Relationship of Ascorbic Acid to Blood Lead Levels

Joel A. Simon, MD, MPH
Esther S. Hudes, PhD, MPH

Lead exposure is an important public health problem. Because millions of American children are believed to have elevated blood lead levels, screening programs for childhood lead exposure have been established by the Centers for Disease Control and Prevention (CDC). In 1984, as many as 3 to 4 million children were estimated to have blood lead levels greater than 0.72 µmol/L (15 µg/dL), and even lower levels of lead exposure have been associated with adverse neuropsychological development. Among adults, work-related lead exposure has been targeted as an area of concern by the Occupational Safety and Health Administration. Calcium EDTA and other chelators are standard treatments for lead poisoning. One animal study that compared the effectiveness of EDTA with ascorbic acid in treating the toxic effects of lead reported that orally administered ascorbic acid had chelating properties similar to those of parenterally administered EDTA. Anecdotal reports from 1939 and 1940 suggested that ascorbic acid may be beneficial in treating occupational lead exposure. However, subsequent small trials among humans have yielded inconclusive results. To our knowledge, there have been no population-based studies examining the relationship of ascorbic acid to lead toxicity.

To ascertain whether ascorbic acid levels are associated with prevalence of elevated blood lead levels, we analyzed data collected from the Third National Health and Nutrition Examination Survey (NHANES III) that included data about serum ascorbic acid levels and blood lead levels in more than 19,000 Americans.

METHODS

Subjects

NHANES III was a national probability survey of Americans conducted between 1988 and 1994 that used a stratified, cluster sampling design to oversample populations of special interest. Participants aged 2 months or older were enrolled, interviewed, and examined by study personnel. Participants older than 90 years were recorded as being 90 years old. For these analyses, participants were excluded if there were missing data on variables judged to be potential predictors of blood lead levels. We

CONTEXT

Some animal studies suggest that orally administered ascorbic acid may chelate lead and decrease the risk of the toxic effects of lead. However, results from several small studies in humans have yielded inconclusive evidence of a beneficial effect of ascorbic acid on lead toxicity.

OBJECTIVE

To examine the relationship between serum ascorbic acid levels and prevalence of elevated blood lead levels.

DESIGN, SETTING, AND PARTICIPANTS


MAIN OUTCOME MEASURES

Elevated and log blood lead levels by serum ascorbic acid level.

RESULTS

A total of 22 youths (0.5%) and 57 adults (0.4%) had elevated blood lead levels (defined as ≥0.72 µmol/L [15 µg/dL] and ≥0.97 µmol/L [20 µg/dL], respectively). After controlling for the effects of age, race, sex, income level, and dietary energy, fat, calcium, iron, and zinc intake, youths in the highest serum ascorbic acid tertile had an 89% decreased prevalence of elevated blood lead levels compared with youths in the lowest serum ascorbic acid tertile (odds ratio, 0.11; 95% confidence interval, 0.04-0.35; P for trend = .002). Adults in the highest 2 serum ascorbic acid tertiles had a 65% to 68% decreased prevalence of elevated blood lead levels compared with adults in the lowest serum ascorbic acid tertile (P for trend = .03). As a continuous predictor, serum ascorbic acid level was independently associated with decreased log blood lead levels among adults (P < .001), but not among youths (P = .14).

CONCLUSIONS

Our data suggest that high serum levels of ascorbic acid are independently associated with a decreased prevalence of elevated blood lead levels. If these associations are related causally, ascorbic acid intake may have public health implications for control of lead toxicity.
did not analyze data from children aged 1 to 5 years because serum ascorbic acid levels were not measured in these participants. We excluded 28 youths (defined as participants between the ages of 6 and 16 years) who reported a history of lead poisoning and hence were likely to have received treatment to lower their blood lead levels; we excluded an additional 36 adult and youth participants with serum ascorbic acid concentrations of questionable validity (ie, >170 µmol/L). After these exclusions, complete data were available from 19,578 participants between the ages of 6 and 90 years for our analyses.

**Measurements**

NHANES III questionnaire data included self-reported age, race, sex, household income, history of smoking, and intake of dietary energy, fat, calcium, iron, zinc, and ascorbic acid. Quantitative nutrition data were collected using a 24-hour dietary recall. The questionnaires, dietary methods, and examination procedures used in NHANES III have been described elsewhere. Questions addressing history of cigarette smoking were not available for the youths.

Blood lead levels were measured at the CDC by atomic absorption spectrometry. Blood lead levels of 0.72 µmol/L (15 µg/dL) or higher in youths and 0.97 µmol/L (20 µg/dL) or higher in adults were considered to be elevated based on the NHANES III cut points for the reporting of abnormal laboratory values. Serum ascorbic acid levels were measured at the CDC by high-performance liquid chromatography and ranged from 0 to 170 µmol/L.

**Statistical Methods**

We examined the distribution of ascorbic acid levels and other variables of interest using sample weights. Because study participants did not have an equal probability of selection, sample weights were required to incorporate these differential probabilities, thereby permitting the results to be generalizable to the US population. We used logistic regression to examine the relationship of serum ascorbic acid, categorized into tertiles, to elevated blood lead levels. Multivariate models controlled for the effects of age, race (white vs other), sex, annual household income (<<$20,000 vs ≥$20,000 per year), cigarette smoking (never, past, current), and dietary intake of energy, fat, calcium, iron, and zinc. We used the dichotomous income variable in NHANES III to maximize the number of participants available for analysis. A logarithmic transformation was performed to improve the symmetry of the distribution of blood lead levels. We then performed linear regression analyses, examining the relationship of serum ascorbic acid level to log blood lead level.

Analyses were performed using Stata software that included commands for the analysis of complex survey data. We calculated odds ratios and 95% confidence intervals to estimate the relative prevalence of elevated blood lead levels. We considered 2-tailed P<.05 to be statistically significant.

**Figure 1** illustrates the independent association between serum ascorbic acid level and elevated blood lead level, plotting the prevalence of elevated blood lead level as a function of serum ascorbic acid. The probability of each individual having an elevated blood lead level was predicted using the multivariate logistic model. We then determined the predicted proportion of participants with an elevated blood lead level within each 0.6-µmol/L (0.01-mg/dL) increment of serum ascorbic acid. Therefore, each point represents the estimated proportion of participants within a given increment of serum ascorbic acid with an elevated blood lead level. **Figure 2** shows the continuous variable, log blood lead level, as a function of serum ascorbic acid. Each participant’s log blood lead

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**Figure 1. Elevated Blood Lead Levels in Relation to Serum Ascorbic Acid**

The relationship between serum ascorbic acid concentration and prevalence of elevated blood lead levels among 4213 youths aged 6 to 16 years (left) and 15,365 adults aged 17 years or older (right) enrolled in the Third National Health and Nutrition Examination Survey, 1988-1994, based on the multivariate model in Table 2. Results are based on 22 youths and 57 adults with elevated blood lead levels, and 4191 youths and 15,308 adults with normal blood lead levels. Each of the points represents the proportion of study participants with an elevated blood lead level within each 0.6-µmol/L (0.01-mg/dL) increment in serum ascorbic acid.
level was predicted using the multivariate linear regression model. We then determined the estimated mean log blood lead level within each 0.6-µmol/L (0.01-mg/dL) increment of serum ascorbic acid. Therefore, each point represents the estimated mean log blood lead level within a given increment of serum ascorbic acid. The curves were smoothed using a procedure that allows for the use of sample weights.17-20

**RESULTS**

The baseline characteristics of 15 365 adults and 4213 youths, aged 6 to 16 years, enrolled in NHANES III, with complete data available for these analyses, are listed in **Table 1**. A total of 57 adults (0.4%) and 22 youths (0.5%) had elevated blood lead levels ($\geq 0.97$ µmol/L [20 µg/dL] for adults and $\geq 0.72$ µmol/L [15 µg/dL] for youths). Blood lead levels ranged from 0.02 µmol/L (0.5 µg/dL) to 2.70 µmol/L (56 µg/dL) among adults and from 0.02 µmol/L (0.5 µg/dL) to 2.36 µmol/L (48.9 µg/dL) among youths. Demographic characteristics, such as race, sex, and level of household income and dietary data, were similar for adults and youths. On average, serum ascorbic acid levels were consistent with normal levels of this micronutrient.13

Among youths, unadjusted, age-adjusted, and multivariate models revealed that serum ascorbic acid levels were inversely associated with prevalence of elevated blood lead levels (**Table 2**). Youths in the highest serum ascorbic acid tertile were 89% less likely (95% confidence interval, 65%-96%) to have elevated blood lead levels compared with youths in the lowest serum ascorbic acid tertile (multivariate P for trend = .002). Among adults, serum ascorbic acid level was also associated with prevalence of elevated blood lead levels; all models revealed that serum ascorbic acid levels were inversely associated with prevalence of elevated blood lead levels.

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**Table 1.** Characteristics of 19 578 Participants Aged 6 Years or Older Enrolled in the Third National Health and Nutrition Examination Survey, 1988-1994

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Youths (n = 4213)</th>
<th>Adults (n = 15 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11 (0.1)</td>
<td>43 (0.5)</td>
</tr>
<tr>
<td>Range</td>
<td>6-16</td>
<td>17-90</td>
</tr>
<tr>
<td>White, %</td>
<td>79 (1.3)</td>
<td>85 (0.8)</td>
</tr>
<tr>
<td>Female, %</td>
<td>49 (1.6)</td>
<td>52 (0.5)</td>
</tr>
<tr>
<td>Cigarette smoker, % Current</td>
<td>32 (1.7)</td>
<td>33 (1.2)</td>
</tr>
<tr>
<td>Cigarette smoker, % Past</td>
<td>28 (0.9)</td>
<td>25 (0.7)</td>
</tr>
<tr>
<td>Cigarette smoker, % Never</td>
<td>47 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Low household income (&lt; $20 000), %</td>
<td>32 (1.7)</td>
<td>33 (1.2)</td>
</tr>
<tr>
<td>Energy intake, kJ/d</td>
<td>9111 (139)</td>
<td>9324 (67)</td>
</tr>
<tr>
<td>Fat intake, g/d</td>
<td>83 (1.4)</td>
<td>85 (1.2)</td>
</tr>
<tr>
<td>Calcium intake, mg/d</td>
<td>975 (21)</td>
<td>854 (12)</td>
</tr>
<tr>
<td>Iron intake, mg/d</td>
<td>15 (0.3)</td>
<td>16 (0.2)</td>
</tr>
<tr>
<td>Zinc intake, mg/d</td>
<td>11 (0.3)</td>
<td>12 (0.1)</td>
</tr>
<tr>
<td>Ascorbic acid intake, mg/d</td>
<td>105 (3.1)</td>
<td>107 (1.9)</td>
</tr>
<tr>
<td>Serum ascorbic acid level, µmol/L</td>
<td>55 (1.1)</td>
<td>43 (0.9)</td>
</tr>
<tr>
<td>Blood lead level µmol/L</td>
<td>0.12 (0.01)</td>
<td>0.17 (0.01)</td>
</tr>
<tr>
<td>µg/dL</td>
<td>2.5 (0.1)</td>
<td>3.5 (0.1)</td>
</tr>
<tr>
<td>Prevalence of elevated blood lead level, % †</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.1)</td>
</tr>
</tbody>
</table>

*All data are presented as mean (SE) unless noted otherwise. Ellipses indicate data were not collected.
†Defined as at least 0.72 µmol/L (15 µg/dL) for youths and at least 0.97 µmol/L (20 µg/dL) for adults.

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**Figure 2.** Log Blood Lead Levels in Relation to Serum Ascorbic Acid

The relationship between serum ascorbic acid concentration and log blood lead level among 4213 youths aged 6 to 16 years (left) and 15 365 adults aged 17 years or older (right) enrolled in the Third National Health and Nutrition Examination Survey, 1988-1994, based on the multivariate model in **Table 2**. The scatterplot on the right is based on the multivariate model in **Table 2** that includes both age and age² terms. Each of the points represents the mean log blood lead level within each 0.6-µmol/L (0.01-mg/dL) increment in serum ascorbic acid.
ASCORBIC ACID AND BLOOD LEAD LEVELS

(2292) Compared with adults in the lowest serum ascorbic acid tertile, adults in the upper 2 tertiles were approximately 65% to 68% less likely to have elevated blood lead levels (multivariate \( P \) for trend = .03). Based on the multivariate models reported in Table 2, we also examined the relationship of serum ascorbic acid to prevalence of elevated blood lead level graphically by plotting elevated blood lead level as a function of serum ascorbic acid level (Figure 1). This figure reveals a curvilinear relationship between serum ascorbic acid and elevated blood lead levels. Approximately 4% of youths and 2% of adults with the lowest serum ascorbic acid levels had elevated blood lead levels.

The relationship between serum ascorbic acid level and log blood lead level was examined using multivariate linear models that controlled for all the variables used in the logistic regression analyses. Youths with the highest serum ascorbic acid levels tended to have the lowest log blood lead levels, but this relationship was not statistically significant (\( P = .14 \)) (Figure 2).

In comparison, adults with the lowest serum ascorbic acid levels had increased log blood lead levels (\( P < .001 \)) (Figure 2). Bivariate correlation coefficients were \( r = .01 \), \( P = .59 \) and \( r = .16 \), \( P < .001 \) for youths and adults, respectively.

We substituted dietary ascorbic acid intake for serum ascorbic acid, and reexamined the relationship between ascorbic acid and prevalence of elevated blood lead level. In multivariate models, each 10-mg increment in dietary ascorbic acid intake among youths was associated with a nonsignificant 1% decrease in prevalence of elevated blood lead level (\( P = .88 \)). However, in multivariate models that substituted serum ferritin level for dietary iron, we detected a trend toward lower prevalence of elevated blood lead levels among adults; each 10-mg increment in dietary ascorbic acid intake was associated with a 3.5% decrease in the prevalence of elevated blood lead level (\( P = .10 \)).

**COMMENT**

Our principal finding was that serum ascorbic acid level was inversely related to blood lead level among adults and youths enrolled in NHANES III. We observed no significant relationship, however, between dietary ascorbic acid intake and blood lead levels, suggesting that dietary estimates derived from NHANES III were too imprecise to permit the detection of the association or that elevated blood lead levels may increase the turnover of ascorbic acid, thereby lowering serum ascorbic acid levels. Although we cannot exclude the latter possibility, there is prior evidence consistent with the hypothesis that ascorbic acid may lower blood lead levels.

Several animal studies have examined the effect of ascorbic acid on lead toxicity. In rats fed a lead-containing diet, combined dietary supplementation with iron and ascorbic acid lowered detectable lead levels in liver, kidney, and bone and prevented growth depression and anemia. These beneficial effects, however, were transient. Comparing the chelating effects of oral ascorbic acid and parenterally administered EDTA in lead-poisoned rats, Goyer and Cherian \(^9\) reported that ascorbic acid and EDTA had equivalent chelating properties. Studies in humans have yielded inconclusive results. Two case series reported significant clinical improvement among 337 workers with occupational lead exposure after daily administration of 100 mg of ascorbic acid. \(^5^,^6\) In an uncontrolled trial, the combined administration of zinc and ascorbic acid was reported to reduce blood lead levels among 1000 psychiatric outpatients, \(^7\) and in a small clinical trial, daily supplementation of 1000 mg of ascorbic acid resulted in marked reductions in blood lead levels (\( P = .001 \)). In another study of 85 subjects who volunteered to consume a lead-containing drink, ascorbic acid supplementation produced small reductions in lead retention. \(^8\) Two other small clinical trials, however, concluded that ascorbic acid supplementation did not lower blood lead levels. \(^9^,^10\) In 1 of these studies, 52 subjects were assigned to receive either ascorbic acid supplementation or placebo. \(^9\) Although reported to

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**Table 2. Relative Prevalence of Elevated Blood Lead Levels Across Tertiles of Serum Ascorbic Acid Concentration Among 19,578 Participants Enrolled in the Third National Health and Nutrition Examination Survey, 1988-1994**

<table>
<thead>
<tr>
<th>Tertiles of Serum Ascorbic Acid Concentration</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Youths</strong></td>
<td></td>
</tr>
<tr>
<td>Mean serum ascorbic acid level, ( \mu \text{mol/L} )</td>
<td>30</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>1431</td>
</tr>
<tr>
<td>No. of prevalent cases</td>
<td>13</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted OR (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivariate-adjusted OR (95% CI)†</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>Mean serum ascorbic acid level, ( \mu \text{mol/L} )</td>
<td>15</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>5178</td>
</tr>
<tr>
<td>No. of prevalent cases</td>
<td>42</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted OR (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivariate-adjusted OR (95% CI)†</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval. Youths were aged 6 to 16 years; adults, 17 years or older.†Adjusted for age, race, sex, level of annual household income (<$20,000 vs ≥$20,000), and intake of energy, fat, calcium, iron, and zinc.

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have no effect, 8 weeks of ascorbic acid supplementation resulted in ( nonsignificant) improvement. Compared with subjects in the placebo group, subjects treated with ascorbic acid were more likely to have a decrease of at least 0.24 µmol/L (5 µg/dL) in blood lead level (relative risk, 0.64; 95% confidence interval, 0.36-1.11; P = .10). In the second study, 45 men received 3 months of ascorbic acid treatment, resulting in 11% to 23% (nonsignificant) lower blood lead levels compared with the placebo-treated group.22 It is possible that these 2 studies might have yielded statistically significant results had larger numbers of participants been enrolled.

Our study has a number of strengths and limitations. Because NHANES III surveyed a large probability sample of Americans, our findings should be generalizable to the US population. Furthermore, the measurement of serum ascorbic acid levels in a large sample of the population allows a more reliable assessment of ascorbic acid status as a correlate of blood lead levels than do studies that use dietary intake estimations only. Plasma ascorbic acid levels are strongly correlated with leukocyte ascorbic acid levels (r = 0.92), an indicator of tissue levels,23,24 and reflect at least the previous several months of dietary intake, even during periods of seasonal variation.23 The correlation between dietary estimates and measured blood levels of ascorbic acid, however, is modest (r = 0.43).25 Although it is biologically plausible that ascorbic acid may affect lead absorption and excretion, it is possible that blood lead may lower serum ascorbic acid levels. It is also possible that higher ascorbic acid levels may represent healthier lifestyles or greater socioeconomic status. Hence, we cannot be certain that differences in serum ascorbic acid levels preceded elevated blood lead levels, and inferences regarding causality should be made cautiously.

In conclusion, serum ascorbic acid level is an important independent correlate of blood lead level among Americans. To our knowledge, this report is the first population-based study to establish such an association. If a causal relationship is confirmed, higher intakes of ascorbic acid may have public health implications for the prevention of lead toxicity.

**Funding/Support:** This study was supported by Hoffmann-La Roche Inc and US Public Health Service grant HL53479.

**Acknowledgment:** We gratefully acknowledge the comments of Stephen Hulley, MD, MPH.

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