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ARTICLE

The effect of chelation on bone Pb stores in Pb poisoned children

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BACKGROUND: Lead exposure remains a key problem for children during development. One treatment for lead poisoning is chelation – a topic that remains controversial with varied results. Bone lead serves as a marker of total body burden of lead and encompasses between 60-90% of lead storage in children.
OBJECTIVE: In this study, we aimed to identify the change in bone lead as a result of chelation therapy in a group of lead poisoned children (blood lead >25 µg/dL).
METHODS: Upon diagnosis with lead poisoning at Xinhua Hospital in Shanghai, China, children were recruited to our study, had their bone lead levels measured, and underwent one-week of intravenous, in-patient ethylenediaminetetraacetic acid chelation treatment. Up to three clinical visits with the same treatment protocol and bone lead measurements were completed over the two-year study. We measured biomarkers of lead exposure for children exposed via various potential sources, including home contaminants, local industrial emissions, traditional medicines, or lead cookware.
RESULTS: We observed significant differences with bone lead after chelation therapy ($p < 0.0001$), even after calculating a conservative model for theoretical decay from known bone turnover ($p = 0.01$). The difference identified between our observed change in bone lead and literature established bone lead change significantly increased with more chelation treatments. A significant reduction in bone lead was observed following chelation treatment of children with lead poisoning – a difference that increased more with more chelation.
SIGNIFICANCE: Study results indicate that chelation treatment is effective in reducing bone lead stores in children with initial blood lead levels greater than 25 µg/dL.
IMPACT STATEMENT: Lead exposure in children is a consistent problem – drastically impacting health across the life span. After exposure, lead stores in the bone of children serving as a potential endogenous source of exposure for years to decades. Our study demonstrated that chelation therapy, while reducing blood lead levels, additionally reduced bone lead levels. A reduction in bone lead would effectively reduce the potential for endogenous release of lead and restrict the damage done by lead exposure.

Keywords: Metals; Child Exposure/Health; Early Life Exposure

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INTRODUCTION

Lead (Pb) exposure continues to plague vulnerable communities with exposure to children causing a litany of health disorders throughout life [1–7]. Previous work in children has focused on the cognitive impacts, but it is likely these early life exposures have lifetime impacts on many major organ systems, as studies have shown cardiovascular disease and neurodegenerative impacts later in life [5, 7, 8]. To combat some of these major health impacts, many hospitals implement clinical treatments for children impacted by high levels of Pb exposure to reduce biological burden. In China, the standard of care in Pb-poisoned children (defined as blood Pb >25ug/dL) involves inpatient chelation using ethylenediaminetetraacetic acid (EDTA) administered intravenously. Chelation has been shown previously to successfully remove Pb from blood, but can have negative impacts on growth with potentially little benefit for cognition [9–11]. The point at which chelation is used as a standard of care varies among treatment facilities, with some widely cited references in the US recommending treatment if blood Pb levels exceed 45 ug/dL and other hospitals not recommending chelation at any level [12, 13]. However, previous studies investigating chelation only identified non-significant effects on cognition at blood lead levels less than 45 µg/dL, with only one study considering the impact of the treatment on total body stores of Pb [14, 15].

It is well-known that Pb in the body is stored primarily in bone, with up to 90% of total Pb stores in adults residing in bone with

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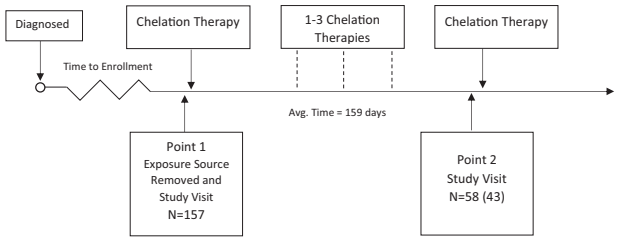

Fig. 1 Study and Treatment Timeline. Subject treatment and follow-up schedule with each study visit point including bone and blood Pb measurements.

studies showing that even for young children more than 60% of total body Pb is in bone [16, 17]. Blood Pb has a half-residence time of about 30 days and thus is typically only reflective of acute exposures within a few months of collection; however, this can depend on the amount of lead in bone that is resorbed into blood over time [18]. Resorption of bone lead to blood lead can result in sustained blood lead levels for years [18, 19]. The storage of Pb in bone can be measured using x-ray fluorescence (XRF) and is reflective of cumulative exposures on the order of years to decades [16, 18, 20]. However, Pb in bone can be remobilized over time and represents a continuing threat to the individual as Pb is resorbed from bone into blood to potentially impact cognitive health, cardiovascular health, and numerous other organ systems impacted by Pb [21–23]. In the major clinical trials of chelation on Pb-poisoned children, the effects were only evaluated using blood measurements; thus, they are missing a critically important aspect of Pb exposure via the total body stores in bone [10, 11, 13, 24]. Chelation, while actively reducing blood Pb levels, would be dependent on bone stores of Pb, which would be released over time after the decrease of Pb in blood. Measuring bone Pb in studies of Pb poisoning is critical to understand the potential for ongoing endogenous release of Pb impacting health. The reduction of bone Pb stores would thus lead to a potential reduction in lifelong exposure from endogenous release of Pb. However, it remains unclear how bone Pb is impacted by chelation treatments. One previous study measured the changes of bone Pb in a pediatric population – noting that the bone Pb did decrease over time [14]. Importantly, this study was not able to clarify if this change could be related to chelation or if this was due to natural decay of bone stores in children [14]. Another case study identified changes in bone Pb associated with treatment, but again did not compare this data to predicted decay from known release of Pb from bone [25]. Understanding the effects of chelation of Pb in bone is important, and with little definitive literature on this critical aspect of chelation therapy, it is difficult to assess the potential effect of chelation on total body Pb stores.

In our study, we evaluated the impact of chelation on bone Pb measured via XRF of Pb-poisoned children in China in comparison to known bone turnover parameters. Thus, we are able to fill a critical gap in evidence relating chelation more directly to decreases in bone Pb. Using repeated measures of blood and bone Pb, we are uniquely able to determine the impact of chelation on bone Pb in comparison with natural bone turnover in a pediatric population.

MATERIALS AND METHODS

Study Population

The study methods were detailed in two previous manuscripts [26, 27]. Fig. 1 shows the treatment schedule and follow-up measurements used for the analysis. Briefly, 157 Pb poisoned children were diagnosed using blood Pb levels, defined as levels >25 ug/dL. The standard of care at Xinhua Hospital incorporated treatment by chelation for children with blood lead levels >25 ug/dL, which differs from the CDC recommendation of 45 ug/dL. The primary sources of Pb exposure for these children were identified and removed prior to the study visit at Point 1 in most cases (Fig. 1). 43% of the children in the study had exposures that were related to in-home exposures or local industrial pollution (removed by separating children from work area or relocation), and 21% had exposures that were attributed to the use of lead cookware. Additionally, source removal was verified in our previous study using blood and bone relationships. A total of 95% variance in blood lead was explained by bone lead one year after source removal [26]. At enrollment, all study subjects underwent bone and blood Pb testing. After the initial testing, children had chelation treatment using intravenous EDTA. The chelator used was Calcium Disodium EDTA with a dosage of 1000 mg/m^2/d [28]. For children's weight ≤30 kg, we used the equation:

$$\text{body surface area} = \text{weight} * 0.035 + 0.1$$

where weight is in kilograms and body surface area is given in m^2. For children's weight >30 kg, we used the equation:

$$\text{body surface area} = (\text{weight} - 30) * 0.02 + 1.05$$

to define body surface area. The intravenous infusion lasted 24 hours with 5 days of follow up. Children who were more highly exposed returned for multiple chelation treatments throughout the study period (between Points 1 and 2 on Fig. 1). Of the 58 subjects that returned for follow-up visits with chelation, 1 had missing data and 14 had initial bone lead levels lower than the uncertainty and were excluded from our analysis of changes in bone lead (since they were starting from effectively undetectable levels). Thus, the final analytic sample was 43 participants.

The study received IRB approval from Purdue University and Xinhua Hospital. Study participants and parents were provided study information and consent documents at recruitment by a trained research assistant. Signed consent forms were received from the parents of each child, as well as assent forms from any child ≥7 years of age.

KXRF bone Pb measurement system

The KXRF bone Pb measurement system was used to measure tibia bone Pb as a metric of each individual's cumulative Pb exposure. We used a cloverleaf Cd-109 based KXRF system to measure bone Pb, which has a detection limit of 2-3 ug/g for bone Pb measurements [29–31]. Prior to measurements, the participants' legs were cleaned using both alcohol and EDTA cotton swabs. The KXRF measurements were 30 minutes and taken while the child watched a movie. The whole body effective radiation dose delivered to the subject from this system was estimated to be < 5 μSv for this population [32].

Blood Pb analysis

Blood was collected in trace metal-free tubes with EDTA-K2 anticoagulants, in a metal free environment. The participants' skin was cleaned using alcohol swabs before the venipuncture collection. Whole blood samples were frozen and stored at -80^0 C immediately after collection. Blood Pb concentrations were measured and analyzed using a Graphite Furnace Atomic Absorption Spectrometer (AAS) (AA900Z, PE) and standard methodology [33]. The sensitivity of our device was 0.01 μg/dL, and inter and intra assay variability was 5%. Typically, GF-AAS has a detection limit of 1-3 μg/dL in most measured data.

Bone kinetic parameters and calculation

In order to identify the effect of chelation therapy on bone Pb, we calculated observed and theoretical values for the bone Pb changes between Point 1 and Point 2 (Fig. 1). Bone Pb biokinetics mostly act under a standard two-compartment model and we assume the source of exposure ceased in our study, thus, there are two parameters that estimate the change in bone Pb over time (Fig. 2). One is the resorption rate of bone over time, which we calculate using a power model fit of data from the International Commission on Radiological Protection (ICRP) [34]. The other necessary parameter is the estimation of Pb uptake from blood into bone, for which we conservatively use a factor reflective of 60% uptake in our analysis [34–37]. An uptake factor of 60% was shown to be the lowest level for bone accumulation from previous studies, with more recent studies indicating this could be much higher than 60% in most children [26, 27, 35].

Because we are looking at a difference over time, we used our observed difference data in comparison to the calculated difference data from Eq. 1 and the corresponding estimate for uptake of 60% (i.e. the difference in

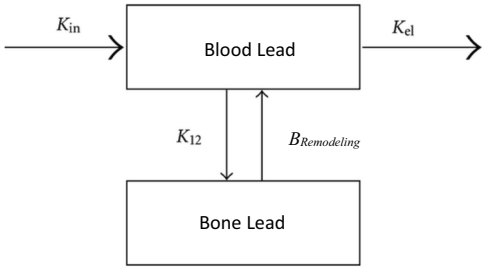

Fig. 2 Compartmental Model for Bone Lead. Two compartment model of lead in bone and blood, where K_{in} is the known source, K_{el} is elimination rate, K_{12} is the lead absorbed from blood to bone, and $B_{Remodeling}$ is the bone turnover releasing bone lead into blood.

time between Point 1 and Point 2 on Fig. 1). The bone turnover per day was calculated using

$$B_{Remodellng} = \int_{t0}^{t2} 125 * t^{-0.568} dt \quad (1)$$

where t is age of the subject integrated over the time during bone turnover and $B_{Remodeling}$ is the bone remodeling rate in percent over the full time between study visits [26, 34]. Thus, solving the integral and implementing unit conversions we used the equation

$$\Delta Bn = 0.4 * BnPb * B_{Remodeling} \approx 116 * BnPb * (t_2^{0.432} - t_0^{0.432}) \quad (2)$$

where $BnPb$ is the initial bone Pb on enrollment of the subject, $B_{Remodellng}$ is the bone remodeling rate in percent, t_2 *and* t_0 are the age of the individual at each respective study visit, 0.4 accounts for the 60% conservative uptake of Pb in bone, and ΔBn is the theoretical change in bone lead.

Statistical Methods

Spearman correlations were used to assess associations between bone lead change, initial bone lead, initial blood lead, treatment number, age, sex, height, and weight. We used Wilcoxon rank sum difference tests to calculate p-values for differences between observed and expected lead measures and chelation number groups. All statistical analysis was done using R version 3.3.3.

RESULTS

Bone and blood Pb concentrations and age, sex, height, and weight measurements in the study population

Table 1 describes the demographic and Pb biomarker data for the Pb poisoned children in our analysis. Our sample was majority male (64%) and had a mean age of 4.2 years. The blood and bone Pb data reflect only the first measurements. 22 participants' blood Pb values are lower than the recruitment criteria, because some subjects had a time gap between being diagnosed as Pb poisoned and being enrolled in the study. However, with the blood Pb being high at a previous time, the median bone Pb level (19.4 µg/g) is still higher in our Pb-poisoned population versus controls from a previous study [26].

Correlation Matrix of Covariates

Figure 3 shows the correlation of different covariates from the study. Difference in bone lead is the observed in the difference between point 1 and 2 on Fig. 1. Excess bone turnover is the difference between the observed difference in bone lead in the study participants and the calculated values from Eq. 2. This value represents the excess bone Pb removed during chelation.

Bone lead change during chelation

The effect of chelation on the difference of bone Pb values is shown in Table 2 and Fig. 4. Additionally, the effect of chelation on the difference in blood lead from at different time points is visualized in Fig. 5. We observed a significant decrease in bone Pb in children undergoing chelation in comparison to previously

Table 1. Population characteristics for the lead poisoned children included in our analysis. N = 43.

	N (%)
Sex	
Male	28 (64%)
Female	15 (36%)
	Median (Q25, Q75)
Age, years	4.2 (1.9, 5.8)
Height, cm	95 (82, 110)
Weight, kg	16.0 (10.9, 19.5)
Blood Pb, µg/dL	23.9 (16.0, 40.5)
Bone Pb, µg/g	19.4 (9.2, 57.2)
Time to Follow-up, days	159 (91, 259.5)

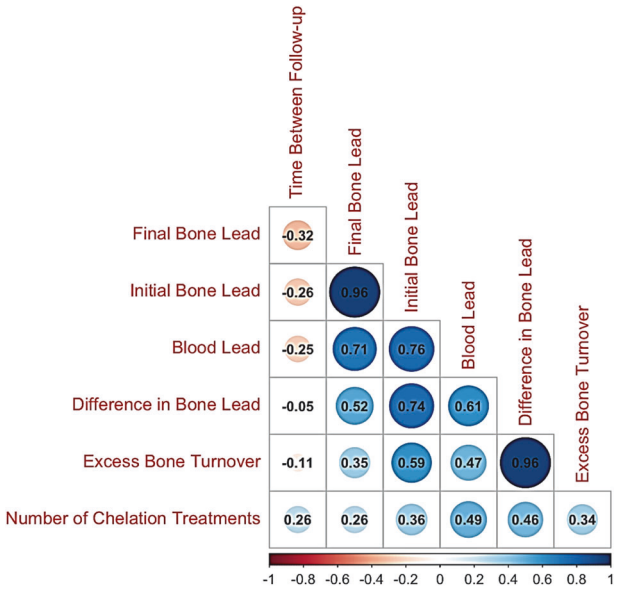

Fig. 3 Correlation Matrix of Covariates. Correlation matrix of covariates and difference in bone lead results (rho values shown in figure). Blood lead is the initial value at the beginning of the study (Point 1 in Fig. 1). Excess bone turnover is the difference between the observed difference in bone lead in the study participants and the calculated values from Eq. 2. This value should represent the excess bone Pb removed during chelation.

Table 2. Differences in bone Pb and bone turnover rate under chelation against literature values (N = 43).

	Median (Q25, Q75)	*P*-value
Observed Values		
Baseline Bone Lead, µg/g	19.4 (9.2, 57.2)	<0.0001
Follow-up Bone Lead, µg/g	15.7 (4.8, 38.2)	
Observed Difference, µg/g	4.6 (2.0, 13.7)	0.01
Theoretical Difference, µg/g	2.3 (0.85, 5.7)	

modeled theoretical values of expected bone Pb change ($p = 0.01$). Figures 4 and 5 show the individual change in bone and blood Pb between the two measurement time points in the study and violin plots of the distribution of bone and blood Pb measures at each point in the study. Finally, those undergoing more than one chelation treatment (1 treatment n = 27, 2 treatments n = 14, 3 treatments n = 1, 4 treatments n = 1) had a

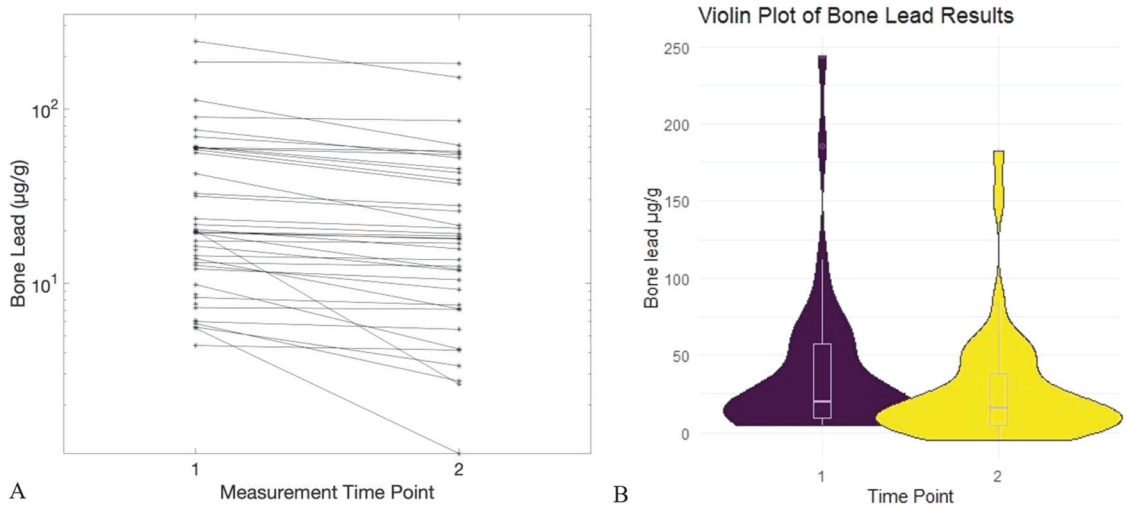

Fig. 4 Bone Lead Change Over Time. Panel **A** Individual bone lead change plotted for each time point in the study showing the decrease in bone lead; Panel **B** Violin plot of bone lead at Point 1 (XRF 1) and Point 2 (XRF 2) in the study showing the decrease in bone lead.

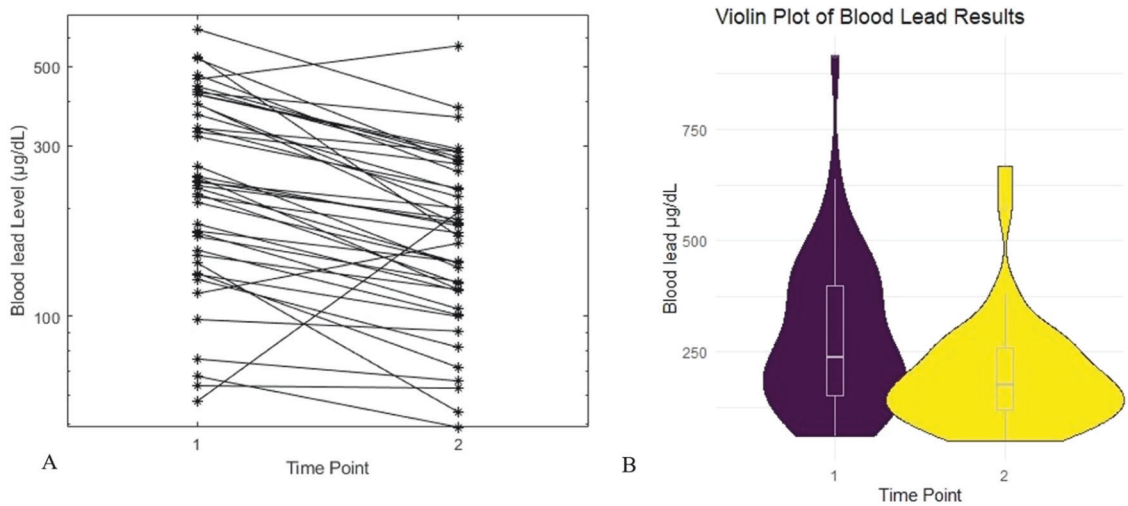

Fig. 5 Blood Lead Change Over Time. Panel **A** Individual blood lead change plotted for each time point in the study showing the decrease in bone lead; Panel **B** Violin plot of blood lead at Point 1 and Point 2 in the study showing the decrease in body burden of lead reflected in blood.

larger difference between observed and expected bone lead change than those who underwent only one chelation treatment (average ± SD 3.5 ± 7.6 µg/g vs 7.8 ± 13.9 µg/g, $p = 0.04$).

DISCUSSION

This study demonstrates the positive effects of chelation in removing Pb from bone and, in-turn, reducing the long-term storage of Pb in the body. Alongside a multi-participant case study by Batuman et al. [25]. and a study by Markowitz et al. [14]. this study bolsters the evidence and found a significant reduction in total body burden stores of Pb as a result of chelation treatments. Although the study by Markowitz et al. did not show a significant reduction after adjustment for initial levels over the 7 week period, which is different from our study. Our results add vital information to the debate surrounding the efficacy of chelation treatment following elevated blood Pb levels.

Notably, this difference was shown to be much greater than could be attributed to bone turnover alone. Our calculation and comparison conservatively assumes a value of 60% uptake of Pb back into bone (K_{12} in Fig. 2), as other studies have reported ~60% for infants and an increase with age that peaks at ~90% in adulthood [18, 35, 38]. If uptake is in fact greater than 60%, resulting differences would be greater than what we found in our analysis. Further, we assumed that the children were completely removed from external Pb exposures. However, if exposures continued, the observed differences would move towards a null association. Thus, based on known bone turnover markers, our results indicate that chelation therapy is significantly effective in reducing bone Pb stores as well as blood Pb in highly exposed children. The bones of children may be more amenable to chelation of lead than the bones of adults because children's bones are more porous than adults - the Haversian canals occupy a larger space in the bones of children, and therefore afford more surface area for chelation to occur. However, a previous case study did show a dramatic reduction in bone lead with chelation treatments in an adult [25]. Finally, the reduction in bone lead was greater with more EDTA treatments – even with a non-significant difference in total time elapsed.

A previous study identifying changes in bone Pb in children after chelation found a similar change in bone Pb on average [14]. In this previous study, bone Pb was measured similarly, but results

were given as total net counts from the XRF measurement. Using the average value for the bone net counts of 191.4 in treated individuals and the average change of this value as 44.9, there is a 23% observed difference in bone lead after chelation. In our study, using the average values for children before treatment and the average difference, we observe at 27% difference in bone Pb. These values are similar and although the previous study used a higher blood lead Pb cut-off of 45 ug/dL, we saw similar, if not greater, differences in bone Pb for children with a blood lead cut-off of 25 ug/dL. This may indicate that chelation has a consistent impact across differing exposure levels. However, we are not able to compare important differences, as the study used different dosing and follow-up procedures in comparison to our study.

Importantly, we were unable to track the potential implications for changes in these children associated with zinc, copper, or iron. These bioessential metals would be additionally impacted by chelation treatments. In a previous clinical trial, children who were treated using succimer, a different chelating agent, were shorter on average [13]. It is unclear how repeated EDTA chelation treatments in our study may additionally impact the nutritional status of these children.

This study did have limitations that should be acknowledged when considering the results. The study relied on modeled data for control results rather than actual measurements of children not undergoing chelation therapy. This study was limited to young children with an average age of 4.1 ± 2.9 years, so the generalizability to other ages is lacking. As identified in our previous study, biokinetic markers vary significantly by age, and this will likely mean any biokinetic changes as a result of chelation would similarly depend on age. This study was also completed on children with blood Pb levels >25 µg/dL. The reduction may not have been so drastic had initial exposure levels been lower. Therefore, the beneficial effects of chelation may also be less. From Fig. 4, children generally had decreases in bone lead on an individual basis, which would support the idea that further ingestion of lead was reduced or eliminated in these individual cases. However, from Fig. 5 three children had increases in blood lead level, which may be from short-term exposure. Further studies would help to reduce these observed limitations and identify the key components in further reducing long-term bone Pb stores as a result of chelation therapy. Furthermore, it would be incredibly beneficial in future studies to identify biochemical markers of Pb toxicity such as protoporphyrin levels or aminolaevulinic acid dehydratase, markers of bone turnover, measurements of urine Pb, and other bioessential elemental changes.

The previous standard of care for chelation was identified based on literature that did not show the complete positive impact of chelation therapy on Pb storage in the body. With our results demonstrating a reduction of bone Pb after chelation therapy, there may be significantly increased advantages to treatment, while the risks remain the same. More research is needed to identify 1) whether there are potential benefits of removal of Pb from bone and 2) if so, at which point treatment should be ceased. These parameters will depend heavily on each individual case. Endogenous exposure from bone stores of Pb are identified as a significant source of exposure for years after the initial lead poisoning event [21–23, 36]. A reduction in bone Pb would mean a significant reduction in endogenous exposure, which could reduce circulating Pb levels years after the initial exposure. This could potentially have a significant positive result on chronic health outcomes related to Pb exposure, as the release of bone stores as endogenous exposure is related to health outcomes [21, 22]. More study is needed to identify how long-term health is impacted after chelation treatments due to a potential decrease in endogenous stores. On the other hand, chelating children with blood Pb levels in the 20-44 ug/dL range failed to result in demonstrable improvements in measures of intelligence in a multi-center NIH-funded randomized trial in the USA [39]. Moreover, the children who received succimer (a lead chelating agent) had significantly lower increases in height, a phenomenon that may reflect chelation's collateral effect of increasing the excretion of nutrients involved in growth [40]. However, succimer did seem to improve motor function for children who had treatment [41]. Finally, succimer did not seem to improve brain function in the treated children and was shown to be potentially harmful. Although succimer, the chelating agent used in the trial, is an oral agent, it otherwise has similar pharmacologic properties to EDTA.

In conclusion, our study suggests that chelating children with various degrees of lead poisoning with EDTA, a treatment that is practiced in China and elsewhere, seems to reduce bone stores of Pb. Whether this ultimately results in improvements to health outcomes remains an important topic for research.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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AUTHOR CONTRIBUTIONS

AJ Specht: Conceptualization, drafting, reviewing; Y Lin: Drafting, reviewing; J Xu: Drafting, reviewing; AS Dickerson: Drafting, reviewing; C Yan[3]: Drafting, reviewing; H Hu: Drafting, conceptualization, reviewing; MG Weisskopf: Drafting, reviewing, conceptualization; LH Nie: Drafting, conceptualization, reviewing.

COMPETING INTERESTS

AS served as an expert witness in litigation for plaintiffs in the Flint Water Crisis and other cases of harm from lead exposure. The other authors have no stated conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received IRB approval from Purdue University and Xinhua Hospital and adhered to all guidelines and regulations set forth. When recruited, a trained research assistant would present the subjects and their parents with the details of the study and the consent forms. Signed consent forms were received from the parents of each subject, as well as an assent form from any child age 7 or older.

ADDITIONAL INFORMATION

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