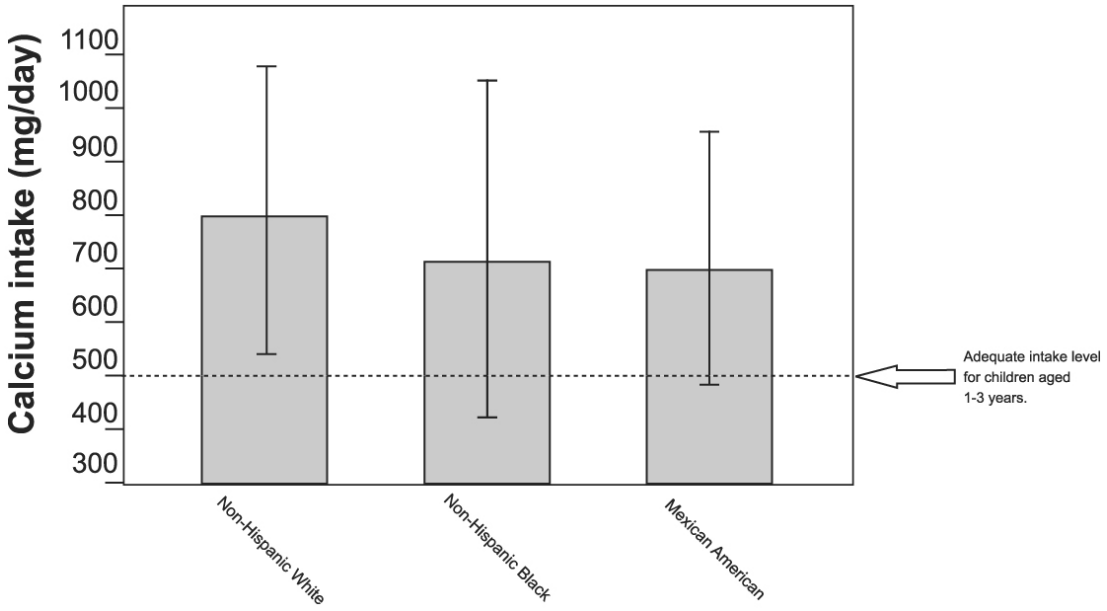

Figure 4.1. Median Calcium Intake by Race from NHANES III
Error bars represent the interquartiles range.