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Accessibility
A δ-Aminolevulenic Acid Dehydratase (ALAD) Polymorphism May Modify the Relationship of Low-Level Lead Exposure to Uricemia and Renal Function: The Normative Aging Study

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In this study we investigated whether a known δ-aminolevulenic acid dehydratase (ALAD) exon 4 polymorphism has a modifying effect on the association of blood or bone lead level with uricemia and indices of renal function among middle-aged and elderly men. We performed a cross-sectional study of subjects who participated between 1991 and 1995 in the Department of Veterans Affairs Normative Aging Study. Information on blood lead levels, bone lead levels (measured by X-ray fluorescence), serum uric acid, serum creatinine, estimated creatinine clearance, and ALAD polymorphism status was available in 709 subjects. Regression models were constructed to examine the relationships of serum uric acid, serum creatinine, and estimated creatinine clearance to blood or bone lead level, stratified by genotype. We also adjusted for age, body mass index, blood pressure, smoking, alcohol consumption, and ingestion of analgesic medications (n = 638). Of the 709 subjects, 7 (1%) and 107 (15%) were homozygous and heterozygous for the variant (ALAD-2) allele, respectively. The mean (range) serum uric acid and creatinine levels were 6.5 (2.9–10.6) and 1.2 (0.6–2.5) mg/dL. No significant differences were found in serum uric acid, serum creatinine, or estimated creatinine clearance by ALAD genotype. However, after adjusting for other potential confounders, we found a significant linear relationship between serum uric acid and patella bone lead (p = 0.040) among the ALAD 1-2/2-2 genotype individuals above a threshold patellar lead level of 15 µg/g. In contrast, among the wild-type (ALAD-1) individuals, there was a suggestion of a significant linear relationship of serum uric acid with patella bone lead (p = 0.141), but only after a threshold of 101 µg/g. There was evidence of a significant (p = 0.025) interaction of tibia lead with genotype (ALAD 1-1 vs. ALAD 1-2/2-2) regarding serum creatinine as an outcome, but in the same linear regression model tibia lead alone was not a significant predictor of serum creatinine. Conversely, for estimated creatinine clearance, patella lead, but not the interaction of patella lead with genotype, was a significantly independent predictor (p = 0.026).

Our findings suggest that ALAD genotype may modify the effect of lead on the renal excretion of uric acid as well as overall renal function among middle-aged and elderly men who had community (nonoccupational) exposures to lead. Additional research is needed to ascertain whether this constitutes a true gene–environment interaction and, if so, its clinical impact. Key words: δ-a-aminolevulenic acid dehydratase, bone lead, serum creatinine, serum uric acid. Environ Health Perspect 111:335–340 (2003). doi:10.1289/ehp.5504 available via http://dx.doi.org/ [Online 31 October 2002]

In 1981, Battistuzzi et al. (5) showed that human ALAD protein is a polymorphic enzyme. Subsequently, Wetmur et al. (6) found that this enzyme is polymorphic because of a G-to-C transversion of nucleotide 177 in a coding region that results in replacement of the amino acid lysine with asparagine. Although no significant difference was noted in the activities of the erythrocyte ALAD 1-1, ALAD 1-2, or ALAD 2-2 (5), Bergdahl et al. (3) reported that the ALAD-2 subunit binds lead more tightly than does ALAD-1 subunit in vitro.

Epidemiologic studies have suggested that among lead-exposed workers and environmentally exposed children (7–9), individuals with either the ALAD 1-2 or 2-2 genotype had blood lead levels that were significantly higher than those of individuals with the ALAD 1-1 genotype. These findings suggest that the ALAD-2 polypeptide binds lead more tightly and effectively than does ALAD-1.

Recently, two occupational epidemiologic studies in 691 members of a construction union and 89 lead-smelter workers have indicated that ALAD genotype may modify the effect of lead on uricaemia and kidney dysfunction (10,11). In this study, we attempted to investigate the impact of ALAD polymorphism on the relationship of lead levels in both blood and bone to uricaemia and kidney dysfunction among environmentally exposed men. Our a priori hypothesis was that our lead biomarkers would be independently correlated with hyperuricemia and renal dysfunction and that the ALAD variant type would modify this effect, particularly when blood lead or bone lead levels are high (12,13).

Methods

Participants. The Normative Aging Study (NAS) is a longitudinal study of aging established by the Veterans Administration in

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Healthy male volunteers from the Greater Boston, Massachusetts area were screened at entry and accepted into the study if they had no history of heart disease, hypertension, diabetes mellitus, cancer, peptic ulcer, gout, recurrent asthma, bronchitis, or sinusitis. Men with either systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg at entry were disqualified. Between 1963 and 1968, a total of 2,280 men who met the entry criteria were enrolled, ranging in age from 21 to 80 years, with a mean age of 42 years at entry. Study participants were asked to return for examinations every 3–5 years. At each visit, extensive physical examination, laboratory, anthropometric, and questionnaire data were collected. Beginning in 1991, during the course of each continuing participant’s regularly scheduled evaluation at the Department of Veterans Affairs outpatient clinic in Boston, a fresh blood specimen was obtained for measurement of lead and other biochemical indicators such as uric acid and serum creatinine after an overnight fast and abstinence from smoking, and permission was sought to take bone lead measurements by K-shell X-ray fluorescence (KXRF). Consenting individuals reported to the outpatient Clinical Research Center of the Brigham and Women’s Hospital in Boston. This study was approved by the Human Subjects Committees of the Brigham and Women’s Hospital and the Harvard School of Public Health.

Uric acid and renal function. Serum uric acid levels were measured by the colorimetric phosphotungstic method (N-30) with the Technicon Autoanalyzer (Technicon Instruments, Tarrytown, NY, USA) (15). The assay included standards from the College of American Pathologists. In addition, the correlation between the NAS colorimetric phosphotungstic method and the more specific uricase method at the clinical laboratory of the Massachusetts General Hospital in 23 split serum samples was 0.93, indicating that these two methods are comparable (15,16).

Serum creatinine was measured by an Astra 8 analyzer (Beckman Instruments, Inc., Fullerton, CA, USA) (17). Creatinine clearance was estimated on the basis of the serum creatinine and estimated creatinine clearance (by genotype (ALAD 1-2 vs. ALAD 1-1) using chi-squared and Student’s t-test statistics. Because only 7 (1%) subjects in this population were ALAD 2-2, our ability to distinguish between effects associated with the ALAD 1-2 versus the ALAD 2-2 genotypes was limited. Nevertheless, initial analyses were conducted comparing wild-type (ALAD 1-1) with ALAD 2-2 individuals alone to see if the homozygous condition was associated with effects that were obscured by combining the ALAD 2-2 and ALAD 1-2 individuals. No such effects were seen; thus, all later analyses were conducted and reported combining ALAD 1-2 and ALAD 2-2 into one category (ALAD 1-2/2-2).

Multivariate linear regression was used to model determinants of uric acid and renal function that started with core models including determinants we had identified in previously published studies (15,19). For uric acid (milligrams per deciliter), these core-model determinants included age (years), body mass index [weight (kilograms)/height (meters)²], log-transformed alcohol consumption (grams per day), diastolic blood pressure (milligrams mercury), and serum creatinine (milligrams per deciliter); for serum creatinine and estimated creatinine clearance, these core-model determinants included age, body mass index, log-transformed alcohol consumption, hypertension (yes/no), current smoking (yes/no), former smoking (yes/no), and use of analgesic medications (yes/no). Then, blood lead, tibia lead, or patella lead levels were separately forced into the models.

To assess whether genotype may serve as an effect modifier (vs. an independent determinant) of the relationships of blood or bone lead to uric acid and renal function, each of these regressions was then repeated after adding an interaction term for blood or bone lead and genotype (ALAD 1-2/2-2 vs. ALAD 1-1). In addition, we also compared the coefficients of core-model and lead biomarker determinants in regressions of uric acid and renal function that were stratified by genotype (ALAD 1-2/2-2 vs. ALAD 1-1). In each of the above regressions, generalized additive models (23) were to examine the shape of associations between continuous variables (e.g., blood or bone lead) and uric acid and renal function. These analyses allowed us to assess for potential nonlinearities and the need for transforming these covariates. Finally, we applied statistical tests to determine whether a threshold existed between blood or bone lead levels and uric acid or renal function. Akaike’s Information Criterion was computed to determine the break point (24). Failure to identify a threshold (break point), if one exists, would erroneously attribute a relationship at low blood or bone lead levels where it is not present (25,26).

In addition, such failure would underestimate both the size and significance of the effect at blood or bone lead levels where it is truly present, by averaging levels where the relationship is nonexistent with those where it is significant. All data were analyzed using the SAS (SAS Institute, Cary, NC, USA) and S-PLUS (Insightful Corp, Seattle, WA, USA) statistical packages. All p-values reported are two sided.

Results
Between 1991 and 1995, there were 1,194 active NAS subjects, of whom 776 participated in the KXRF bone lead study. Of these, 710 subjects had all information on serum uric acid and creatinine levels, genotype status, and blood and bone lead levels. One subject with a serum creatinine of 9.0 mg/dL (severe renal disease) was excluded (19). No significant differences were found with respect to the distributions of age, body mass
expected, with a mean ± SD of 6.2 ± 4.1 µg/dL. We found that mean blood lead level in ALAD 1-1 subjects was slightly and significantly higher than that in ALAD 1-2/2-2 individuals (p = 0.044). The same results were not noted with respect to mean bone lead levels by genotype. The mean ± SD serum uric acid and creatinine were 6.5 ± 1.3 and 1.2 ± 0.2 mg/dL, respectively, for all subjects. We did not find any meaningful difference in mean serum uric acid, serum creatinine, or estimated creatinine clearance between the allele groups.

Our hypotheses were that a) blood lead or bone lead level was a risk factor for hyperuricemia and renal dysfunction and b) ALAD variant type modified this effect especially when blood lead or bone lead level was relatively high (12,27). Table 2 shows the relationship of serum uric acid with bone lead level (patella or tibia lead) with and without an additional term for the interaction of bone lead with genotype, and before (n = 709) and after (n = 638, because of missing data in body mass index, alcohol consumption, and diastolic blood pressure) adjusting for other potential confounders identified in our previous investigation (15). Bone lead level marginally predicted uric acid level after adjusting for age, body mass index, alcohol consumption, diastolic blood pressure, and serum creatinine level (for patella lead, p = 0.078; for tibia lead, p = 0.190; Table 2). When the interaction of patella lead and genotype was added to the regression model, the predictive slope coefficients of serum uric acid by patella or tibia lead level in ALAD 1-2/2-2 individuals was about 50–100% higher than that of ALAD 1-1 subjects (β = 0.006 vs. 0.004 for patella lead and β = 0.009 vs. 0.004 for tibia lead), but the significance levels of the terms were marginal. When we reset the negative values of tibia and patella lead (of which there were only four) to zero, the results were almost identical. We did not find any significant relation of blood lead or its interaction with genotype to serum uric acid (data not shown).

Table 3 shows the relationship of serum creatinine or estimated creatinine clearance with bone lead level with and without an interaction term for bone lead and genotype and before (n = 709) and after (n = 670, because of 39 missing data in body mass index and alcohol consumption) adjusting for other potential confounders identified in our previous investigation (19). Although bone lead level significantly predicted serum creatinine in the crude analysis, we found no significant independent effect of either blood lead or bone lead (tibia lead or patella lead) to serum creatinine after adjusting for age, body mass index, alcohol consumption, hypertension, current smoking status, and current analgesic medications. However, we found a significant interaction of tibia lead (but not blood lead or patella lead) and genotype in relation to serum creatinine (p = 0.025), even though tibia lead level was not a significant independent predictor (Table 3). For estimated creatinine clearance, patella lead was a significant predictor (p = 0.024) after adjusting for age, body mass index, alcohol consumption, hypertension, current smoking status, and current analgesic medications. Neither tibia lead nor blood lead significantly predicted estimated creatinine clearance after adjusting for other covariates. In addition, no interaction was found of blood lead or bone lead with genotype in relation to estimated creatinine clearance (Table 3).

In a smoothed plot of serum uric acid in relation to bone lead that is stratified by genotype and adjusted for other covariates in the model (Figure 1), there is a suggestion of a threshold effect, especially with respect to patella lead, with break points among ALAD 1-1 and 1-2/2-2 genotype individuals at patella lead levels of 101 µg/g and 15 µg/g, respectively, based on the Akaike’s Information Criterion (24). Using “hockey stick” regression analyses (25,26), we found a significant linear relationship of serum uric acid with patella lead (p = 0.040; Table 4) above the apparent
Discussion

We have previously demonstrated that the patella lead level is independently associated with serum uric acid (15). In the present study, our sample was slightly different and the independent effect of patellar lead on serum uric acid was only of marginal significance ($p = 0.078$); however, we found a significant linear relationship of serum uric acid with patella lead among $ALAD$ (1-2) genotypes. In this study, the relationship between hyperuricemia and bone lead, especially patella lead, is not significant.

This difference between the $ALAD$ (1-2) and $ALAD$ (1-1) individuals is fairly striking, and suggests that $ALAD$ status modifies the relationship between lead and hyperuricemia with $ALAD$ (1-2) individuals having a higher risk for lead-induced hyperuricemia. On the other hand, there were relatively few subjects with patella lead levels $> 101$ µg/dL in this community-exposed population (Figure 1). Similar results were found with respect to tibia and blood lead, but they were not as impressive as those for patella lead. The $ALAD$ (2) variant individuals had about a 0.5–2-fold higher serum uric acid than did those with the wild-type $ALAD$ (1-1) (Table 2).

Hyperuricemia is the strongest risk factor for gout. Campion et al. (16) found an increased incidence of gout with serum uric acid levels $> 9.0$ mg/dL. Among patients with lead nephropathy, there is no evidence of overproduction of uric acid (28, 29). Therefore, chronic lead toxicity causes hyperuricemia mainly due to a defect in the tubular secretion of uric acid. In this study, we found an association between hyperuricemia and bone lead, especially patella lead. Totally, levels of lead (e.g., blood lead levels $> 60$ µg/dL) are clearly associated with gouty arthritis (15, 28). However, to what extent low-level lead exposure contributes to the development of hyperuricemia and clinical risk of gout is unclear. The middle-aged and elderly men in this cohort currently have low levels of lead in blood (mean, 6.2 µg/dL), which may help to explain why our results are not stronger.

Table 2. Relationship of uric acid (mg/dL) with bone lead (µg/g) in multivariate linear regression without and with $ALAD$ genotype interaction in the Normative Aging Study, 1991–1995.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude analyses ($n = 709$)</th>
<th>Adjusted analyses ($n = 638$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>p-Value</td>
</tr>
<tr>
<td>Patella</td>
<td>Lead</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
<tr>
<td>Tibia</td>
<td>Lead</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
</tbody>
</table>

*Adjusted for age (years), body mass index index, log-transformed alcohol consumption (g/day), diastolic blood pressure (mm Hg), and serum creatinine (mg/dL); some variables have missing data. $^D$ Lead–$ALAD$ interaction in the regression model. $^*$ Interaction between bone lead and genotype ($ALAD$ (1-2) vs. $ALAD$ (1-1)).

Table 3. Relationship of serum creatinine or estimated creatinine clearance with bone lead (µg/g) without and with $ALAD$ genotype interaction in the Normative Aging Study, 1991–1995.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude analyses ($n = 709$)</th>
<th>Adjusted analyses ($n = 638$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>p-Value</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>Patella</td>
<td>Lead</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
<tr>
<td>Tibia</td>
<td>Lead</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
<tr>
<td>Estimated creatinine clearance (mL/min)</td>
<td>Patella</td>
<td>Lead</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
<tr>
<td>Tibia</td>
<td>Lead</td>
<td>—0.271</td>
</tr>
<tr>
<td></td>
<td>Lead–$ALAD^D$</td>
<td>—</td>
</tr>
</tbody>
</table>

*Adjusted for age (years), body mass index, hypertension (yes/no), current smoking (yes/no), former smoking (yes/no), log-transformed alcohol intake (g/day), and current analgesic medications (yes/no); some variables have missing data. $^D$ Lead–$ALAD$ interaction in the regression model. $^*$ Interaction between genotype ($ALAD$ (1-2) vs. $ALAD$ (1-1)).
the ratio of urinary creatinine/serum creatinine were significantly lower in the seven \textit{ALAD 1-2} 2-2 subjects compared with those of the 82 \textit{ALAD 1-1} lead workers [median urinary calcium (mg/L), 76 vs. 188; urinary creatinine/serum creatinine ratio, 84 vs. 180]. Thus, their study did suggest the presence of \textit{ALAD} allele-specific differences in kidney function. In another study, Smith et al. \cite{11} investigated the association between the presence of \textit{ALAD 2} allele, renal function, and lead concentrations in blood and bone among 688 members of a construction trade union. They found marginally higher levels of blood urea nitrogen \((p = 0.06)\) and uric acid \((p = 0.09)\) among the \textit{ALAD 2}-genotype individuals after adjusting for blood lead level, age, and alcohol consumption. Smith et al. \cite{11} suggested that \textit{ALAD 2} genotype may influence chronic renal toxicity by differential binding of lead to the variant \textit{ALAD 2} protein. Our results are consistent with these previous reports in demonstrating that \textit{ALAD} genotype status may modify the relationship between lead and kidney function.

In addition to our findings with serum creatinine, we observed that creatinine clearance, estimated by age, body weight, and serum creatinine, is significantly and negatively associated with bone lead, especially patella lead. One possible explanation is that serum creatinine is not as sensitive a marker for subclinical renal damage as is estimated creatinine clearance. Notably, Nolan and Shaikh \cite{30} found that \textit{N-acetyl-D-glucosaminidase}, a lysosomal marker of tubular cell toxicity, is a sensitive marker for detecting subclinical kidney damage and is associated with blood lead levels.

We did not find any significant association between blood lead and impaired renal function as measured by serum creatinine or estimated creatinine clearance. Current blood lead level does not represent long-term lead exposure, which may explain why it is not an adequate dosimeter with respect to kidney toxicity. Regarding our measures of bone lead, it is not clear why we found that patella bone lead was the best predictor of elevated serum uric acid whereas tibia bone lead was the best predictor of elevated serum creatinine. Compared with the patella, which is composed mostly of trabecular bone, the tibia is mostly cortical bone with a slow rate of bone turnover and a longer half-life with respect to lead levels. As a consequence, the tibia is a better reflection of long-term cumulative lead exposure, whereas the high resorption rates of trabecular bone make it the most important skeletal source of circulating lead \cite{31}. It is possible that lead-induced rises in serum uric acid are mostly dependent on active resorption of bone lead stores, whereas lead-induced rises in serum creatinine are mostly dependent on a cumulative effect of lead on the kidney taking place over many years.

How might this \textit{ALAD} polymorphism modify the impact of lead on uric acid? The effect of lead on uric acid metabolism has been thought to be mediated by a toxic effect on the proximal renal tubule, which is the site of uric acid excretion as well as active secretion by renal tubular cells. It is possible that the lead–\textit{ALAD 2} subunit complex is more toxic to proximal tubular cells than is the lead–\textit{ALAD 1} subunit \cite{11}. This same mechanism might be more broadly explanatory of a modifying effect of the \textit{ALAD} polymorphism on general kidney function, as reflected by our findings with respect to serum creatinine.

Although in \textit{in vitro} studies and epidemiologic studies suggest that the \textit{ALAD 2} polypeptide binds lead more tightly and effectively than does \textit{ALAD 1} \cite{3,7,8}, the theoretical differential binding of lead by the \textit{ALAD} iso-enzymes does not indicate greater susceptibility to lead for persons with the \textit{ALAD 2} genotype. Susceptibility is dependent on different partitioning of lead and how bioavailable different complexed forms of lead are in different tissues. In the present study, \textit{ALAD 2}-modified lead’s relation to uricemia and indices of renal function. However, the modifying influence of \textit{ALAD} polymorphism on the neurologic effect of lead may be different \cite{12,33}. An elevated concentration of plasma \(\delta\)-aminolevulinic acid, an early biologic effect of lead poisoning, was higher in 44 battery workers with homozygous \textit{ALAD 1}, compared with 21 \textit{ALAD 2}-workers \cite{12}. Sthitharsan et al. \cite{12} suggested that if the neurologic effects of lead poisoning are partly due to elevated \(\delta\)-aminolevulinic acid, then the \textit{ALAD 2} genotype may be protective for this end point. This is consistent with the results of a study of neuropsychologic effects of lead in adolescents, showing that the \textit{ALAD 2} subjects performed better on tests of attention than did the \textit{ALAD 1} subjects after adjusting for lead exposure \cite{32}. These potential contrasting roles of \textit{ALAD} genotype demand further study to clarify the effect of susceptibility to lead toxicity.

Our study has a number of limitations including its cross-sectional epidemiologic design and, perhaps most important, its focus on community-exposed men with relatively modest lead burdens, as reflected by bone lead levels less than a third of those seen in workers in a primary lead industry, such as lead smelting \cite{11,33}. It is quite possible that the modifying effect of \textit{ALAD} polymorphism on lead toxicity would be more apparent among populations with higher levels of lead exposure. Clearly, our findings must be viewed only as suggestive, and other studies are needed to see if these relationships can be replicated.

In conclusion, we found evidence that a polymorphism of \textit{ALAD} that has been the recent focus of research may modify the impact of lead on uric acid excretion and general kidney function, with \textit{ALAD 2} carriers manifesting effects at levels of lead burden with an apparently lower threshold than that of \textit{ALAD 1} individuals. Additional research is required to determine if this represents a true gene–environment interaction with clinical significance.

\textbf{REFERENCES AND NOTES}


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