The "Lead Diet": Can Dietary Approaches Prevent or Treat Lead Exposure?

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Although blood lead levels (BLLs) have been declining in the US for decades, pediatric lead exposure is an ongoing public health issue.[1] Given the well-documented cognitive deficits at BLLs <10 μg/dL, in 2012 the Centers for Disease Control and Prevention (CDC) called for renewed efforts for the primary prevention of any lead exposure in children.[2] Recent events in Flint, Michigan, also have served to refocus the public and health professionals on the seriousness of lead exposure. According to CDC statistics for years 2010-2014, 0.5%-0.6% of children (13 000-26 000) had confirmed BLLs ≥10 μg/dL and 4%-6% (106 000-282 000) ≥5 μg/dL.[3] Only 10%-18% of all children in the US aged <6 years, however, had a BLL test during that period. A recent study based on a national clinical laboratory database reported an overall prevalence of BLLs ≥10 μg/dL at 0.58% and ≥5 μg/dL at 2.95% for the years 2009-2015, with certain US states and cities particularly affected.[4]

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Whether through contaminated water, lead-based paint, or a combination of sources, the problem of lead exposure resurfaces periodically in US municipalities like Flint, Michigan, Washington, DC, or Buffalo, New York,[5-7] highlighting issues of aging infrastructures, under-resourced communities, poor decision making, and environmental injustice. Overlaid on these systemic causes are personal poverty and complex family situations, potentially creating multiple threats to optimal child health and development, including factors such as poor diet or low developmental stimulation.

Parents and frontline health workers often are left to figure out how to help affected children, posing questions regarding effective interventions. Because dietary approaches seem relatively easy to implement compared with, for example, lead abatement or replacing old plumbing infrastructure, the conversation often turns to dietary recommendations. The 2012 CDC report highlights the role of pediatricians in educating families on nutrition as one primary prevention approach.[2] It should be emphasized that the prevention of lead exposure among vulnerable populations is the best solution to this problem and that intervening in exposure via dietary approaches does not address the root cause. Furthermore, careful examination of the links between nutrition (nutritional status, nutrients, diet) and lead exposure reveals limited and tenuous evidence.

BLL	Blood lead level
CaT1	Calcium transport protein 1
CDC	Centers for Disease Control and Prevention
DMT1	Divalent metal transporter 1
RCT	Randomized controlled trials

It is important for pediatricians, public health workers, and researchers to understand the state of the evidence so that recommendations to affected communities can be formulated appropriately. This is particularly important in the face of crises such as Flint, Michigan, which lend understandable urgency to the needs of frontline health workers to offer concrete guidance to anxious families.

This commentary will briefly review the state of the science, critically appraise the quality of the evidence, and highlight research gaps. A systematic and exhaustive review of the literature is beyond the scope of this commentary. Publications included in the review were identified through searches in PubMed via use of key words such as "diet," "nutrition," and "nutrient" in combination with "lead" and "blood lead." Reference sections of publications were scanned for further sources of information.

My objective is to create a deeper awareness of the existing evidence and, based on this body of work, a reasonable expectation with regard to the effectiveness of dietary approaches for children exposed to lead. The evidence is first organized by type of dietary component (for example, specific nutrients), followed by a discussion of the potential for prevention of exposure vs lowering of already-elevated BLLs. Because each nutrient-based study may include findings with respect to nutritional status or intake (and therefore different aspects of nutriture and metabolism), it is important to caution that studies of underlying nutritional deficiencies may produce different findings from evaluating intake. I will focus on the literature related to children to provide an accurate reflection of the state of evidence in the population group to which current recommendations apply. When data from studies with human children or adults are scarce, animal-based studies are included. It is also important to acknowledge that exposure in utero may be a common scenario and that separate literature exists on potential links between diet, nutrition, metabolism, and lead exposure during pregnancy.

Current Recommendations

In 2002, the CDC published guidelines on the medical and nutritional management of children with elevated BLLs.[8] The

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nutrient/food-specific interventions contained in that document are to advise and encourage caregivers to provide children with an adequate intake of iron-containing foods, vitamin C-containing foods, and calcium. Specifically, to address the recommendation on iron-rich foods, the CDC promotes introducing pureed meats as soon as the child is developmentally ready and providing 1 serving of lean red meat per day to older children. For vitamin C-rich foods, the recommendation is to give 2 servings of fruit juices or fruits daily. To ensure adequate intake of calcium, 2 servings daily of dairy products or other calcium-rich foods are recommended. Supplements should only be given under supervision of a physician or a nutritionist, and in the case of iron, only when anemia or iron deficiency has been diagnosed.

The CDC document is careful to point out that "nutritional measures have not yet been proven to have a clinically important impact on elevated blood lead levels in children" (p. 61), and that the aforementioned recommendations are based on "generally accepted nutritional principles, as well as on the results of adult human, animal, or cross-sectional studies" (pg. 62).[8] As stated previously, evidence on the links between diet and lead exposure is limited—very few well-designed and conclusive studies on this subject have been published. Yet, given that dietary recommendations are made routinely to parents, it appears that the tenuous nature of the evidence has been lost. Therefore, it is important to emphasize that, based on currently available evidence, there is little to suggest that making dietary changes or adopting dietary measures would lower children's BLLs substantially.

Iron Status, Intake, and Supplementation

There is strong epidemiologic evidence that children's underlying nutritional deficiencies, particularly iron deficiency, are associated with elevated BLLs.[9] There is also good biological plausibility, because lead competes for absorption in the gut with several divalent metals. The divalent metal transporter 1 (DMT1) has been shown to shuttle both iron and lead across cell membranes.[10] Furthermore, when yeast cells are incubated in buffer containing lead but also low iron concentrations, lead absorption increases; conversely, lead absorption is reduced when greater iron concentrations are present, indicating that iron blocks the uptake of lead by the DMT1.[10]

Consistent with this finding, a longitudinal study of iron status at 2 clinic visits separated by approximately 1 year suggests that iron deficiency increases lead absorption in children,[11] but most of the evidence is cross-sectional. Work on polymorphisms in genes regulating the expression of proteins related to iron metabolism also suggests a modest but potentially causal association.[12,13] The DMT1, however, is not the only intestinal transporter used by lead to access the body. A DMT1-knockout study demonstrated that elimination of this transporter resulted in lower, but not completely reduced, absorption of lead.[14] It is also possible that instead of being causally related, iron deficiency and elevated BLLs share common behavioral or environmental risk factors, including the larger systemic issues referred to previously.[8] The recommendations issued by the CDC on the nutritional management of children exposed to lead are based on the premise that iron deficiency co-occurs with elevated BLLs in many population groups, with insufficient evidence to establish causal links.[8]

In a longitudinal, observational study, Schell et al[15] reported an inverse association between dietary iron intake at 3-6 months of age and 6-month BLLs, and between dietary iron intake at 9-12 months of age and 12-month BLLs, as well as rate of change in BLL from 6 to 12 months. In another study (cross-sectional), greater iron intake was associated modestly with lower BLL in preschool children.[16] Costa Rican children (13-24 months of age) with BLLs < 25 μg/dL and varying severity of iron deficiency and anemia were assigned nonrandomly to receive oral iron supplements for 12 weeks. Only children without anemia who had depleted iron stores (low serum ferritin) experienced a decrease in BLLs following iron supplementation, with no other groups benefitting.[17] In the same study, children with sufficient iron status received placebo drops. They had greater BLLs after 12 weeks compared with pretreatment, but this difference disappeared when initial BLLs were taken into account.[17]

Three randomized controlled trials (RCTs) of iron supplementation or fortification were conducted among pre- and school-aged children. One trial tested the efficacy of iron supplements (30 mg of ferrous fumarate for 6 months) in lowering BLLs in Mexican children with moderately high levels of exposure, but fairly low prevalence of iron deficiency, and showed little benefit.[18] Another evaluated the efficacy of iron-fortified rice (~15 mg iron as ferric pyrophosphate for ~4 months) against a control meal among Indian children with iron deficiency and found a reduction in the prevalence of BLLs ≥10 μg/dL in the group consuming iron-fortified meals.[19] Moroccan children (3-14 years old) received biscuits fortified with ~8 mg of iron ($FeSO_4$), ~ 41 mg of sodium EDTA (Na_2EDTA), both together, or placebo for ~7 months. Iron and Na_2EDTA each independently resulted in modest but statistically significant reductions in children's BLLs.[20]

The trials in Mexico and India enrolled children with similar BLLs (mean of 11.4 and 12.0 μg/dL, respectively), and Moroccan children had lower BLLs (adjusted geometric mean of 4.3 μg/dL). In contrast, 12% of the Mexican children, ~70% of the Indian children, and 32% of Moroccan children had iron deficiency. These trials represent mixed findings, and design differences among them prevent direct comparisons; however, they suggest the possibility that iron fortification may benefit children exposed to lead by effecting reductions in BLLs. These findings are fairly consistent with the observational literature but need to be confirmed in future studies along with other details, such as formulation, dosage, and timing (fasting or with food) of iron delivery. Furthermore, the additional iron may be most beneficial to children with moderate-to-high iron deficiency. This is an important consideration in the US context, where the prevalence of iron deficiency is likely to be similar or even lower than in the Mexican study. Finally, based on the totality of iron-related evidence, it is still difficult to recommend any changes to typical dietary intakes as the basis for treating or reducing lead exposure in children.